



Efficacy of Vitamin D3 Supplementation on Osseointegration of Implants

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Fundamental criteria for the overall success of dental implant therapy include formation of direct bone to implant contact (BIC), primary stability, and development of functional ankylosis of implant.^{1,2} Studies^{3–6} have reported that adjunct treatments (such as use of growth factors and/or stem cells, hormone replacement, and vitamin D supplementation) in conventional implant placement protocols play a role in enhancing BIC, which may in turn improve the overall success and survival of dental implants. Moreover, it has also been reported that increasing surface roughness of implants favors osteoblastic proliferation, collagen synthesis, and expression of integrins in the extracellular matrix, thereby improving the mechanisms associated with osseointegration.^{7–9} Such modernizations in traditional implant therapy have been shown to facilitate

Purpose: The aim was to systematically review the efficacy of vitamin D3 (VD3) supplementation on the osseointegration of implants.

Methods: The addressed focused question was “does VD3 supplementation affect osseointegration around implants?” Indexed databases were searched from 1969 up to and including March 2015 using various key words including: “Bone to implant contact”; “implant”; “vitamin D”; and “osseointegration.” Letters to the editor, case reports/case series, reviews, and articles published in languages other than English were excluded. The pattern of the present systematic review was customized to primarily summarize the pertinent data.

Results: Six experimental studies (4 in rodents and 2 in rabbits) were included. Number of titanium im-

plants placed ranged between 28 and 100 implants. Results from 5 studies showed that VD3 supplementation enhanced new bone formation and/or bone to implant contact (BIC) around implants. One study showed no significant difference in BIC and new bone formation around VD3 coated and noncoated implants. One study reported that insulin therapy with adjunct VD3 supplementation enhances new bone formation around implants in diabetic rats than when insulin replacement therapy is used alone.

Conclusion: Efficacy of VD3 supplementation on osseointegration of implants remains controversial and requires further investigations. (*Implant Dent* 2016;25:1–7)

Key Words: bone to implant contact, implant, osseointegration, vitamin D

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osseointegration even in immunosuppressed conditions (such as chronic kidney disease, osteoporosis, and diabetes mellitus); which were previously believed to negatively affect osseointegration.^{10–12}

Vitamin D is a fat-soluble biomolecule, which is obtained through vitamin D rich diet or is generated in the skin on ultraviolet light exposure.^{13,14} Vitamin D, in its active form (1,25-dihydroxy VD3), plays a vital role in bone mineral homeostasis by stimulating intestinal absorption of calcium and phosphate.¹⁵ It regulates

bone mineralization by activation of bone-forming osteoblasts and bone-resorbing osteoclastic cells.^{16–18} Therefore, VD3 is also being successfully used in the prevention and management of osteoporosis.^{19,20} In an experimental study, Satué et al²¹ assessed biological effect of titanium (Ti) implants coated with UV-activated 7-dehydrocholesterol (7-DHC), the precursor of VD3, on cytotoxicity and osteoblast differentiation. These *in vitro* results showed that Ti implants coated with 7-DHC demonstrated positive effects on osteoblast

proliferation and differentiation compared with control implants (implants without 7-DHC coating).²¹ Although VD3 supplementation has been shown to enhance BIC,^{22,23} negative results have also been reported.²⁴ For instance, Zhou et al²⁵ and Dvorak et al²³ showed significantly better bone volume and osseointegration of Ti implants in VD3 administered rats as compared with controls. However, Naito et al²⁴ showed no significant effect of VD3 supplementation in terms of increased BIC.

There seems to be a debate over the efficacy of VD3 supplementation in terms of augmenting BIC, therefore, the aim of this study was to systematically review the available evidence in relation to the efficacy of VD3 in the osseointegration of implants.

MATERIALS AND METHODS

Focused Question

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a specific question was constructed according to the Participants, Interventions, Control, Outcomes (PICO) principle (Fig. 1).²⁶ The addressed focused question was “does VD3 supplementation influence osseointegration around implants?”

(P) Participants: it was essential for subjects to have undergone implant treatment.

(I) Types of interventions: the intervention of interest was the effect of VD3 supplementation on osseointegration.

(C) Control intervention: osseointegration without VD3 supplementation.

(O) Outcome measures: BIC, new bone formation and/or BV/tissue volume around implant with and without VD3 supplementation.

Eligibility Criteria

The eligibility criteria were as follows: (a) original studies (clinical and experimental); (b) inclusion of a control group (osseointegration around implants without VD3 supplementation); (c) intervention: effect of VD3 supplementation on osseointegration; and (d) studies published only in English language. Letters to the editor, historic reviews, commentaries, case series, and case reports were excluded.

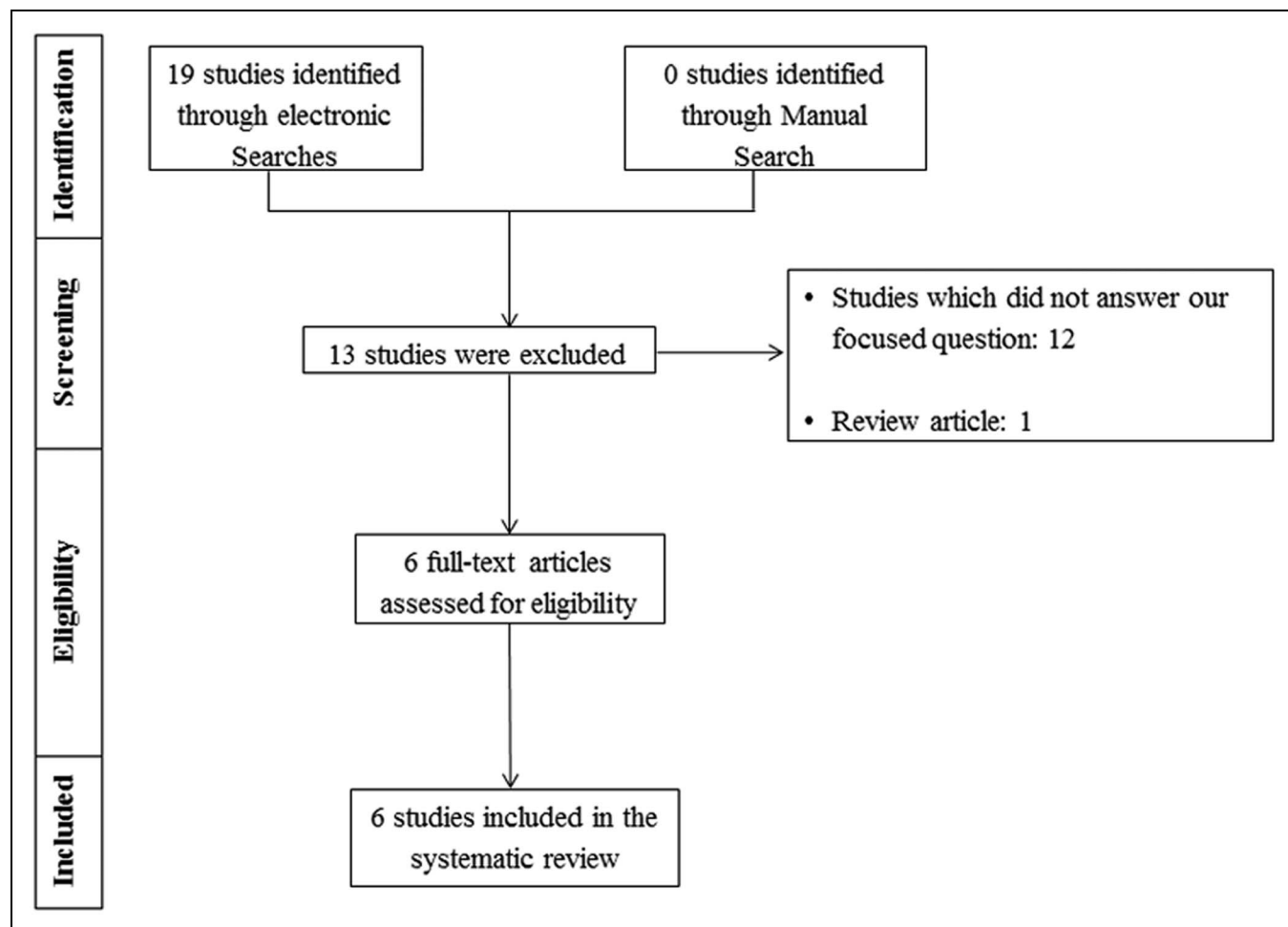


Fig. 1. Flow chart showing the search strategy that was adopted to identify studies that fulfilled the eligibility criteria. This flow chart was constructed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Table 1. Characteristics (Authors and Year of Study, Study Design and Subjects, Geometry and Location of Implant Placement, Study Groups, Follow-up Period, and Outcomes) of Studies Included in the Present Systematic Review

Authors	Study Design	Study Subjects, n	Number of Implants, n	Implant Dimensions, D × L in mm	Implant Location	Study Groups, n = subjects	Follow-up, wk	Outcome
Wu et al ²²	<i>In vivo</i> prospective	30 rats	NA	1 × 10	Femur	Group-1 (n = 6): control rats; group-2 (n = 6): diabetic rats; group-3 (n = 6): insulin-treated diabetic rats; group-4 (n = 6): VD3-treated diabetic rats; group-5 (n = 6): insulin + VD3-treated diabetic rats	12	BV/TV ratio was higher in group-3 than groups 1 and 2. BV/TV ratio was higher in group-5 than other groups
Dvorak et al ²³	<i>In vivo</i> prospective	50 rats	100 implants	1 × 3	Tibia	Group-1 (n = 16): VD3 depletion; group-2 (n = 17): VD3 repletion; group-3 (n = 17): controls	4	New bone formation was significantly higher in group-2 than groups 1 and 3
Naito et al ²⁴	<i>In vivo</i> prospective	12 rabbits	28 Ti implants	3.75 × 7	Tibia	Group-1 (n = 3): control; group-2 (n = 3): VD3 (10 ⁻⁸) coated implants; group-3 (n = 3): VD3 (10 ⁻⁷) coated implants; group-4 (n = 3): VD3 (10 ⁻⁶)	6	There was no significant difference in BIC and NFB between the groups
Zhou et al ²⁵	<i>In vivo</i> prospective	20 rats	40 Ti implants	1.8 × 3.5	Tibia	Group-1 (n = 10): control; group-2 (n = 10): VD3 + MCT	8	BIC and BV/TV around implants were significantly higher in group-2 than in group-1
Liu et al ²⁷	<i>In vivo</i> prospective	30 mice	60 Ti implants	1 × 4	Femur	Group-1 (n = 10): control; group-2 (n = 10): CKD; group-3 (n = 10): CKD + VD3 at 100 ng/kg body weight	2	BIC and BV/TV around implants were significantly higher in group-3 than in groups 1 and 2
Cho et al ²⁸	<i>In vivo</i> prospective	12 rabbits	48 Ti implants	3.75 × 7	Tibia	Group-1 (n = 6): control; group-2 (n = 6): implants coated with VD3	4 and 12	BIC was significantly higher in group-2 than group-1

BV, bone volume; CKD, chronic kidney disease; D, diameter; L, length; MCT, medium-chain triglyceride; NFB, newly formed bone; TV, tissue volume.

Literature Search Protocol

PubMed/Medline (National Library of Medicine, Washington, DC), EMBASE, Scopus, Web of knowledge, and Google-Scholar databases were searched from 1969 up to and including March 2015 using different combinations of the following key words: “Bone to implant contact”; “implant”; “vitamin D”; and “osseointegration.” Titles and abstracts of studies identified using the above-described protocol were screened by the authors (F.J. and S.V.K.) and checked for agreement. Full texts of studies judged by title and abstract to be relevant were read and independently evaluated for the stated eligibility criteria. Reference lists of potentially relevant original and review articles were hand searched to identify any studies that could have remained unidentified in the previous step. Once again, the articles were checked for disagreement through discussion among the authors (Fig. 1). The pattern of the present systematic review was customized to mainly summarize the relevant data.

The initial search yielded 19 studies. Thirteen studies which did not fulfill the eligibility criteria were excluded (Appendix A). In total, 6 experimental studies^{22–25,27,28} were included and processed for data extraction.

RESULTS

General Characteristics

All studies^{22–25,27,28} were prospective and performed *in vivo*. Two studies^{24,28} were performed in rabbits and 4 studies^{22,23,25,27} were performed in rodents. Three studies^{23,25,27} were performed in female rodents and 1 study²² was performed in male rats. In 2 studies,^{24,28} sex of the animals used was not reported. In all studies,^{22–25,27,28} Ti implants were used and their numbers ranged between 28 and 100 implants. In the study by Wu et al,²² the number of implants placed was not reported. Dimensions (diameter × length in millimeters) of implants used ranged between 1 × 2 and 3.75 × 7 millimeters.^{22–25,27,28} Implants were placed in tibiae and femur in 4^{23–25,28} and 2 studies,^{22,27} respectively. In all studies,^{22–25,27,28} the follow-up period ranged between 2 and 12 weeks. In 2 studies,^{24,28} osseointegration

around VD3 coated and noncoated implants was assessed. In 2 studies,^{23,25} the effect of VD3 supplementation on osseointegration was assessed in ovariectomized rats. Wu et al²² evaluated the effect of combined VD3 and insulin therapies on implant osseointegration in rats with streptozotocin (STZ)-induced diabetes (Table 1).

Assessment of Osseointegration

In 3 studies,^{24,25,27} osseointegration was assessed using histologic analysis. Zhou et al²⁵ also performed biomechanical testing to assess new bone formation and strength of newly formed bone around implants, respectively. In 2 studies,^{22,25} new bone formation around implants was assessed using 3-dimensional (3D) microcomputed tomography (micro-CT). In 2 studies,^{22,23} osseointegration was assessed using histomorphometry, and Cho et al²⁸ used scanning electron microscopy (SEM) to assess new bone formation around implants. Push-in and push-out mechanical testing was performed in studies by Liu et al²⁷ and Wu et al,²² respectively.

Main Outcomes

Results from 5 studies^{22,23,25,27,28} showed that VD3 supplementation enhanced new bone formation and/or BIC around implants. Results by Naito et al²⁴ showed no significant difference in BIC and new bone formation around VD3 coated and control (noncoated) implants. One study²² reported that insulin therapy promotes osseointegration in diabetic rats compared with diabetic rats without insulin therapy. This study also reported that insulin therapy with adjunct VD3 supplementation enhances new bone formation around implants in diabetic rats than when insulin replacement therapy is used alone (Table 1).²²

DISCUSSION

From the literature reviewed, 6 studies^{22–25,27,28} fulfilled our eligibility criteria; however, results from nearly 83% studies^{22,23,25,27,28} showed that VD3 supplementation enhanced new bone formation around implants. Interestingly, results by Naito et al²⁴ showed no significant difference in new bone formation around implants with and

without VD3 coatings. An explanation in this regard is that both VD3 coated and noncoated implants had rough surfaces. In a recent study, Deng et al²⁹ reported that optimal implant surface roughness regulates cellular behaviors and enhances biocompatibility and osseointegration. Moreover, it has also been proposed that implant surface roughness may also positively influence the level of primary stability achieved at the time of implant placement.³⁰

It is known that VD3 plays an important role in bone mineral homeostasis and its active form (1 α ,25-dihydroxyvitamin D3) may also act as a bioactive protein, which augments osteogenesis.^{14,31,32} VD3 also stimulates calcium absorption in the intestine, thereby maintaining normal calcium homeostasis, and indirectly regulating osseous mineralization.^{33,34} It was therefore tempting to speculate that VD3 exhibits the potential to regenerate bone in areas with periimplant osseous defects. However, it is pertinent to mention that all the studies^{22–25,27,28} which assessed the effect of VD3 supplementation on osteogenesis around implants were performed in animals and the methodologies used markedly varied among the studies included. For example, Naito et al²⁴ and Cho et al²⁸ assessed osteogenesis around VD3 coated and noncoated implants placed in systemically healthy rabbits; whereas in studies by Zhou et al²⁵ and Wu et al,²² effects of VD3 supplementation on osseointegration were assessed in ovariectomized and STZ-induced diabetic rats, respectively. Although some studies^{24,25,27} relied on histologic analysis to evaluate new bone formation, others used micro-CT^{22,25} or SEM analysis²⁸ to assess newly formed bone around implants. Although micro-CT analysis allows assessment of samples in a 3D plane³⁵; histological analysis continues to be a goal standard in assessing bone formation on a cellular level.^{35,36} This reflects that an absolute methodology for assessing bone formation around implants (with or without VD3 supplementation) is yet to be formulated.

Authors of the present systematic review applaud the results by Wu et al,²² which showed that insulin

replacement therapy in rats with STZ-induced diabetes reversed the impaired osseointegration and enhanced by 1.6 times. These original results are in accordance with another study in which Javed and Romanos³⁷ reported that dental implants can osseointegrate and remain functionally stable over long durations among patients with well controlled diabetes mellitus in a manner similar to systemically healthy individuals. An explanation in this regard maybe derived from the fact that glycemic maintenance reduces oxidative stress and receptors for advanced glycation end products in periodontal tissues.^{38–41} These factors may promote healing and osteogenesis around implants. This suggests that optimal glycemic control and VD3 supplementation facilitate osseointegration in medically challenged patients, such as those with diabetes mellitus and osteoporosis.

It is worth mentioning that the follow-up period for all the studies^{22–25,27,28} included in the present systematic review was relatively short (up to 12 weeks). It is hypothesized that had these experimental studies been followed up for longer durations (at least 12 months), they would have provided stronger evidence regarding the efficacy of VD3 supplementation on the osseointegration of implants. Although it is speculated that VD3 supplementation facilitates long-term survival and success of dental implants in medically compromised patients (such as patients with osteoporosis); further longitudinal, randomized controlled trials are needed to test this hypothesis. Moreover, it is well known that poor oral hygiene, advancing age, and tobacco habits (such as cigarette smoking and tobacco chewing) are significant risk factors of alveolar bone loss.^{42–46} Because all studies^{22–25,27,28} including in this systematic review were performed in animals, it remains to be determined whether or not VD3 supplementation would facilitate new bone formation in elderly individuals (>65 years old), patients with a poor plaque control and habitual tobacco product users. It is postulated that the outcomes of VD3 supplementation therapy in terms of augmenting new

bone formation around implants are compromised in vulnerable populations (such as patients with a poor plaque control, habitual tobacco product users, and elderly individuals). Hence, additional studies are warranted in this regard.

CONCLUSION

Within the limits of the present systematic review, it is concluded that the efficacy of VD3 supplementation on osseointegration of implants remains controversial and requires further investigations.

DISCLOSURE

The authors claim to have no financial interest, either directly or indirectly, in the products or information listed in the article.

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Appendix A: List of Excluded Studies. Reason for Exclusion Is Shown in Parenthesis

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