Original Article - Prospective Study

Is Vitamin D Deficiency a Risk Factor for Osseointegration of Dental Implants - A Prospective Study

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Abstract

Introduction: Early dental implant failure (EDIF) can occur even when optimal materials are used, surgical protocols are strictly followed and the quantity and quality of bone at the recipient site are sufficient. The existence of specific patient-related risk factors require an investigation into the regulatory mechanisms controlling bone metabolism, bone remodelling and bone turnover as well as serum Vitamin D. The implant stability quotient is used as a prognostic indicator for possible implant failure. The aim of the study is to investigate the relationship between serum Vitamin D levels and EDIF. **Materials and Methods:** A total of 143 implant placement sites were identified in 53 patients enrolled in this study. All patients had the assessments of serum Vitamin D levels side by side with assessments of primary and secondary implant stability at proposed implant sites at the time of implant placement and after 12 weeks using a resonance frequency analysis device. **Results:** Ten early failures (7%) were recorded. There was no correlation between gender, age, smoking, hyperglycaemia or an increased incidence of early failures. Statistical analysis reported two early failures (4.5%) in patients with serum levels of Vitamin D >30 ng/mL, two early failures (2.3%) in patients with levels between 10 and 30 ng/mL and six early failures (46.2%) in patients with levels <10 ng/mL. **Discussion:** The role of Vitamin D as a risk factor for early implant failure should be considered in patients with Vitamin D deficiency. The incidence of early implant failures was higher in patients with low serum levels of Vitamin D. Patients with low serum Vitamin D levels had a greater rate of early implant failure.

Keywords: Dental implant stability, early dental implant failure, serum Vitamin D

Introduction

Dental implants are a common treatment option for those who have lost teeth because they offer both a cosmetic and functional solution. However, not all implants are expected to be successful, and unfavourable outcomes requiring implant removal are unavoidable in everyday practice due to the presence of multiple contributing factors. Recently, research found that Vitamin D deficiency (VDD) increased the risk of early implant failure by 300%.[1]

Vitamin D is a fat-soluble steroid hormone that can be obtained from two sources: sunlight and food supplementation. By activating osteoclasts and osteoblasts, Vitamin D regulates mineral (calcium and phosphate) homeostasis, bone metabolism and bone mineralisation. By combining bone resorption with osteoblast bone matrix formation, it forms and maximises bone remodelling. Because it enhances calcium absorption in the intestine, it reduces parathyroid hormone (PTH) release and systemic bone resorption while possibly inhibiting osteoclastogenesis.[2]

The mechanisms through which VDD affects the mineralisation of teeth and bones have been covered in detail elsewhere. The biological explanation is that hypophosphataemia, hypocalcaemia and secondary hyperparathyroidism (resulting from hypocalcaemia) are all induced by severe VDD (<10 ng/mL). This hyperparathyroidism promotes bone turnover and

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results in elevated $Ca2^+$ serum levels and reduced inorganic phosphate (Pi) serum levels by improving intestinal absorption of $Ca2^+$ and renal synthesis of 1,25-dihydroxyvitamin D(1,25$[OH]_2$D). This significantly exacerbates the initial hypophosphataemia. Finally, mineralisation defects arise from the loss of Vitamin D signalling pathways in tooth cells with low $Ca2^+$ and Pi ion concentrations, which prevents teeth and bones from correctly mineralising.[2] The purpose of this research is to look into the relationship between serum Vitamin D levels and early dental implant failure (EDIF).

Materials and Methods

A prospective observational, cross-sectional study was designed for this study. This study was carried out in accordance with the principles of the Helsinki Declaration and the STROBE recommendations. Power analysis was used to estimate the sample size for the number of implants. Before beginning the trial, we estimated that a sample size of at least 132 implants was required to achieve a power of 80% (alpha, two-tailed, was set at 0.05), allowing for dropouts (10%). This research involved 53 adult patients with a total of 143 implant implantation sites between September 2020 and April 2023. The clinical trials registration number is NCT05956561, and the Ethical Committee Clearance number is OMS863/2020.

The inclusion criteria included patients aged over 18 with at least three months following tooth extraction and appropriate oral hygiene. Patients who required or had pre-surgical augmentation for the alveolar ridge, sinus lift or immediate implant placement were excluded, as were patients with a history of intravenous and/or oral bisphosphonate use, irradiation of the head-and-neck region, infection, pregnancy, immunocompromised and uncontrolled diabetes. Medical history, gender, age, smoking habits and other parafunctional behaviours are amongst the data acquired from each patient through chart, besides clinical evaluation of implant sites and oral hygiene. For all patients, cone-beam computed tomography (CBCT) was performed using the identical exposure parameters for implant simulation analysis. Bone density in terms of grey scale (GS) values at 1 mm (outside) around the virtual implant site was measured using the verification tab in the PLANMECA programme [Figure 1]. Every patient had their Vitamin D level measured using an enzyme immunoassay (EIA) test right before implant insertion. The results were sorted by mean serum Vitamin D level into three categories: sufficient (>30 ng/mL), insufficient (10–30 ng/mL) and deficient (<10 ng/mL).[3,4]

The surgical phase involved primarily: (A) taking a biopsy for histological assessment before implant insertion using a hollow trephine bur (1.7 mm diameter) instead of the original implant drill, stained with Masson trichrome (MT) stain and gathered for histomorphometric analysis of the percentage of immature collagen to mature collagen. (B) To avoid the impact of differences in implant systems in terms of surface treatment, design and other variables, the current study only included patients who received implant therapy using the same implant system and following the manufacturer's insertion protocol. The implant stability quotient value was calculated with an Osstell radiofrequency device by screwing a transducer peg into the implant. A periapical radiograph was taken as a baseline to assess marginal bone loss (MBL) later. All patients were followed for suture removal and additional examination. At 12-week follow-up [Figure 2], all patients were assessed clinically, radiographically and with a radiofrequency device.

Early implant failures were determined in this study until the 12th week postoperatively by the presence of at least one of the following signs: (A) lack of osseointegration and consequent implant movement in the absence of clinical evidence of infection; (B) infection of bone tissue surrounding the implant manifested clinically as fistula, pain, oedema, pus and/or exudate; (C) bleeding pocket with a depth of more than 6 mm and (D) MBL >2.5 mm [Table 1].[5]

Statistical analysis

SPSS® for Windows® version 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. To compare the two means, the independent sample *t*-test was utilised. The one-way analysis of variance (ANOVA) test was used to perform the statistical analysis comparing continuous variable differences across the three groups. The *post hoc* test was used to determine which two groups differed significantly from one another. The Chi-square test and the Fisher's exact test were used to calculate the influence of cofactors on the incidence of early implant failure.

Results

With a mean age of 40.6, the study included 36 (67.9%) females and 17 (32.1%) males. Females had lower mean serum Vitamin D levels than men, but there was no statistically significant difference. The study included six smokers who smoked <10 cigarettes and had 25 implants and 10 diabetic patients who had 46 implants with HBA1c <6.5 [Table 2]. The difference in pre-operative bone density GS values between each serum Vitamin D level group was statistically significant, with $P = 0.003$. The mean bone density values in the sufficient and insufficient Vitamin D level groups were statistically significantly greater than the bone density in the deficient Vitamin D level group [Table 3].

In a histomorphometric study of bone biopsies collected from both the maxilla and the mandible, we discovered a statistically significant difference in the proportion of immature collagen per mature collagen (IM/M) in connection to Vitamin D level groups using ANOVA, with $P < 0.001$ and $P < 0.001$, respectively [Table 3 and Figure 3]. The difference in implant stability T1 and T2 between serum Vitamin D groups was statistically significant using ANOVA ($P \leq 0.001$ and <0.001 correspondingly), indicating a statistically significant difference in T1 between the sufficient and insufficient groups,

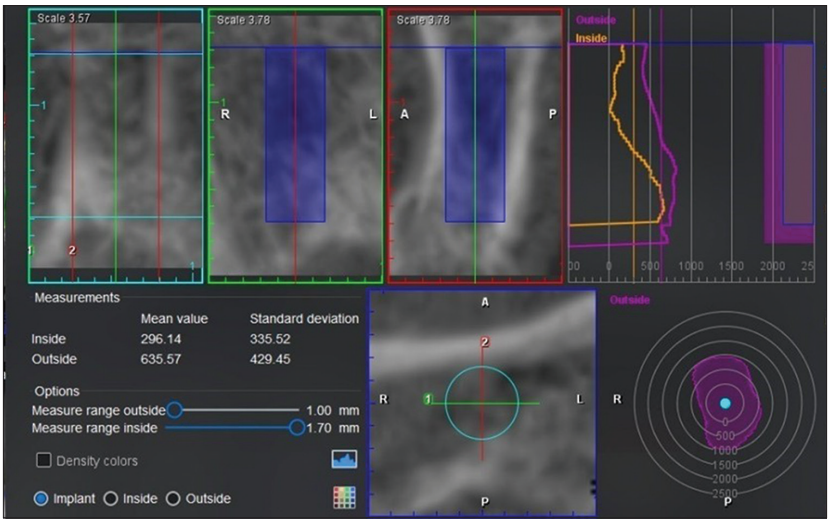

Figure 1: Bone density in terms of grey values was measured 1 mm around virtual implant using the verification tab

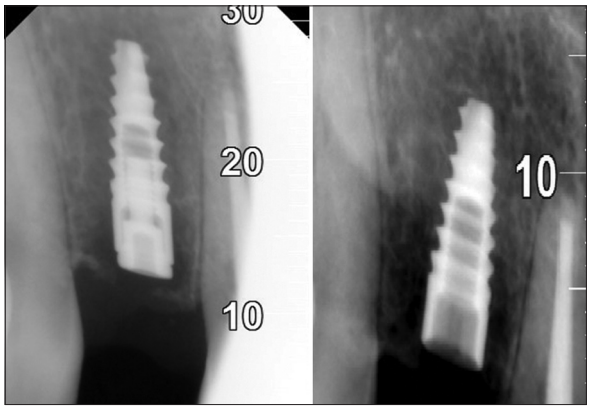

Figure 2: Dental implant immediately after placement and 12-week post-operative after showing marginal bone loss

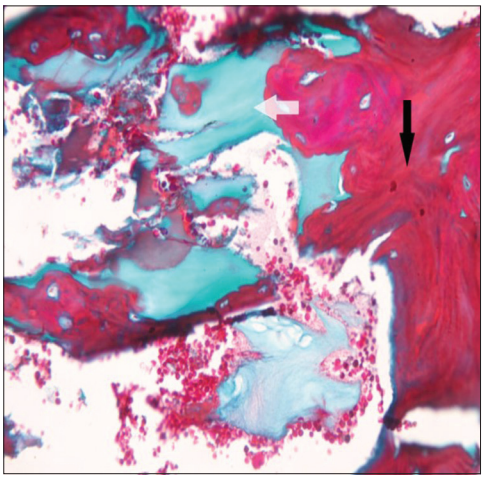

Figure 3: Photomicrograph showing specimen stained by Masson trichrome showing immature collagen (white arrow) and mature collagen (black arrow) from bone biopsy obtained from maxilla from patient with deficient Vitamin D level

as well as a statistically significant difference in T2 between both (the insufficient and deficient groups) and the sufficient group [Table 3].

Early failure in relation to Vitamin D level and other variables

From a total of 143 implants, the frequency of early failure was 10 (6.9%). The Chi-square analysis revealed a statistically significant difference ($P = 0.0007$) in the frequency of early implant failure in Vitamin D level groups, indicating a higher incidence of failure in individuals with Vitamin D insufficiency. The differences in implant failure incidence between the deficient group (6/13 = 46.2%) and both the insufficient group (2/86 = 2.3%) and the sufficient group (2/42 = 4.5%) were statistically significant ($P < 0.001$ and <0.001). Using Chi-square analysis, the difference between the sufficient and insufficient groups was found to be statistically insignificant. There were no differences in the rate of early implant failures between males and females, nor between age and other comorbidities such as smoking and diabetes mellitus history [Table 4].

Discussion

The initial phase disruption, in which fibrous scar tissue grows between the surrounding bone and the implant surface, is primarily responsible for EDIF. EDIF occurs 3–4 months after placement, before the prosthetic abutment is connected and functional loading begins.[6,7] Inadequate surgical and prosthetic protocols, low bone volume or quality at the recipient site, behaviours (smoking and parafunctions) or systemic disorders may contribute to EDIF.[8,9]

According to the criteria of clinical or absolute implant failure established by Albrektsson *et al*., the implant should be removed and recorded as a failure if any of the following conditions exist: Pain on palpation, percussion or function, horizontal and/or vertical mobility, uncontrolled progressive bone loss, uncontrolled exudate or more than 50% bone loss around the implant.[7,10] The striking method like Periotest (Med-Gulden

Table 1: Early implant failures data

Patient number	Gender	Age	Smoking	Diabetes mellitus	Sign of failure	Serum Vitamin D level	Implant position
2	Male	55	No	Yes	Infection/pain	25	17
14	Male	58	No	Yes	Infection	35	46
19	Female	42	No	No	Infection/pain	11	12
23	Female	27	No	No	FO	6	16
33	Male	48	No	Yes	MBL/pain	31	14
34	Female	36	No	Yes	MBL	9	15
38	Female	36	No	Yes	MBL/pain	8	15
41	Female	24	No	No	MBL	7	36
43	Female	40	No	Yes	Infection/pain	4	16
52	Male	63	No	No	MBL/pain	8	37

FO: Failure to osseointegrate, MBL: Marginal bone loss

e.K., Germany) or resonance frequency analysis is one of the ways used to examine the horizontal mobility of the implant.[11] The most popular strategies in the literature for assessing implant failure are MBL around the implant fixture in periapical radiography and the presence of pain under vertical or horizontal stresses after primary healing.[3,10]

It is believed that a significant part of implant failure is associated with VDD.[12,13] To reduce the danger of skewed readings, all patients in this study had their 25-hydroxy Vitamin D levels checked preoperatively using EIA at the same laboratory. Females showed considerably lower mean serum Vitamin D levels than males in our study, which is consistent with studies done in the Middle Eastern communities with similar cultures.[14-16]

At nine weeks following implant placement, one of the early failures was due to loss of integration with full implant loss, in addition to 5 implants with MBL and 4 implants with evidence of infection. There was no significant link between implant failure and any of the analysed group's sociodemographic factors or comorbidities for the failed implants in this study. In contrast to what we discovered, several studies have observed the great effect of age on implant failure.[17,18] However, Guido Mangano *et al.,* found no significant correlation between age, gender or smoking and early implant failure,[1] which supports our findings.

This study included 24.5% of diabetic individuals who had 46 implants. Only 13% of them had EDIF, which showed no significant relationship between implant failure and diabetes. To reduce the variables that could affect our results, we excluded individuals with any concomitant conditions, with the exception of diabetic patients with HBA1c <6.5. The frequency of implant failure is allegedly higher during the early period than during the late phase, which is the sole focus of the current investigation.[9] The rate of early failure in this study was 6.99%, which is slightly higher than the rate reported by Kang *et al*., (1.3%–6.36%).[11] We believe this increase is the result of a sample size difference and a different cut-off point for assessment in their study, which could be up to 16 weeks. It should state that failure rates change according to follow-up duration.

Table 2: Demographic variables data

Variable	Frequency of patients (%)	Frequency of implants (%)
Smoker patients	6 (11.3)	25 (17.5)
Non-smoker patients	47 (88.7)	118 (82.5)
Diabetic patients	13 (24.5)	46 (32.2)
Healthy patients	40 (75.5)	97 (67.8)
Sufficient Vitamin D	11 (20.8)	44 (30.8)
Insufficient Vitamin D	36 (67.9)	86 (60.1)
Deficient Vitamin D	6 (11.3)	13 (9.1)
Implant site		
Posterior maxilla	16 (30.2)	52 (36.36)
Anterior maxilla	7 (13.2)	23 (16.08)
Posterior mandible	23 (43.4)	56 (39.16)
Anterior mandible	7 (13.2)	12 (8.39)

The great effect of vitamin level on implant failure in our study may be considered a reflection of the effect of Vitamin D level on bone density that is present in our results. Regarding the differences in mean grey level values between Vitamin D level groups, our results showed a significant relationship between Vitamin D level and bone density around virtual implant sites. This correlation agreed with studies that correlated the *t*-score values of osteoporotic patients and Hounsfield Unit in CBCT.[19] Few studies have been performed to assess the effectiveness of CBCT in evaluating bone density and correlating it with DXA or *t*-score values.[20] Grey level values in patients with deficient Vitamin D levels were substantially lower in the current study than values in patients with sufficient and insufficient Vitamin D levels. This is consistent with the findings of both Sghaireen and Al Habib, Barngkgei *et al*., who proposed that measuring bone density with CBCT can predict osteoporosis.[21,22]

Bone histomorphometry contributed as a research tool for understanding bone biology, tissue level dynamics, bone cellular activity, bone mineralisation and bone remodelling. Parfitt clarified that Vitamin D is related to osteomalacia as an abnormal course of bone remodelling, in which a moiety of resorbed old bone is replaced by an unmineralised bone matrix (or osteoid tissue).[23] Bhan *et al*., and Priemel

Table 3: Relationship between bone density of the recipient alveolar ridge, implant stability and percentage of immature collagen per mature collagen of bone biopsies with Vitamin D level

Variable	Sufficient, mean (SD)	Insufficient, mean (SD)	Deficient, mean (SD)	*P*	*F*	Effected size (%)
Bone density	660.3 (294.1)†	643.22 (282.02)†	370.66 (204.16)			
95% CI	570.9–749.7	582.7–703.7	247.2–494.02	0.003*	5.89	7.8
Subgroups	44	86	13			
ISQ (T1)	77.52 (3.05)[aa]	75.33 (2.71)	71.54 (8.69)			
95% CI	76.6–78.4	74.7–75.9	66.2–76.7	0.000003**	13.88	16.6
Subgroups	44	86	13			
ISQ (T2)	78.02 (2.59)	76.09 (2.52)+	73.50 (4.62)+			
95% CI	77.2–78.8	75.5–76.6	70.5–76.4	0.000002**	14.62	17.4
Subgroups	44	86	13			
IM/M in mandibular biopsies	0.68% (0.42)†	6.39% (0.75)†	30.1% (7.83)			
95% CI	0.16–1.22	5.42–7.32	20.36–39.83	0.0000006**	58.7	90.7
Subgroups	5	5	5			
IM/M in maxillary biopsies	2.36% (0.47)†	17.92% (5.9)†,+	48.7% (3.5)+			
95% CI	1.77–2.94	10.60–25.24	44.45–53.1	0.0000001**	177.8	96.7
Subgroups	5	5	5			

*P<0.05, **P<0.01, [aa]Statistical significance in relation to insufficient group using *post hoc* test, †Statistical significance in relation to deficient group, +Statistical significance in relation to sufficient group using *post-hoc* test (Tamhane's T2 and Bonferroni). CI: Confidence interval, SD: Standard deviation, IM/M: Immature collagen per mature collagen, ISQ: Implant stability quotient

et al., found an increase in osteoid area per bone surface in histomorphometric analyses of transiliac bone samples from patients with VDD.[24,25] These findings were consistent with ours, as they revealed an increase in the percentage of IM/M in patients with VDD from MT-stained bone samples collected from the mandible and maxilla, respectively, with a slight difference in percentages in our study, which can be attributed to the larger sample size and different staining procedures used in the primary studies versus our analysis.

The literature showed variability in Vitamin D impact on implant failure. Guido Mangano *et al*., and Mangano *et al*., evaluated 822 and 885 humans, respectively, and found no significant relationship between implant failure and VDD; however, a dramatic increase in EDIFs with the lowering of Vitamin D levels in the blood has been reported.[1,5] Similarly, Boas and Casado clarified that there is no clinical link between osseointegration and bone remodelling systems, and VDD is not a true contraindication for placement of implants.[26] However, Bryce and MacBeth discovered failure of implant osseointegration after five months after surgery in one patient who had an extremely low Vitamin D level. It has been proposed that VDD may play a role in the failure of osseointegration in dental implants.[27]

Table 4: Early failures in relation to Vitamin D level and other variables (age, gender, smoking and diabetes mellitus)

Variable	Number of implants	Early failures	Incidence of early failure (%)	*P*
Age (years)				
<40	61	4	6.6	0.968
40–60	66	5	7.6	
>60	16	1	6.3	
Gender				
Male	56	4	7.1	0.955
Female	87	6	6.9	
Serum Vitamin D level				
Sufficient	44	2	4.5	0.0007**
Insufficient	86	2	2.3	
Deficient	13	6	46.2	
Smoking				
Smoker	25	0	0	0.131
Non-smoker	118	10	8.5	
Diabetes mellitus				
Diabetic	46	6	13	0.051
Non-diabetic	97	4	4.1	

**Statistical significance using Chi-square test

Fretwurst *et al*., found that Vitamin D treatment had a great effect on implant success in individuals with VDD and previous implant failure.[28] Nastri *et al*., (2020) in a Scoping review, reveal that nutraceuticals have a limited effect on promoting the osseointegration of dental implants. He found that there is a strong correlation between vitamin D deficiency, poor osseointegration, and EDIF, necessitating proper supplementation.[29] Schulze-Späte *et al*., discovered no significant difference in bone growth or graft resorption according to Vitamin D supplementation. However, a significant histological correlation was identified between increasing Vitamin D levels and a number of bone-resorbing osteoclasts around graft particles in the Vitamin D3 group.[30] According to these findings, Vitamin D supplementation may help reduce dental implant loss. All of these findings, and others, imply that additional research is required.

Conclusion

Since a large increase in EDIFs has been linked to a decrease in Vitamin D levels, our findings confirm the significance of Vitamin D as a risk factor for early implant failure in patients with VDD. Patients with low serum Vitamin D levels had a greater rate of early implant failure. We advocated for a better-designed randomised clinical trial to look into the effect of Vitamin D blood levels on early implant failure.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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