

Significance of 25(OH) D3 in Early Dental Implant Failure (EDIF) during osseointegration—A systematic review

ABSTRACT

Bone metabolism is a key factor for successful osseointegration, and low vitamin D levels may negatively impact the process of osseointegration after implant placement. The study was aimed at evaluating the relation of vitamin D levels with dental implant osseointegration and subsequently the success or failure of the implant. The focused questions were—What is the effect of vitamin D levels on successful dental implant osseointegration and what is the effect of vitamin D supplementation on successful implant osseointegration? A search was conducted on PubMed and Google Scholar using the terms “vitamin D,” “cholecalciferol,” “1,25(OH) D,” “dental implant,” “osseointegration,” and “bone implant contact” for a period of 10 years from 2011 to 2020. Clinical trials, cross-sectional studies, case series, and case reports were included. A total of ten studies were included after the screening process. Five of these studies evaluated the effect of vitamin D supplementation on osseointegration, whereas five only evaluated the effect of vitamin D deficiency on dental implant osseointegration. Only five of these studies reported dental implant failure varying from 7% to 13% in vitamin D deficient/insufficient groups. Positive relationship exists between serum vitamin D levels and dental implant osseointegration; however, few studies failed to report any relation. More prospective clinical research studies as well as randomized controlled trials are needed to show a significant correlation between decreased serum levels of vitamin D and increased risk of dental implant failure in perspective of vitamin D supplementation which can promote the osseointegration of dental implants.

Keywords: Early dental implant failure, Implant stability, Osseointegration, Peri-implant tissue, Vitamin D

INTRODUCTION

The concept of osseointegration, since its introduction by Dr. Per-Ingvar Brånemark a Swedish orthopedic in 1957, has come a long way. The chance discovery that bone could grow in proximity with titanium (Ti) and that it could effectively be adhered to the metal without being rejected was later defined as a direct structural and functional connection between ordered, living bone, and the surface of a load-carrying implant.^[1,2] The first dental implant was placed in 1965, and from that point onward, its shape and surface characteristics have been ever evolving to achieve better osseointegration of the implant.^[3] It has been established that an increase in surface area by using threaded implants with surface roughness increases the bone implant contact (BIC) thus, contributing to increased osseointegration, the other variables that affect implant success are bone quality and

the medical status of the patient pertaining to the absence of debilitating diseases.^[4] Bone availability with desirable

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dimensions (quantitative aspect) allows for the placement of an implant of appropriate size which is important to achieve primary stability, but the quality of bone helps achieve secondary stability and, therefore, successful osseointegration leading to the long-term success of the implant.^[5] In patients with the poor bone quality especially due to osteoporosis, efforts have been made to increase the success rate of dental implants. Few studies have reported improved success rates of dental implants in patients on bisphosphonate therapy for osteoporosis, while others do not report a significant difference.^[6,7] Conflicting views also exist regarding the effect of hormone replacement therapy on implant osseointegration.^[8,9]

Vitamin D is a fat-soluble vitamin synthesized by the skin and obtained from natural sources in its inactive form which undergoes hydroxylation in the liver followed by the kidney to form the active form, that is, 1,25 dihydroxy vitamin D3 as shown in Figure 1.^[10] It plays a major role in the maintenance of serum calcium and phosphorous levels. Vitamin D deficiency may occur as a result of insufficient exposure to Ultraviolet B (UVB) light or insufficient dietary intake of sources rich in vitamin D. Deficiency of vitamin D has been defined as 25(OH) D levels of less than 20 ng/ml, and vitamin D insufficiency has been defined as a 25(OH) D of 21–29 ng/ml.^[11]

As vitamin D levels fall enough to cause deficiency, osteoporosis may develop in adults and osteomalacia in children is characterized by low bone mass, deterioration of bone tissue, and disruption of bone microarchitecture resulting in weak bones that are at an increased risk of fracture.^[12] Bone

metabolism is a key factor for successful osseointegration. Studies suggest low vitamin D levels may negatively impact the process of osseointegration after implant placement, but studies have also reported the lack of a definitive link between low serum vitamin D levels and implant failure, and therefore, the association remains controversial.^[13,14] Some studies suggest that 1,25-dihydroxyvitamin D3 positively affects cell differentiation and matrix mineralization and, thus, may act as a stimulating factor in osteoblastic bone formation.^[15]

The present study was aimed at evaluating the relation of vitamin D levels with dental implant osseointegration and subsequently the success or failure of the implant.

METHOD

Search protocol

This review adheres to the 2009 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews.^[16]

Focused questions

The focused question included

1. What is the effect of vitamin D levels on successful dental implant osseointegration?
2. What is the effect of vitamin D supplementation on successful implant osseointegration?

Eligibility criteria

Clinical studies that evaluated the relation of vitamin D levels with implant osseointegration were taken. Along with

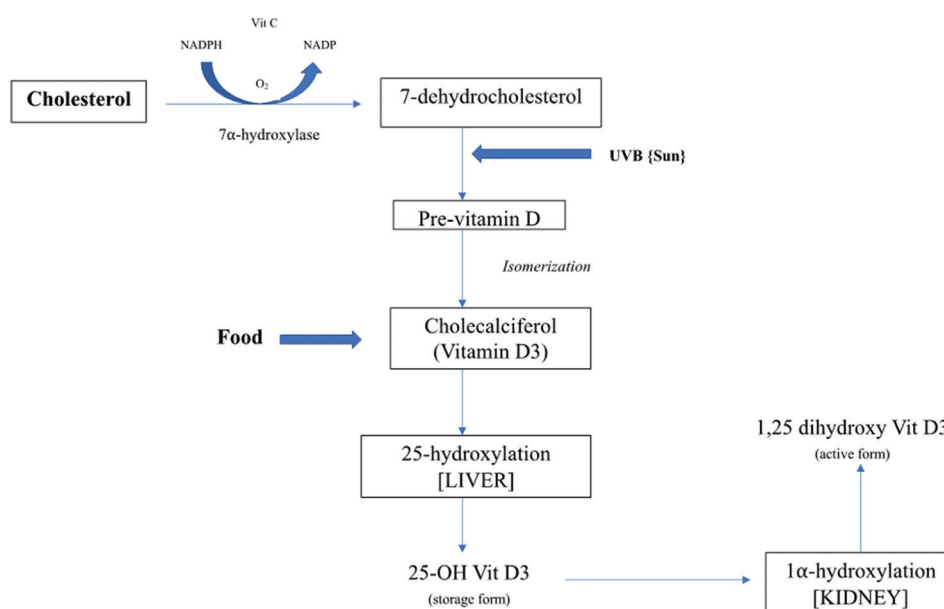


Figure 1: Synthesis of the storage and active form of Vitamin D

randomized clinical trials, retrospective studies, case series, and case reports were also considered in this review. Studies that evaluated the effects of vitamin D supplementation on the success rate of implants were also included. The outcome of the studies was represented in the form of dental implant success or failure.

Data sources and search strategies

The PubMed database was searched for potentially relevant articles by using Medical Subject Headings (MeSH) terms “vitamin D” OR “cholecalciferol OR 1,25(OH) D AND dental implant” OR “osseointegration” OR “bone implant contact.” Articles were searched for a 10-year period from 2011 to 2020. The search strategy attempted to identify 1) articles that report effects or relation between vitamin D levels and dental implant success/failures and 2) implant success or failure as affected by vitamin D supplementation. A search on Google Scholar was also performed to include relevant articles.

All abstracts were read by three authors (author number 1,2,4), and disagreements were resolved by consensus after discussion with the two authors (author number 3 and 5).

Inclusion criteria

Studies on the relation or effect of serum vitamin D levels on dental implant success or failure rates were included. Clinical trials that evaluated the effect of vitamin D supplementation on dental implants were included. Randomized clinical trials (RCTs), cross-sectional studies, case series, and case reports were included in the review.

Exclusion criteria

Studies that described the effect of vitamin D on bone metabolism without any context to dental implants were not considered. Animal studies and review articles were excluded.

RESULTS

Ten studies were considered for the review after the screening process [Figure 2] and details are given in Table 1. Number of patients and dental implants placed is depicted in Graphs 1 and 2.

General characteristics

Out of ten studies, five studies were clinical trials, three retrospectives, and two case reports were included. Two studies included only postmenopausal women^[22,24], while in both the case reports^[23,25] all patients were male. In three clinical trials^[17-19] and two retrospective studies,^[15,21] patients were divided into two groups depending on their serum

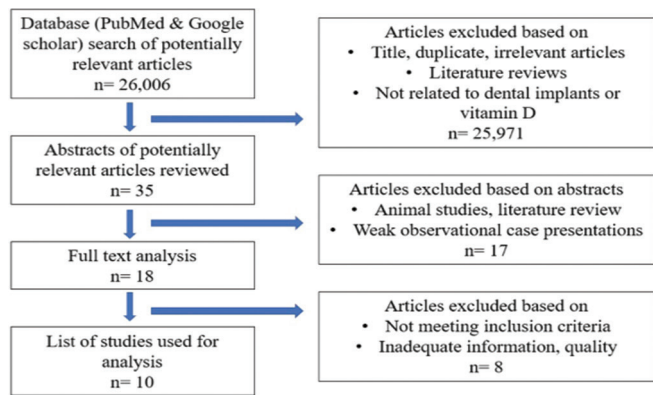
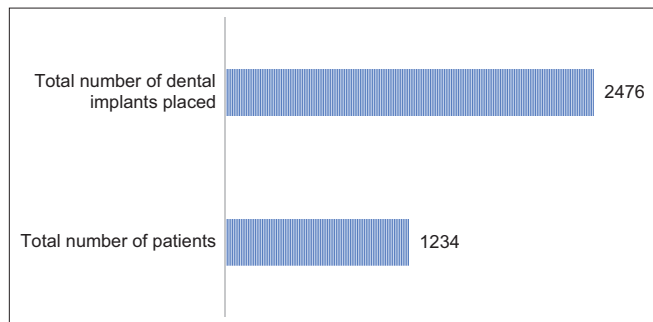
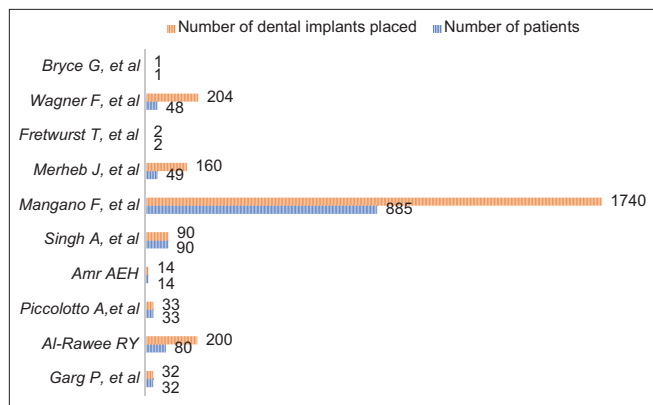


Figure 2: Procedural flowchart of the screening process



Graph 1: Total number of dental implants and total number of patients



Graph 2: Number of patients and dental implants placed in each study

vitamin D levels, and levels below 30 ng/ml were classified as vitamin D deficiency. In one multicentric clinical trial, patients were classified into three groups as osteoporosis, osteopenia, and control based on dual-energy X-ray absorptiometry (DXA) scan.^[22] One retrospective study categorized postmenopausal women into two groups as healthy and osteoporosis.^[24] In one clinical trial, patients were divided into two groups, one group received dental implant simultaneously with alveolar ridge augmentation performed using customized titanium mesh and xenografts mixed with vitamin D3.^[20] Vitamin D oral supplements were given in three clinical trials^[17-19] and two case reports.^[23,25] Follow-up duration varied from 2 to 6 months in six studies.

Table 1: Observations of the studies included in the present systematic review

Authors	Year	Type of study	Study design	Age (years)	Vitamin D supplementation	Follow-up duration (months)	Study findings	Failure rate of dental implant (%)
Garg P, Ghalaut P, Dahiya K et al. ^[17]	2020	RCT	Thirty-two patients divided into test group (vit D <30 ng/ml) and received cholecalciferol sachet <30 ng/ml, treated with dental implant and not received vitamin D3 supplements)	20-40	Test group received cholecalciferol sachet 60000 IU/month for 3 months and continued for 6 months depending on level of vitamin D	6	Crestal bone level (CBL) was evaluated at 1 week, 3 months, and 6 months. Statistically significant difference seen for the values between the groups ($P < 0.01, 0.05$) for 3 months distal CBL with higher values for test group as compared to control group. The study that cholecalciferol has systemic effects on accelerating bone formation around titanium implant.	None
Al-Rawee RY ^[18]	2020	RCT	Eighty patients were divided into test (vit D > 30 ng/ml) and control group (vit D < 30 ng/ml)	20-50	Calcium and cholecalciferol (calcium carbonate 1000 mg + VitD3 0.025 mg) one tablet once daily for three months was given to test group. One month before surgery and two months after surgery.	4	Seven dental implants are failed from total 100 implants, at the time of second step surgery in patients with insufficient level of vitamin D3. The study concluded that low vitamin D3 levels may negatively impact healing after implant placement.	7%
Piccolotto A, Toyama G, Busato M. et al. ^[19]	2019	Clinical trial	Implants were placed in 33 patients. Two groups were formed control (19) and test (14)	35-60	The test group was vitamin D deficient group, where supplementation was given with 50,000 IU of vit D capsule once a week for 8 weeks.	2	Vitamin D levels improved significantly for the test group. For probing depth (PD), width of keratinized mucosa (wKM), bleeding (mBl), and peri-implant plaque index (mPI) were not significantly different for the groups.	None
Amr AEH ^[20]	2019	RCT	Fourteen subjects divided into test group (7 patients) and control group (seven patients) treated with dental implant	28-40	In test group, alveolar ridge augmentation using customized titanium mesh and xenografts mixed with vitamin D was done and control group received the same treatment without the vitamin D.	4	The mean percent increase in the width of the augmented alveolar ridge (buccolingual dimension) was statistically higher for the group that received vitamin D. A statistically higher increase in the mean implant stability quotient (ISQ) was also recorded for the test group (a percent change of 8.54 ± 0.38) than the control group (percent change of 2.35 ± 0.58)	None
Singh A, Aganwal M, Prasad A ^[15]	2019	Retrospective study	Ninety patients were divided into Group 1 (≥ 40 yrs of age) and Group 2 (≤ 40 yrs of age). Vitamin D level was recorded at the time of implant surgery, and primary outcome of implant failure within 5 months was evaluated	<40 and >40	No supplementation	5	Fifteen patients had vitamin D < 10 ng/ml, showed two cases of early implant failure, and three out of 44 patients with vitamin D levels 10-30 ng/ml had early implant failure. Only one failure case was reported among 31 patients with serum vitamin D levels in excess of 30 ng/ml. A definitive link between low serum vitamin D levels and early dental implant failure could not be established.	Vitamin D: Deficient group: 13.33% Insufficient group: 6.8% Sufficient group: 3.23%
Mangano F, Mortellaro C, Mangano N. et al. ^[21]	2018	Retrospective study	Data were acquired for the period between 2003 and 2017, and the outcome studied was early dental implant failure (EDIF), that is, 885 patients treated with 1740 implants were enrolled in the study. Vitamin D levels were evaluated, and three groups were evaluated.	>18	No supplementation	4	The study failed to demonstrate a significant relationship between low serum levels of vitamin D and increased risk of EDIF.	Vitamin D: Deficient group: 11.1% Insufficient group: 4.4% Sufficient group: 2.9%

Contd...

Table 1: Contd...

Authors	Year	Type of study	Study design	Age (years)	Vitamin D supplementation	Follow-up duration (months)	Study findings	Failure rate of dental implant (%)
Merheb J, Tenmerman A, Rasmusson L. <i>et al.</i> ^[22]	2016	Multicenter clinical trial	Seventy-three patients were divided into three groups osteoporotic/osteopenic/control. Forty-nine patients received dental implants, and ISQ was measured at implant placement and prosthetic abutment placement	>60 females	No supplementation	-	Lower ISQ (63.3±10.3) values were observed in osteoporotic group compared to osteopenia (65.3±7.5) and control (66.7±8.7) groups at implant placement and prosthetic abutment placement.	None
Fretwurst T, Grunet S, Woelber JP, <i>et al.</i> ^[23]	2016	Case report	In two patients, implants placement was done and early failure was observed	48 and 51	Implants were again placed 6 months after vitamin D supplementation.	-	Implant placement was followed by severe pain even though no soft tissue inflammation was seen and was removed within the week. At removal zone of osteolysis was seen around the implant. Implants placed after vitamin D supplementation were successful.	-
Wagner F, Schuder K, Hof M, <i>et al.</i> ^[24]	2016	Retrospective study	Two hundred and four implants were evaluated in 48 postmenopausal women. Thirty subjects were found to be healthy, and 18 suffered from osteoporosis. Marginal bone loss (MBL) was evaluated at implant placement and 1 year after placement	>54	Vitamin D was considered as a confounding factor	-	For healthy group mean MBL mesial (0.6±1.2 mm) and distal (0.5±1.5 mm) and for the osteoporotic group mean MBL mesial was (1.1±1.3 mm) and distal was (1.2±1.3 mm). The study concluded that osteoporosis significantly influenced peri-implant bone remodeling and vitamin D supplementation indicates significant beneficial effects	-
Bryce G, MacBeth N. ^[25]	2014	Case report	One dental implant placement immediately after tooth extraction	29	No supplementation	-	No osseointegration of implant was found 5 months after immediate implant placement and immediate cantilever resin bonded restoration. Patient was found to be osteoporotic, and it was stated that vit D deficiency could have played a possible role in implant failure.	-

Clinical and radiological evaluation of Osseointegrated implants

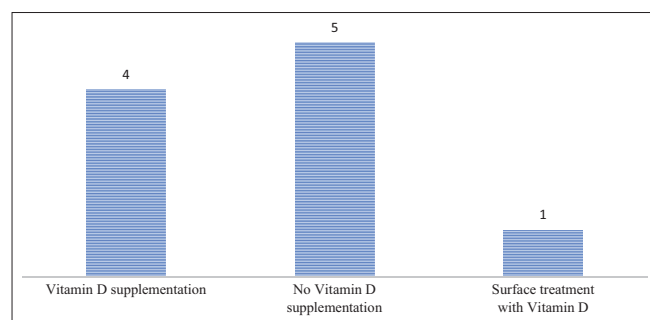
In all the studies, intraoral periapical view (IOPA) and/or orthopantomogram (OPG) were considered to assess the implant osseointegration and study by *Amr AEH*^[20] investigated radiological bone loss by cone-beam computed tomography (CBCT) system. While three studies evaluated implant stability by measuring ISQ value.^[18,20,22] Apart from these, all studies conducted a clinical examination and periodontal health.

Study outcomes

Three studies reported implant osteointegration after vitamin D supplementation in which two studies^[17,19] observed no failure in vitamin D deficient group, while *Al-Rawee RY*^[18] reported implant failure. One study observed no implant failure after surface treatment with vitamin D.^[20] Two studies assessed the implant failure rate without vitamin D supplementation based on vitamin D deficiency, insufficiency, and sufficiency.^[15,21] *Merheb J et al.*^[22] reported no implant failure in postmenopausal women with osteoporosis and osteopenia. One study stated a significant beneficial effect in peri-implant bone remodeling at the time of osseointegration.^[24] Two case reports observed implant failure due to vitamin D deficiency.^[23,25]

DISCUSSION

The review was aimed at studying the possible effect of vitamin D as well as the effect of vitamin D supplementation on successful implant osseointegration. A total of ten articles were taken for the review, of which only five evaluated the effect of vitamin D supplementation [Table 1]. Out of five, oral vitamin D supplementation was given in four studies, while one study opted for surface treatment with vitamin D [Graph 3]. After vitamin D supplementation, three studies reported no dental implant failure, while one study observed implant failure in vitamin D deficient group after vitamin D supplementation [Table 2].



Graph 3: Number of studies based on vitamin D supplementation and surface treatment

All studies selected for this review utilized human subjects. In two randomized clinical trials, *Al-Rawee RY* and *Piccolotto A et al.* divided their subjects into a vitamin D deficient group and a control group with normal vitamin D levels, and subsequently, vitamin D supplements were given to the vitamin D deficient group.^[18,19] One of the studies (*Garg P et al.*) gave supplementation in the form of cholecalciferol sachet 60000 IU/month for 3 months and continued for 6 months and reported that cholecalciferol has systemic effects on accelerating bone formation around titanium implant,^[17] whereas *Al-Rawee RY* utilized calcium and cholecalciferol (calcium carbonate 1000 mg + Vit D3 0.025 mg) one tablet once daily for three months, one month before, and two months after surgery as supplementation.^[18] The study only included patients below 50 years of age to eliminate senile osteoporosis or other diseases as a cause for dental implant failure. They concluded that low vitamin D3 levels may negatively impact healing after implant placement. Another trial included in the review reported vitamin D supplementation at a dosage of 50,000 IU capsules once a week for 8 weeks.^[19] The serum vitamin D levels of the test group improved after 8 weeks, but no significant difference was observed for the clinical parameters of the test and control groups. In another clinical trial,^[20] vitamin D was locally administered with xenograft in ridge augmentation prior to implant placement. Greater ridge augmentation was observed for the test group with significantly higher ISQ values for implants placed in the test group. On the other hand, a conflicting view was presented by studies (two of which were retrospective studies) that failed to report a significant relationship between low serum vitamin D levels and early dental implant failure.^[15,21] The study by *Singh et al.* reported no link between early dental implant failures and age, gender, smoking, and history of periodontitis. The study failed to demonstrate a significant relationship between low serum levels of vitamin D and increased risk of EDIF despite the increased incidence of

Table 2: Studies observed dental implant failure and effect of vitamin D supplementation

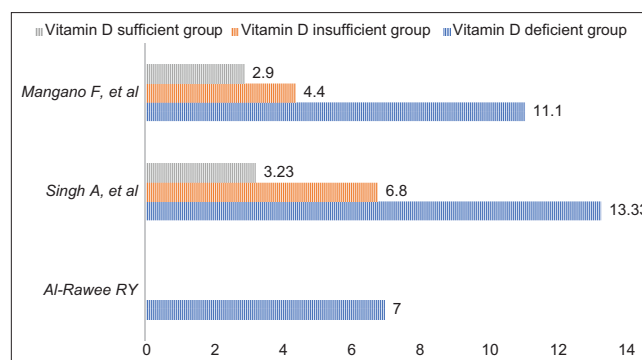
Studies reported failure in findings	Dental implants failure observed (n=10)	Effect of vitamin D supplementation observed
<i>Garg P, et al.</i>	None	Yes
<i>Al-Rawee RY</i>	Yes	Yes
<i>Piccolotto A, et al.</i>	None	Yes
<i>Amr AEH</i>	None	Yes (surface treatment)
<i>Singh A, et al.</i>	Yes	No
<i>Mangano F, et al.</i>	Yes	No
<i>Merheb J, et al.</i>	None	No
<i>Fretwurst T, et al.</i>	Yes	Yes
<i>Wagner F, et al.</i>	None	No
<i>Bryce G, et al.</i>	Yes	No

EDIF with lowering of serum vitamin D levels.^[15] In the study conducted by *Mangano et al.*, patients with debilitating systemic diseases, pregnancy, and insufficient oral hygiene were excluded from the study. The study although did not report any statistically significant results, the EDIF rate was higher in patients with vitamin D insufficiency and vitamin D deficiency. Study also reports a higher failure rate among smokers compared to non-smokers, but the difference was not statistically significant.^[15] *Merhab J et al.* reported the existence of a moderate relationship between the skeletal bone density and implant stability after observing ISQ values in osteoporosis, osteopenia, and control groups.^[22] A retrospective cross-sectional study of postmenopausal women with 30 subjects that were osteoporotic reported that osteoporosis significantly influenced peri-implant bone remodeling and vitamin D supplementation indicates significant beneficial effects.^[24] Case reports^[23,25] also suggested that vitamin D deficiency may be a cause for early dental implant failure and that vitamin D supplementation may play a role in successful osseointegration in dental implants.

Al-Rawee RY^[18] reported 7% failure rate of dental implant in patients with vitamin D level below 30 ng/ml, while *Singh A et al.*^[15] observed 13.33% and 6.8% failure rates in vitamin D deficient (<10 ng/ml) and insufficient group (10–30 ng/ml); however, no significant correlation between serum vitamin D levels and implant failures was found Graph 4. *Mangano F et al.*^[21] reported the maximum percentage of early dental implant failures (11.1%) in vitamin D deficient (<10 ng/ml) group, 4.4% in insufficient (10–30 ng/ml) group, and least percent of failed implants in the group of patients with optimal levels of vitamin D; however, the study concludes a significant relationship between low serum levels of vitamin D and increased risk of EDIF. Vitamin D level was below 20 ng/ml in all the patients included in case reports of *Fretwurst T et al.*^[23] and *Bryce G.*^[23]

In most of the studies, factors associated with the systemic diseases were excluded to rule out the impact of vitamin D on implant failure which shows a direct connection of vitamin D and implant failure. If factors such as poor oral hygiene, smoking habit, infection around implant, and immunocompromised condition are considered as other associated factors at the time of treatment planning and surgical intervention in this situation, we can state that vitamin D and implant failure also have the same impact toward the implant failure.

Vitamin D is known to regulate bone mineralization by activation of bone-forming osteoblasts and bone-resorbing



Graph 4: Percentage of failed dental implants in vitamin D deficient/insufficient/sufficient group

osteoclastic cells. Vitamin D3 also stimulates calcium absorption in the intestine, thereby maintaining normal calcium homeostasis and indirectly regulating osseous mineralization; therefore, it may play a critical role in dental implant osseointegration.^[26] Despite numerous advancements in the field of dental implantology, implant failures have been reported.^[27,28] *Castellanos-Cosano et al.* (2019) reported the implant failure rate to be 2.1%,^[28] while in the year 2022, another study reported the implant failure rate to be 3.1%.^[29] Vitamin D deficiency is rampant worldwide with a prevalence of 30–60% in Western, Eastern, and Southern Europe and <20% in Northern Europe showing a wide range of prevalence on the continent.^[30] Studies in Southeast Asian population show a prevalence of vitamin D deficiency ranging from 6% to 70% population, with a prevalence of around 70% across various regions in India.^[31] Vitamin D deficiency also leads to poor healing after dental surgery, as vitamin D is a factor responsible for adequate bone remodeling essential after implant surgery.^[32] During osteointegration, calcitriol affects the processes of activation and differentiation of osteoblasts and osteoclasts. Vitamin D has also been found to be essential for the maturation and proper functioning of bone cells by the production of a factor stimulating osteoclast precursor fusion and stimulation of osteoblast differentiation. Vitamin D also increases osteoid mineralization.^[33,34]

Apart from bone metabolism, vitamin D also plays a role in immunity as many cells have been found to possess vitamin D receptors (VDR). Antigen presenting cells, T cells, and B cells have the ability to synthesize and respond to 1,25 D.^[35] Vitamin D inhibits B cell proliferation, differentiation, and immunoglobulin secretion, thereby maintaining a regulatory effect on the immune system. Alternatively, vitamin D deficiency may result in an overproduction of antibodies which is thought to be a contributing factor to autoimmune diseases.^[36,37] Vitamin D suppresses T cell proliferation and results in a shift from a Th1 to a Th2 phenotype. It also decreases the maturation of T cells into Th17 subset and

increases the maturation into T regulatory cells. This results in a downregulation of the pro-inflammatory cytokines and an upregulation of the anti-inflammatory cytokines.^[35]

Vitamin D affects different stages of peri-implant bone formation during osteogenesis. It has become an active factor in dental and implant surgery because of its effects on bone metabolism and the immune system. The proper evaluation of vitamin D levels prior to dental implant planning seems to be of utmost importance followed by proper treatment to resolve the deficiency. Proper regulation of the vitamin D supplementation and dietary intake is also necessary as intake increased amounts may result in lower bone mineral densities and increased bone resorption.^[38]

The prognosis of dental implant in maxilla and mandible may not be consistent while observing EDIF which is quite crucial because of the nature of calcification of jaw bone, for example, maxilla and mandible have uneven quality and quantity of anterior and posterior region. Also biochemical and radiological investigations like ionized calcium, parathyroid hormone (PTH), and bone mineral density (BMD) along with vitamin D status will provide greater insight about the cause of early dental implant failure in patients with osteoporosis. Regarding crestal bone loss around the dental implant either mesial or distal certainly, bone loss occurs depending on the design of the prosthesis, quality of peri-implant bone, and type of bone graft use. Hence, the preferred follow-up period should be from 6 months to 12 months along with long-term recall maintenance after final prosthetic restoration.

The limitations of the study include the fewer number of clinical studies and small sample sizes. Our search shows that there are few clinical studies in this field; also, some of them contain a small sample size; this point should be resolved in future studies.

CONCLUSION

The majority of the studies included in the present systematic review established positive effect and relation between vitamin D levels and successful osseointegration of dental implants contrary to this, a few studies have failed to report any correlation between low vitamin D levels and early dental implant failure because of the lack of hypothesis and study design between healthy and systemic diseases such as osteoporosis and vitamin D deficiency. More prospective clinical research studies as well as randomized controlled trials are needed to show more validation and correlation between decreased serum levels of vitamin D and increased

risk of dental implant failure in perspective of vitamin D supplementation which can promote the osseointegration of dental implants.

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Conflicts of interest

There are no conflicts of interest.

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