Diploma Thesis

The influence of vitamin D levels on the healing process after oral surgical procedures – a narrative literature review

Submitted by

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Graz, September 9, 2024

Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, September 9, 2024 Sori Kim m.p.

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Zusammenfassung

Einführung:

Vitamin D ist weithin für seine entscheidende Rolle bei der Wundheilung bekannt. Nach dem neuesten wissenschaftlichen Kenntnisstand, beeinflusst Vitamin D die allgemeine Mundgesundheit und die Ergebnisse oralchirurgischer Eingriffe erheblich, da es sich direkt auf den Knochenumsatz und die Immunzellen auswirkt(1,2). Vitamin-D-Mangel ist jedoch nach wie vor ein weit verbreitetes Problem in verschiedenen Altersgruppen weltweit, dessen Schwere oft übersehen wird. Die positiven Auswirkungen einer Vitamin-D-Supplementierung und die nachteiligen Folgen eines Vitamin-D-Mangels wurden bereits durch zahlreiche Tierstudien sowie In-vivo- und In-vitro-Versuche nachgewiesen. Trotz dieser Fülle von Erkenntnissen haben sich nur wenige Humanstudien speziell mit den Auswirkungen des Vitamin-D-Status im Zusammenhang mit oralchirurgischen Eingriffen befasst. Ziel dieser Übersichtsarbeit ist es, die Ergebnisse verschiedener Studien, die die Auswirkungen von Vitamin D auf eine Reihe von chirurgischen Eingriffen untersucht haben, zusammenzufassen, wobei ein besonderer Schwerpunkt auf deren Bedeutung für die Mundgesundheit und die chirurgischen Ergebnisse liegt.

Material und Methoden:

Für die Durchführung dieser narrativen Übersicht wurden die folgenden digitalen Datenbanken verwendet: PubMed, Medline, Google Scholar und Cochrane Library. Bei der Suche wurden die folgenden themenrelevanten Schlüsselwörter in verschiedenen Kombinationen verwendet: Vitamin D, Vitamin-D-Mangel, Vitamin-D-Suffizienz, Oralchirurgie, Wundheilung, Osseointegration, Zahnextraktion, Zahnimplantat, Komplikationen. 53 Publikationen aus dieser Suche wurden ausgewertet.

Ergebnisse:

In den verschiedenen untersuchten Studien zeigten die Ergebnisse durchwegs einen optimalen Heilungsprozess bei den Teilnehmern, die über ausreichend Vitamin D verfügten oder Vitamin-D-Supplemente erhielten. Die statistischen Analysen ergaben signifikante Unterschiede in den Heilungsergebnissen zwischen den Teilnehmern, die

eine Vitamin-D-Supplementierung erhielten, und denen, die einen Vitamin-D-Mangel hatten.

Konklusion:

Diese Ergebnisse unterstreichen, wie wichtig die Aufrechterhaltung eines ausreichenden Vitamin-D-Status ist, um die Wundheilungsmechanismen zu unterstützen. Die Erkenntnisse deuten stark darauf hin, dass die Behebung eines Vitamin-D-Mangels eine entscheidende Rolle in der Förderung besserer chirurgischer Ergebnisse spielen kann, insbesondere im Zusammenhang mit oralchirurgischen Eingriffen(2). Diese Ergebnisse haben essenzielle Auswirkungen auf die zahnärztliche Gesundheitsversorgung, die eine Bewertung und Behandlung des Vitamin-D-Status als Teil der umfassenden Behandlung von Patienten in Betracht ziehen sollte.

Abstract

Introduction:

Vitamin D is widely recognized for its crucial role in wound healing. The significant influences of vitamin D on overall oral health and outcomes of oral surgical procedures, given its direct impact on bone turnover and immune cells is being highlighted nowadays(1,2). However, vitamin D deficiency remains a prevalent issue across various age groups worldwide, with its gravity often overlooked. A substantial body of research, including numerous animal experiments and other studies, has already established the positive impacts of vitamin D supplementation and the detrimental consequences of vitamin D deficiency. Despite this wealth of knowledge, limited human studies have specifically focused on the implications of vitamin D status in the context of oral surgical procedures. This narrative review aims to synthesize and summarize the findings of different studies that have looked into the effects of vitamin D on a range of surgical procedures, with a particular emphasis on its relevance to oral health and surgical outcomes.

Material and methods:

For conducting this narrative review, the following digital databases were used: PubMed, Medline, Google Scholar, and Cochrane Library. The search utilized the following topic-relevant keywords in various combinations: Vitamin D, vitamin D deficiency, vitamin D sufficiency, oral surgery, wound healing, Osseointegration, tooth extraction, dental implant, and complications. 62 publications from this search were utilized for this diploma thesis.

Results:

Across the various examined studies, the findings consistently demonstrated an improved healing process in participants who were vitamin D sufficient or received vitamin D supplements. The statistical analysis revealed significant differences in the healing outcomes between those who were vitamin D-supplemented and those who were vitamin D deficient.

Conclusion:

These results accentuate the value of maintaining sufficient vitamin D status to support wound-healing mechanisms. The evidence strongly suggests that addressing vitamin D deficiency can play a crucial role in promoting better surgical outcomes, particularly in the context of oral surgical procedures(2). These findings hold important implications for dental healthcare providers, who should consider evaluating and addressing vitamin D status as part of the comprehensive management of patients.

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Abbreviations

#

(1,25(OH)2D)……..1,25-dihydroxyvitamin

(25(OH)D ……....25-hydroxyvitamin D / Calcidiol

A

ATP……..…….Adenosine triphosphate

B

BOP……..……Bleeding on probing

C

Ca++……..……...Calcium

CAL……Clinical attachment loss

E

EDIF……..……...Early dental implant failure

Et al. ……..……..And others

I

IL-1-beta……..…….Interleukin 1 beta

IL-6…….....Interleukin 6

ISQ……....Implant stability quotient

IU……International Unit

IQR……..Interquartile range

L

LDIF……..……Late dental implant failure

L……..……..…..Liter

O

ONJ……..Osteonecrosis of the jaw

MRONJ……..Medication-related osteonecrosis of the jaw

OPMDs…….Oral potentially malignant disorders

OSCC……..…..Oral squamous cell carcinoma

M

Ml……..……..Milliliter

Mm……...Millimeter

Mg……Milligram

Mo…….Mouth Opening

N

Ng……..Nanogram

NHANES…….National health and nutrition examination survey

Nmol……....Nanomol

N……Study size

P

P…….P-value

PD……...Probing depth

Per os……...Orally / Through the mouth

PPD……Pocket probing depth

PTH……Parathyroid hormone

R

RANKL……..Receptor activator of nuclear factor kappa-B ligand

S

SE……..Statistical error

T

TL……Tragus-labial commissure

TNF-alpha……...Tumor necrosis factor - alpha

TP……...Tragus-pogonion

TM…….....….Trismus

U

UV……...Ultraviolet

V

VAS……Visual analog scale

VDRs…….……Vitamin D receptors

Vitamin D2……..…Ergocalciferol

Vitamin D3……..…….Cholecalciferol

W

WHQ……Wound healing quality

Tables

Figures

1.Introduction

Vitamin D has been gaining more attention from the medical community due to its crucial role in wound healing. Vitamin D deficiency which remains a prevalent issue worldwide has detrimental consequences on oral health(15).

While numerous animal studies and in vitro and in vivo experiments have demonstrated vitamin D's positive impact on wound healing, there are a limited number of human clinical studies specifically investigating its implications for oral surgical procedures(27).

This narrative review aims to provide a comprehensive overview of the current relevant research that may prove valuable in daily dental practice. The objective is to offer a basic summary of the existing researches examining the influence of vitamin D on various oral surgical procedures.

2. Basics

2.1 Physiology of Vitamin D

Vitamin D, which technically belongs to cholesterol derivatives rather than vitamins, is gained in different ways(3). Plants synthesize vitamin D2 when exposed to UV radiation(3). Vitamin D3 is produced photochemically by exposing the skin to a certain wavelength of radiation from sunlight(3). It can also be consumed through fatty fish, although in a very small amount, 10% at most (3).

Once vitamin D enters the body, it undergoes a series of transformations. After the isomerization, it is transferred to the extracellular matrix(3). This will then be released into the blood, where it binds to a specific globulin, which in turn binds vitamin D(4). In the liver, the first hydroxylation occurs: both vitamin D3 and D2 are transformed to form 25-hydroxyvitamin D (25(OH)D, calcidiol), which can be found in the body as the main state of vitamin D(4). The excess will use adipocytes for storage(4). The 25(OH)D is then transported to the kidneys, where it’s further hydroxylated to 1,25-dihydroxyvitamin D (1,25(OH)2D). Once 1,25(OH)2D binds to its receptor, it triggers a series of events that consequently produce proteins such as osteocalcin and calcium-binding

proteins(4). These proteins play a key role in regulating calcium absorption in the small intestines(4).

Calcium is transported from the small intestines to the extracellular fluid through a mechanism that relies on adenosine triphosphate (ATP) and is vitamin D dependent. The extracellular fluid can only absorb a certain amount of calcium before reaching a plateau. This process makes sure that calcium levels in the blood remain stable. Additionally, calcium can also diffuse through the paracellular space. This process does not require ATP and is influenced by the calcium gradient (through passive diffusion and is vitamin D independent). 1,25(OH)2D has a significant influence on the target organ. It activates calcium transport from these organs, such as bone, intestines, and kidneys, to the blood, ensuring calcium levels remain within a healthy range(5). The formation of 1,25(OH)2D is controlled by parathyroid hormone(5). When calcium levels are low, PTH stimulates the production of 1,25(OH)2D, enhancing calcium absorption(5). This negative feedback loop ensures calcium levels are maintained within a healthy range(5). Additionally, 1,25(OH)2D directly inhibits PTH, further regulating its production(6). It shows a very high affinity to the vitamin D receptors(7). VDRs that are present in various target organs can then bind and activate “the formation of a hormone-receptor complex.(3)” This then stimulates the production of diverse proteins such as calcium-binding protein, osteocalcin, and osteopontin, as mentioned above, or inhibitions of inflammatory proteins(8,9). The regulating function of Vitamin D also affects the calcium-phosphate metabolism, bone remodeling (figure 1) and the Immune system, which can also gravely affect general oral health(2,5,7,10).

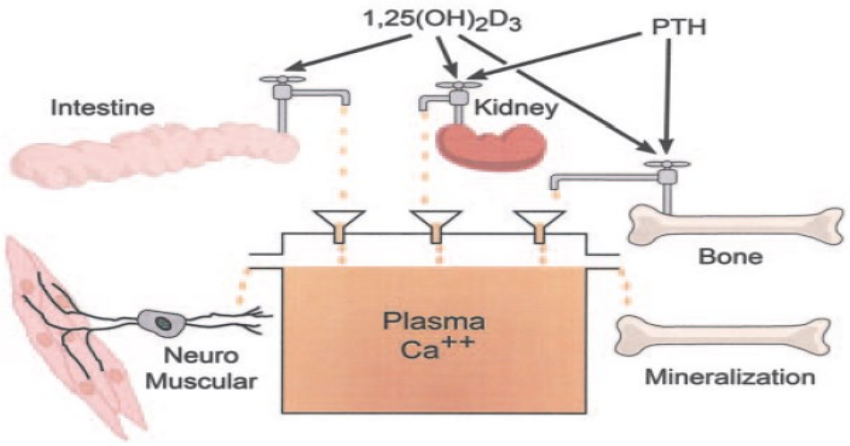

Figure 1 Representation of the role of the vitamin D hormone on mineralization of the skeleton (21)

2.2 Vitamin D Deficiency in the Population

Vitamin D deficiency is a widespread issue affecting populations across all age groups (Figure 2)(11). Due to modern lifestyle with increased time spent indoors, people are deprived of the primary natural source of vitamin D - sunlight exposure(12). This lack of sun-derived vitamin D intake is exacerbated by the fact that the body's ability to absorb and utilize vitamin D tends to decline with age(12). Epidemiological research indicates that up to 70% of the global population may suffer from inadequate vitamin D levels(12).

2.3 Consequences of Vitamin D Deficiency

Vitamin D deficiency positively influences bone loss, promoting increased PTH secretion(13). It speeds up bone turnover and resorption, especially from cortical bone, which might contribute to the pathogenesis of osteoporosis(13). Together with osteoporosis, vitamin D deficiency can also cause ricket or osteomalacia(13). So, besides these aforementioned problems, such as bone mineralization, resorption, or osteomalacia, it can lead to bone fractures, especially hip fractures. In elderly people, it can also have severe consequences since the deficiency can negatively influence bone mineral density(14).

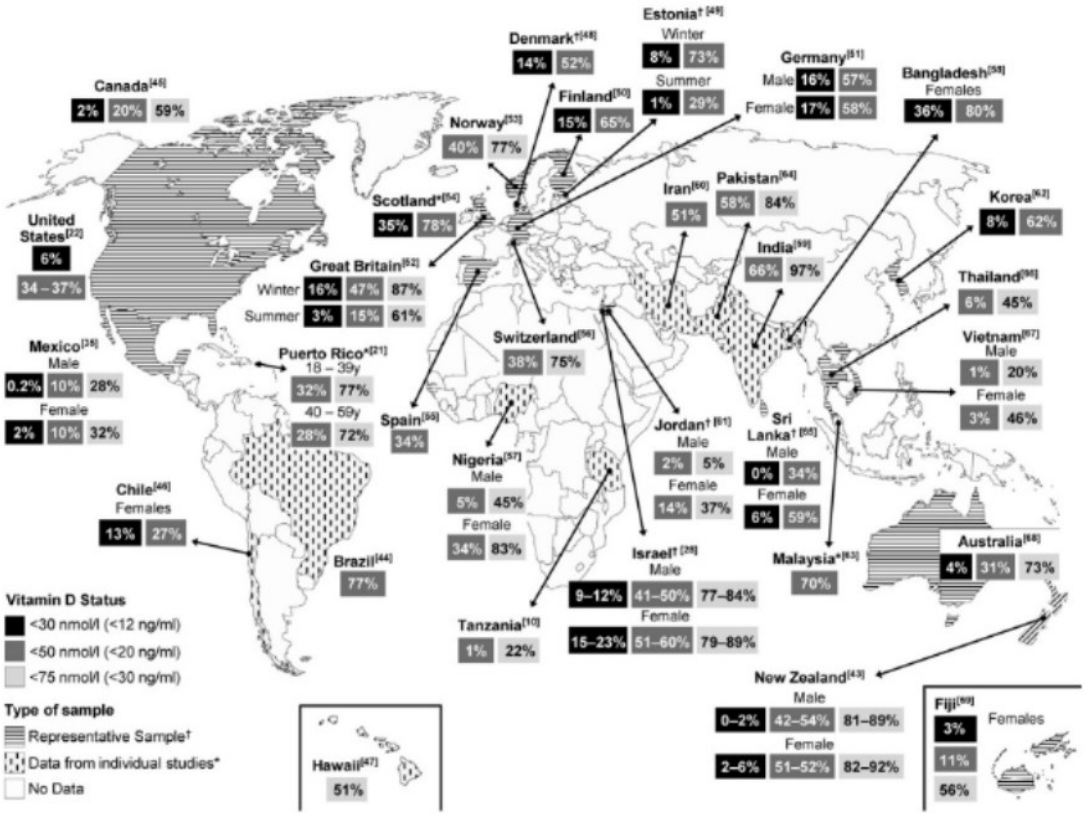

Figure 2: Prevalence of vitamin D deficiency worldwide in adults (11)

2.4 Vitamin D and General Oral Health

Studies showed that vitamin D is pivotal in minimizing different diseases in the maxillofacial region, such as squamous cell carcinoma (OSCC), periodontitis, and wound healing after oral surgeries(15).

Vitamin D and Oral Cancer

A systematic review highlighted that hypovitaminosis D might raise the risk of developing OSCC from oral potentially malignant disorders (OPMDs). The review noted that alterations in vitamin D levels might favor the progression of OPMDs to OSCC by affecting the immune response and increasing the recurrence of tumors post-surgery. Moreover, vitamin D sufficiency was related to increased levels of anti-inflammatory mediators and T lymphocytes in intratumoral tissue, which could enhance the antitumor

immune response. Supplementation of vitamin D was also found to lower harmful aspects correlated with chemotherapy(15).

Vitamin D and Periodontal Health

A systematic review found that vitamin D plays a crucial role in maintaining periodontal health through its anti-inflammatory properties and its ability to produce antimicrobial peptides(16). The review indicated a linear relationship between vitamin D levels and periodontal health, although the evidence was deemed insufficient and heterogeneous(16). Another systematic review emphasized that vitamin D supplementation, often combined with calcium, significantly improved periodontal health outcomes, particularly in reducing gingival inflammation and improving bone density(17). Plus, a clinical trial involving patients with severe chronic periodontitis showed that vitamin D deficiency at the surgery of periodontium had negative influence on outcomes for until one year later. Patients with sufficient vitamin D levels had better clinical attachment loss (CAL) gain and probing depth (PPD) reduction(18).

Vitamin D and Osteonecrosis of the Jaw (ONJ) / Medication-related Osteonecrosis of the Jaw (MRONJ)

Vitamin D plays a fundamental role in a part of bone formation, angiogenesis, and immune response, all of which are involved in the prevalence of ONJ/MRONJ(19). While some observational studies suggest vitamin D deficiency may increase ONJ risk, a randomized controlled trial failed to find a correlation(20). The biological plausibility for vitamin D's influence on ONJ pathogenesis exists, but the clinical evidence is currently mixed. However, in a hypothetical study, vitamin D is suggested to play a positive role in preventing MRONJ (13,21). Furthermore, in a retrospective study with 63 individuals, a higher prevalence of MRONJ within the patients with vitamin D deficiency was observed(22).

Correlation between vitamin D and Caries

The ability to identify and address key risk factors for dental caries, including vitamin D status, is crucial for dentists to provide effective, personalized care and improve overall oral health(23).

Recently, more attention has risen to the possible connection between the prevalence of caries and vitamin D deficiency. The negative influence of vitamin D deficiency on odontogenesis hence on primary dentition, has already been researched and proven by several studies(24). A study conducted with 1688 Korean children between the ages of ten to twelve showed that children with serum vitamin D levels lower than 50nmol/L had a 1.295 times bigger tendency to develop first-molar caries than the children with serum vitamin D levels higher than 50nmol/L(25).

A retrospective study conducted with data collected from the National Health and Nutrition Examination Survey (NHANES) has shown that people with serious Vitamin D deficiency had a 2.22 times higher risk of dental caries than people who had physiologically acceptable vitamin D levels(23).

3. Material and Methods

3.1 Material and Methods

A narrative literature review was researched utilizing the following digital databases: PubMed, Medline, Google Scholar, and Cochrane Library. The search involved the following topic-relevant keywords in various combinations: Vitamin D, vitamin D deficiency, vitamin D sufficiency, oral surgery, wound healing, Osseointegration, tooth extraction, dental implant, and Augmentation. The search was limited to articles published between 2004 and 2024. The following criteria were applied:

Inclusion:

- Human studies
- Articles in English
- Systematic reviews, literature reviews, meta-analyses

- Clinical studies, comparative studies, observational studies
- Articles published after 2000
- Dental reference

Exclusion:

- Experimental laboratory studies
- Duplicated articles
- Surveys, commentaries
- Animal experiments
- Lack of dental reference

This approach aimed to identify the most relevant and up-to-date literature on the topic, focusing on human studies with a direct dental reference published in the last 20 years.

4. Results

4.1 Results of Literature Research

A thorough literature search was conducted to gain a general understanding of the role of vitamin D in oral surgical procedures. The key terms explored and filtered based on the time period included:

- Vitamin D (72,676 results)
- Vitamin D deficiency (27,050 results)
- Vitamin D sufficiency (3,974 results)
- Oral surgery (195,297 results)
- Wound healing (149,795 results)
- Dental implant osseointegration (8,060 results)
- Tooth extraction (16,812 results)

- Dental implants (48,910 results)
- Bone augmentation (20,708 results)

The combination of these keywords yielded 786 literature search results. Studies were selected from this pool based on predefined exclusion criteria, such as language, study type, and dental relevance.

Following the initial screening, a more detailed selection was carried out based on the titles and abstracts of the remaining studies. This step ensured that only the most relevant articles were accepted for the review.

After the title and abstract review, 65 selected papers in total underwent a final evaluation to confirm their suitability for the topic at hand. This rigorous selection process ensured that only high-quality, relevant studies were included in the work. These studies comprised:

- 36 Review articles
- 18 Clinical studies
- 10 Retrospective studies
- 1 Hypothetical study

Specifically, the selected literature was divided according to the topics and reviewed. Figure 3 provides an overview of the selection process used in this narrative review.

Vitamin D and Oral Health

- 10 Clinical studies on various theoretical aspects of vitamin D and oral health
- 26 Reviews on various theoretical aspects of vitamin D and oral health

Tooth Extraction

- 2 Clinical studies on the impact of vitamin D on tooth extraction outcomes

Periodontal Health

- 5 reviews on the correlation between vitamin D and periodontal health

- 1 clinical study on the consequences of vitamin D in surgery of periodontium

Bone Augmentation

- 2 clinical studies on the role of vitamin D in bone augmentation procedures

Dental Implants

- 14 clinical studies investigating the influence of vitamin D on dental implant osseointegration
- 2 systematic reviews

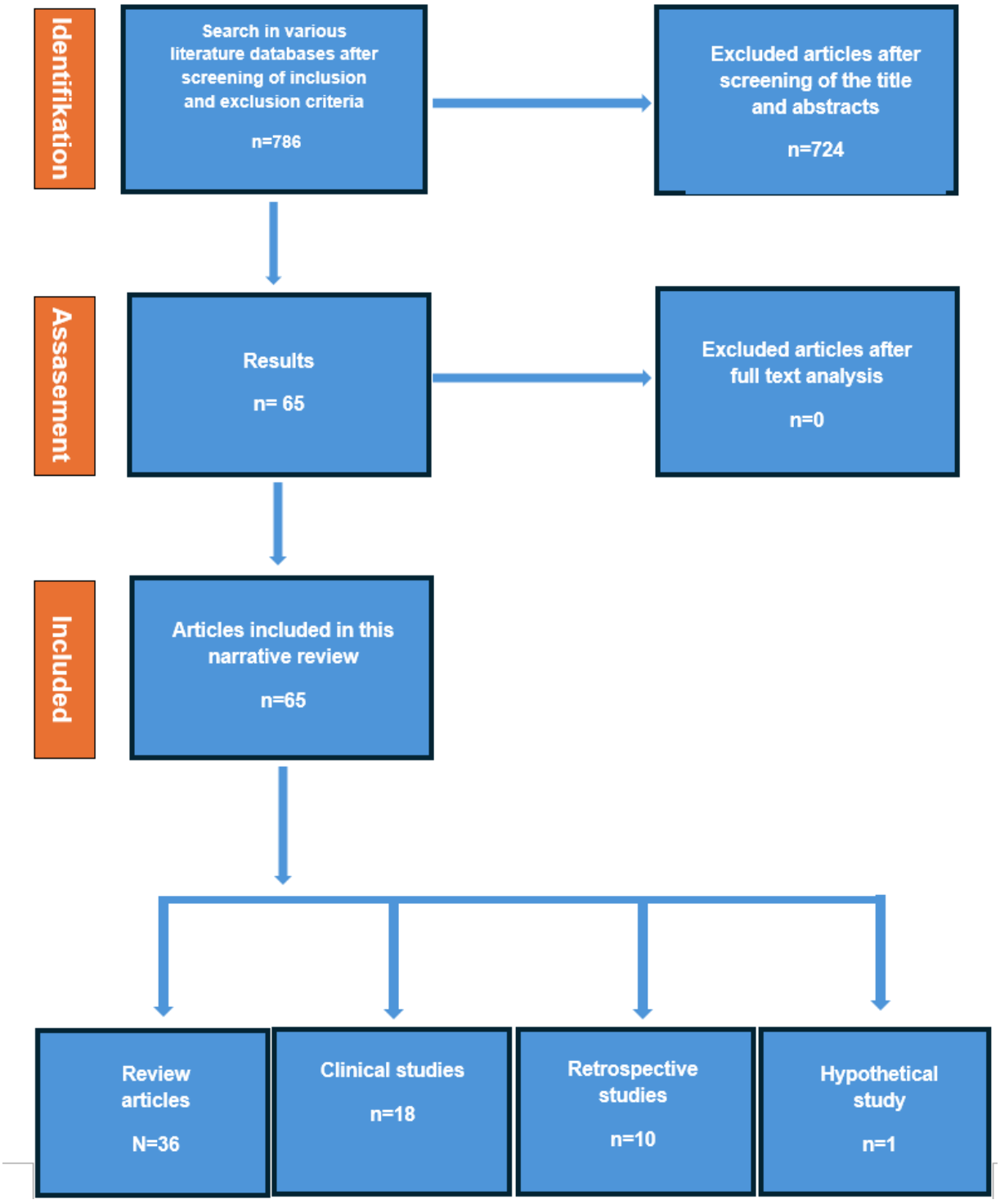

Figure 3:Flowchart of literature research

4.2 Results in Different Surgical Procedures

Authors	Year of publication	Type of study	Number of participants	Age of participants	Timing of vitamin D sampling	Vitamin D supplementation	Follow up	Outcome
Mameledzija et al.	2022	Clinical Study	23	22.47 ±5,15 Years mean	Initial examination	None	10 Days after surgery	No significant differences in TL, TP, TS or wound healing quality
Oteri et al.	2015	Clinical Study	72	18-40 Years	-T0= Initial examination -T2= Seven days after T0	High dose administration at T0 =300.000 IU	10 Days after T0	No significant difference in TL, TP, TS, but significant difference in inflammatory indexes
Bashutski et al.	2011	Clinical Study	40	31-65 Years	-Initial examination -6 weeks post surgery -6 months post surgery	-1000 mg Calcium + 800IU Vitamin D + 20 µg Teriparatide for six weeks per os	-6 weeks post surgery -6 months post surgery	-Minimal difference in radiological resolution, no significant variations in both BOP and CAL -Enhancement in radiographical resolution, 12% increase in BOP, 39% decrease in CAL
Schulze-Späte et al.	2016	Clinical study	20	49,11± 12,24 Years mean	-Initial examination -After two weeks -After twelve weeks -At the time of implant placement	-5.000IU starting at the surgery until bone cores were harvested + 600mg Calcium per os	-6-8 months after sinus augmentation surgery	No significant differences in bone formation, but increased number of osteoclasts in the harvested bone cores
Ahmed Elsayed	2019	Clinical study	14	28-40 Years	No measurement	-80IU Vit D3 gel added to surgery site	-4 months after implant placement	Significantly higher mean value in both the buccolingual ridge width and the implant stability quotient than the control group
Kwiatek et al.	2021	Retrospective study	122	43,8±12,15 Years mean	-On the day of surgery -after six weeks -after twelve weeks	-8,000 IU daily for the entire duration of the study	-3 Months	Significant and positive differences at the bone level in the vitamin D sufficient + supplementation group
Mangano et al.	2018	Retrospective study	885	57,3±14,4 Years mean	-Two weeks prior to surgery	-No supplementation	-168 Months mean	No significant correlation between low vitamin D serum levels and increased EDIF
Garg et al.	2020	Retrospective study	32	20-40 Years	-Initial examination -after three months -after six months	-60.000IU per month for three months and up to six months depending on serum vitamin D levels	-6 months	Statistically significant difference between the test group an control group in bone formation around the dental implant
Tabrizi et al.	2021	Prospective study	90	-G1:41,50±10,13 -G2:45,03±11,16 -G3:40,73±9,95 Years mean	-At the time of prosthetic loading -12 months later	-No supplementation	-12 months	Statistically significant differences indicating a relationship between serum vitamin D levels and marginal bone loss around dental implants

Figure 4: Overview of the studies analyzed in depth in the narrative review

Figure 4 demonstrates an overview of the studies reviewed in depth of this narrative review. In the following chapters a more detailed analysis of the studies mentioned, especially regarding their respective fields is provided.

4.2.1 Effect of Vitamin D in Recovery After Extraction

Two studies Oteri et al.(26) and Mameledzija et al.(27) observed wound healing qualities after operative third molar extraction under the influence of vitamin D. Although they used similar methods for collecting data and examining at different stages, the results varied (26,27).

Oteri et al.(26) explored the clinical impact of a single oral high dose of cholecalciferol concerning the operative extraction of third molars. They evaluated 72 patients who required lower third molar extraction over the course of 8 months. Patients underwent 2 bilateral split-mouth operations conducted by a single oral surgeon at a 6-month interval (26).

Procedure of the study

In the Study conducted by Oteri et al.(26), patients were engaged in 4 stages from T0 to T3. From 72 patients who were inspected, 25 of them showed vitamin D3 serum levels ≤30 ng/mL. They were given a placebo saline solution before the first third molar removal on one side, then 300,000 IU of cholecalciferol 4 days before the second third molar removal(26).

T0: Patients had already gone through preliminary radiographic and clinical examinations to ensure that they were a good fit for the research prior to the procedure. Baseline clinical parameters such as edema, trismus, and blood test for biochemical analysis were collected(26).

Edema was measured by the length between the tragus and labial commissure (TL) and the length between the tragus and pogonion (TP). Trismus is measured by the length of the interincisal distance between the upper and lower jaw (Figure 4). Pain intensity was determined using the visual analog scale (VAS), where the intensity is recognized as no pain (VAS 0) as score zero, mild =1 (VAS 1-3) as score one, moderate pain (VAS 4-7) as score two, severe pain (VAS 8-10) as score three(26).

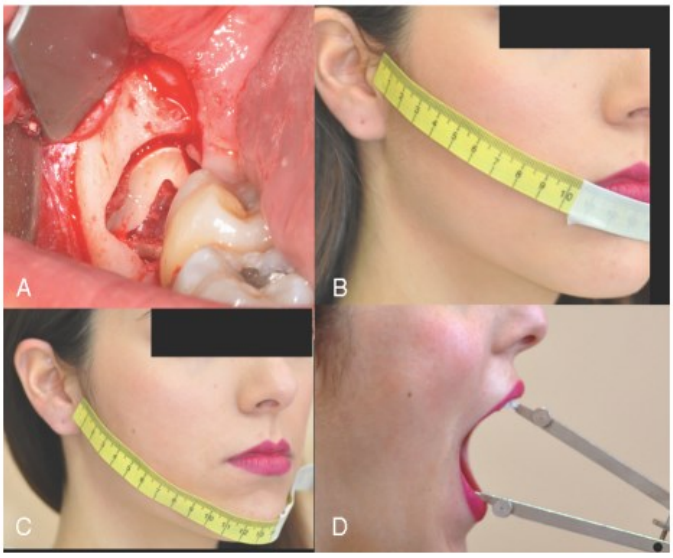

Figure 5: A: Surgery site of an impacted third molar in lower jaw B: Measurement between tragus and labial commissure. C: Measurement between tragus and pogonion. D: Interincisal length between upper and lower jaw (26).

- T1: four days after T0, patients were engaged in the surgical procedure, where blood samples were gathered(26).
- T2: blood samples and the same clinical parameters as in T0 were obtained a week after the initial examination(26).
- T3: the clinical measurements were assessed again. Subsequently, sutures were removed(26).

Outcome of the study

The clinical outcomes of this study clearly demonstrate the superior healing outcomes and better relief of discomfort of patients with high vitamin D3 levels. Although the pain scoring system did not reveal a statistically substantial ($p < 0.05$) improvement after patients consumed biscuits saturated in cholecalciferol solution, it is noteworthy that the test group reported less pain after the T2 timepoint, which corresponds with the peak in 25(OH)D serum levels (Table 1)(26).

Clinical Parameters Δ%: Test Group

	T2-T0			T3-T0		
	T-P	T-L	MO	T-P	T-L	MO
1	7.5	3.8	−22.9	3.8	0.9	−12.5
2	7.4	2.9	−44.0	2.2	1.0	−30.0
3	1.4	3.5	−17.1	1.4	4.4	0.0
4	6.7	4.3	−20.8	5.3	1.7	−11.3
5	3.1	−0.9	−53.7	1.5	−0.9	−46.3
6	−1.3	4.5	−40.0	−3.3	1.8	−22.2
7	11.6	6.7	−50.0	3.6	4.8	−16.7
8	5.0	8.1	−46.7	1.4	1.8	−24.4
9	4.5	5.9	−20.0	0.8	1.0	0.0
10	6.1	4.8	−33.3	0.8	2.9	−11.1
11	−1.5	−1.9	−38.0	−1.5	−1.9	−10.0
12	6.2	1.7	−23.3	3.4	1.7	−16.7
13	0.0	2.7	−44.4	−1.5	0.0	−33.3
14	5.7	1.7	−4.3	2.9	0.0	0.0
15	5.3	6.8	−21.1	3.3	4.3	−12.3
16	7.5	5.4	−16.0	2.0	1.8	−2.0
17	−0.7	0.0	−14.9	−0.7	0.0	−4.3
18	3.9	2.5	−34.9	0.7	0.0	−23.3
19	6.1	8.9	−25.9	3.1	5.0	−16.7
20	8.8	0.0	−10.9	5.1	−0.9	−4.3
21	3.3	3.5	−32.7	6.0	3.5	−18.2
22	7.9	0.9	−8.0	5.8	0.0	−4.0
23	7.1	6.4	−42.9	5.0	3.6	−24.5
24	5.9	3.9	−37.2	1.3	2.3	−27.9
25	0.0	0.9	−12.0	0.0	0.9	0.0
Mean	4.70	3.48	−28.60	2.09	1.59	−14.88

Clinical Parameters Δ%: Control Group

	T2-T0			T3-T0		
	T-P	T-L	MO	T-P	T-L	MO
1	6.1	5.8	−22.9	4.5	4.8	−16.7
2	9.0	4.8	−50.0	4.5	−1.0	−34.0
3	−2.0	0.9	−5.7	−4.0	−0.9	14.3
4	6.0	2.6	−15.1	4.7	0.0	−5.7
5	2.3	0.0	−42.3	0.8	0.0	−32.7
6	4.1	3.6	−34.8	2.1	1.8	−13.0
7	13.1	7.6	−51.7	5.8	6.7	−20.0
8	4.9	5.4	−40.0	2.8	1.8	−17.8
9	6.1	7.8	−28.0	2.3	2.0	−4.0
10	9.1	2.8	−66.7	3.8	1.9	−28.9
11	7.7	5.8	−22.0	3.1	2.9	−20.0
12	6.7	13.7	−33.3	4.0	6.8	−16.7
13	2.4	0.9	−33.3	0.8	0.0	−11.1
14	7.1	3.5	−11.1	4.3	1.7	−2.2
15	4.6	2.6	−38.6	7.8	11.1	−29.8
16	6.9	4.5	−12.0	2.8	2.7	0.0
17	6.4	7.3	−46.8	4.3	6.4	−25.5
18	0.7	0.0	−41.9	0.0	0.0	−34.9
19	0.0	7.8	−16.7	0.0	2.9	−7.4
20	7.2	1.7	−9.1	4.3	0.9	2.3
21	5.3	4.3	−54.5	6.0	4.3	−45.5
22	8.7	3.6	−20.0	8.7	1.8	−10.0
23	6.4	8.2	−38.8	6.4	4.5	−28.6
24	5.2	0.0	−45.7	1.3	2.3	−34.8
25	3.8	4.5	−20.0	1.5	0.9	−4.0
Mean	5.51	4.39	−32.04	3.30	2.66	−17.07

Clinical Parameters Δ% Analysis

	T2-T0			T3-T0		
	T-P	T-L	MO	T-P	T-L	MO
p	0.1151	0.1193	0.0994	0.0105	0.0306	0.1800

Legend
T-P: tragus-pogonion.
T-L: tragus-labial commissure.
MO: mouth opening at incised edges (at max opening).
Measurements are expressed in cm.

Table 1 Clinical Parameters (26)

Furthermore, Oteri et al.(26) also investigated changes in biochemical parameters. Inflammatory indexes were also assessed at every blood sample collection along with the vitamin D values (Table 2 and 3). As explained in the literature, “Inflammatory indexes (time of erythrocyte sedimentation, C-reactive protein, Alpha-1-glycoprotein, interleukin (IL)-1-beta, IL-6, tumor necrosis factor (TNF)-alpha)” (26), showed significantly lower values ($p<0.01$) at T2 and T3 in the test group (26).

	Biochemical Parameters Δ%: Test Group							
	Vit D3 ng/mL	PCR mg/dL	TNF-ALPHA pg/mL		IL-1 BETA pg/mL		IL-6 pg/mL	
	T2-T0	T2-T0	T1-T0	T2-T0	T1-T0	T2-T0	T1-T0	T2-T0
1	282	1000	60	20	−83	−83	−83	−83
2	517	600	−17	0	−33	−33	−33	−33
3	367	0	−30	−50	0	0	0	0
4	190	700	−63	−25	100	67	100	67
5	571	450	138	−63	25	−50	25	−50
6	499	450	−31	0	−60	−20	−60	−20
7	185	400	0	−50	600	600	600	600
8	180	200	10	−10	−30	−90	17	−83
9	334	1000	−44	13	−33	100	−33	100
10	241	100	−36	−14	−67	−67	−67	−67
11	218	0	18	45	300	100	300	100
12	554	67	18	−82	−10	−90	20	−60
13	459	300	−8	−8	−20	−80	−25	−88
14	175	400	11	−11	0	−78	67	−33
15	91	1000	−33	−33	−33	−11	−33	−11
16	516	600	38	13	13	−88	100	0
17	376	500	33	50	100	200	100	200
18	168	300	0	−11	40	−40	40	80
19	381	0	−21	−47	−33	−67	−33	−67
20	201	−25	−9	0	0	14	0	14
21	205	200	11	−56	−10	−90	−22	−67
22	246	100	−18	−9	20	0	20	0
23	138	400	−8	−15	25	25	25	25
24	47	450	0	0	0	0	0	0
25	124	233	9	−73	0	−89	0	−83
Mean	290.58	377.00	1.16	−16.66	32.37	5.23	40.91	17.63

	Biochemical Parameters Analysis							
p	VitD	PCR	TNF-ALPHA (T1)	TNF-ALPHA (T2)	IL-1-BETA (T1)	IL-1-BETA (T2)	IL-6 (T1)	IL-6 (T2)
Flat Values	0.0000	0.1454	0.0009	0.0080	0.0098	0.0000	0.0046	0.0013
Δ%	0.0000	0.2956	0.0391	0.0034	0.2513	0.0455	0.3423	0.0499

Table 2: Biochemical Parameters Test group (26)

	Biochemical Parameters Δ%: Control Group							
	Vit D3 ng/mL	PCR mg/dL	TNF-ALPHA pg/mL		IL-1 BETA pg/mL		IL-6 pg/mL	
	T2-T0	T2-T0	T1-T0	T2-T0	T1-T0	T2-T0	T1-T0	T2-T0
5	−30	800	−5	−50	−20	140	50	17
6	10	250	20	−20	300	300	0	0
7	−20	0	−14	−7	−73	20	13	50
8	−7	300	70	50	200	300	171	143
9	−13	1400	−47	−37	40	160	0	367
10	−11	100	0	60	200	500	−71	−43
11	−6	1100	50	−17	0	30	25	−25
12	−1	650	70	50	100	140	43	114
13	25	450	33	44	400	−50	160	0
14	−18	−21	33	33	25	150	200	800
15	35	900	114	43	100	140	300	400
16	9	600	80	50	38	63	200	900
17	18	400	83	167	−9	−45	−83	0
18	20	1000	25	50	175	0	300	200
19	60	100	86	71	0	25	−33	−33
20	46	−33	−38	−31	−50	−44	200	300
21	−20	0	25	25	33	33	29	−14
22	15	300	−45	9	0	−29	0	−67
23	−9	1100	−35	−50	11	−44	−88	−75
24	−8	−13	0	−14	−20	−10	−33	−11
25	16	100	23	23	10	20	29	71
Mean	3.27	427.31	23.37	17.68	61.36	85.94	55.94	118.92

Table 3: Biochemical Parameters Control Group(26)

In contrast, in the of Mameledzija et al.(27) no additional vitamin D supplementation was provided to the patients. The researchers measured the patients' initial 25(OH)D status and divided them into vitamin D-deficient (≤20 ng/mL) and vitamin D-insufficient (>20 ng/mL) groups(27).

Procedure of the study

The Study conducted by Mameledzija et al.(27) followed a similar four-stage approach, from the preoperative stage to the final follow-up stage, evaluating various clinical outcomes such as edema, trismus, pain, signs of dry socket (as a postoperative complication)(27).

After measuring the 25(OH)D levels of the patients, with the lowest number being 7,55 ng/mL and the highest being 33,69ng/mL, most of them were within the range of physiologically acceptable. This made them to separate D-deficient group (≤20 ng/mL) of 12 people and an insufficient group (>20ng/mL) of 11 people(27).

The investigation was also guided into 4 stages as mentioned above, whereas they named the stages S0 to S3. In this study, the need for antibiotics was determined based on the surgeon's evaluation of the difficulty of the procedure and any complications that arose intraoperatively.(27) In addition to monitoring standard clinical parameters, the researchers also recorded the number and dosages of painkillers taken by patients during the study period(28)

Outcome of the study

In this study, the outcomes were not able to show significant differences in tragus labial commissure, trismus pain, or wound healing quality between the vitamin D-insufficient group and the vitamin D-deficient group (Table 3). Plus, none of the participants established signs of dry socket(27).

The results of this study do not confirm the research hypothesis due to the small number of participants and the large number of people suffering from deficient 25(OH)D levels, as 91% of the patients have displayed. Unlike previous studies that administered additional vitamin D supplements to maximize the results, this study relied on the participants' natural vitamin D levels. The generally low vitamin D levels observed across

the sample and the lack of significant differences in vitamin D status between the groups may have limited the ability to detect a more pronounced impact on dental outcomes. Whereas the study by Oteri et al.(26) clearly highlights the importance of addressing vitamin D as a powerful agent to promote the wound healing process(27).

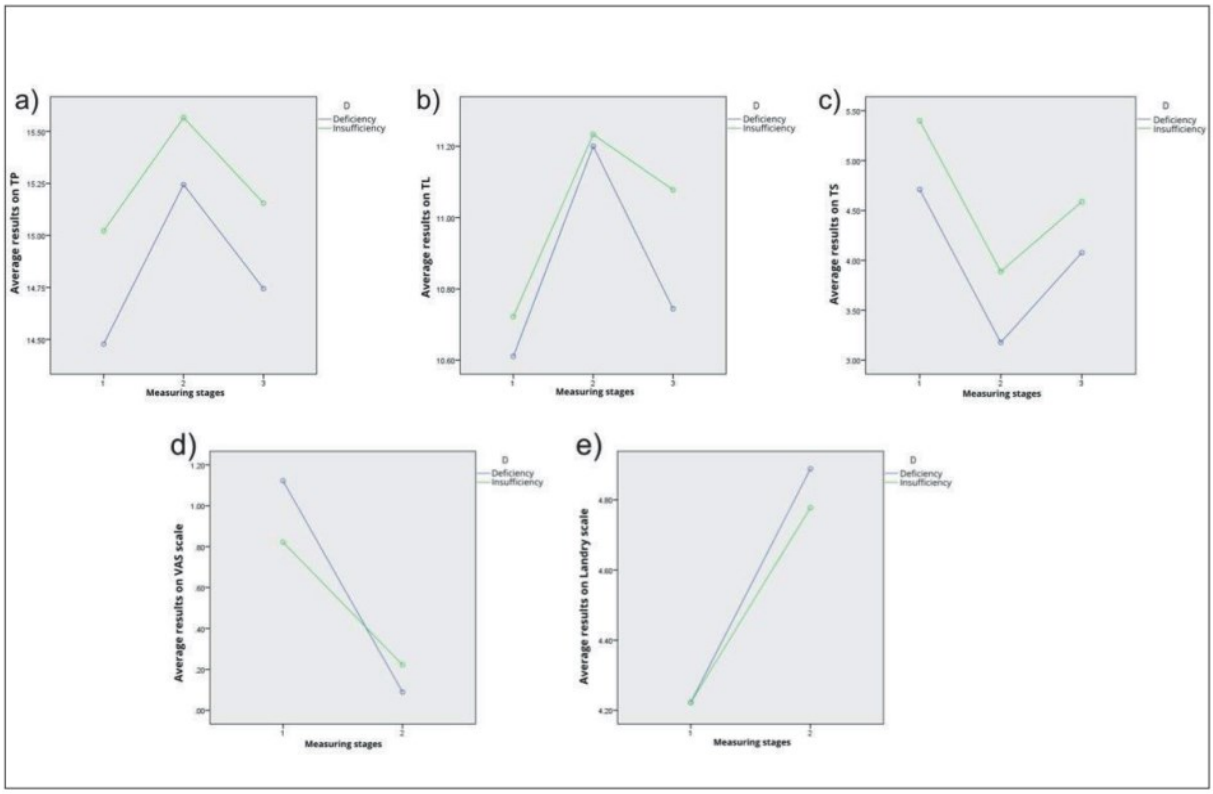

Table 4: a) Tragus–pogonion, b) Tragus –labial commissure, c) Trismus, d) Pain, e) Wound healing quality (WHQ), values between the deficient and the insufficient group measured at three stages (1-S0, 2-S2, 3-S3) (18)

On the contrary, Oteri et al.(26) have presented an obvious improvement in the healing process with a high vitamin D level after the surgical procedure(26).

There was a great difference in 25(OH)D levels in patients during the period of both studies. The individuals who took part in the research from Oteri et al. (26)showed mean 25(OH)D levels of 87.4ng/mL at stage 2, which is more than double the number of patients with the highest 25(OH)D levels in blood from the study by Mameledzija et al.(27).

Furthermore, vitamin D levels appear to play an important role in the patient's inflammatory response since they exhibit a decrease of TNF-alpha, IL-1-Beta, and IL-6(26). This speeds up the tissue healing process, suggesting that enhancing vitamin D levels may benefit the healing process after small surgeries(26).

4.2.2 Vitamin D Deficiency in Periodontal Surgery

Vitamin D is known to be essential for maintaining healthy bones and regulating the immune system(18). It is hypothesized that a deficiency in vitamin D could potentially have an adverse impact on the health of the periodontium since periodontitis is defined by the degradation of alveolar bone caused primarily by the body's immune system responding to certain bacterial infection(18). Moreover, calcium, phosphorus, and parathyroid hormone levels all play a role in the transformation of 25(OH)D into its active form(1). PTH can have both catabolic and anabolic effects on bone, depending on its concentration and dosage(29). Recent research has shown that maintaining sufficient blood levels of 25(OH)D at or above 28 ng/mL helps to maintain stable PTH levels and normal calcium availability in the body(30).

Analysis of cross-sectional data from NHANES III and other studies have demonstrated some key insights. It is suggested that people with the highest 25(OH)D blood concentration levels tend to show up to 20 % less bleeding on probing than individuals with the lowest levels. Demonstrating that maintaining adequate vitamin D levels may be an important factor in minimizing or reducing gingival inflammation, attachment loss, and tooth loss risk(18).

Since there are rarely any studies about the effect of vitamin D on periodontal surgeries, the number of patients and sample size observed on the correlation between vitamin D sufficiency and oral bone formation as part of recovery after periodontal surgeries is very small(18).

A study published by Bashutski et al.(18) from the University of Michigan involved 40 individuals with severe periodontal disease. They underwent a specific periodontal surgical procedure called open flap debridement in one sextant of their mouth and were followed up for one year after the surgery(18).

The primary outcome measure evaluated was infra-bony defect recovery, which was compared between two groups of people who took teriparatide or placebo medication. Three days before the surgery, the two groups of patients received teriparatide or placebo medication, randomly assigned by the pharmacy. They then were instructed to take oral supplements containing 1000 mg of calcium and 800 IU of vitamin D along with the study medication. This regimen continued for six weeks, aligning with the expected timeframe for bone healing(18).

To be able to monitor adherence to the medications, the researchers collected any unused medication. They tracked the participants' serum bone alkaline phosphatase levels during the period of the drug administration(18).

The surgeries were performed by two blinded operators, who did not evaluate the individuals on whom they were assigned again blindly. Supra- and sub-gingival scaling, polishing, and oral hygiene instruction were provided regularly postop(18).

Outcomes of the study

Other than two missed follow-ups, the participants demonstrated high compliance. The study population was well-balanced, with no significant differences in baseline demographics between the groups(18).

Vitamin D Status

At the start of the study, 28% of the participants were vitamin D-deficient, and four of these were in the teriparatide group. Five vitamin D-deficient patients achieved sufficiency in the placebo group at six weeks, but four returned to a deficient state after six months. In contrast, all vitamin D-deficient teriparatide patients attained sufficiency at six weeks, with only one becoming deficient again at six months, as seen in Table 5(18).

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

Table 5: Serum 25(OH) Vitamin D changes over time based on status (deficient or sufficient) at baseline (18)

Outcomes for the placebo group

Among the placebo patients, those with sufficient vitamin D levels ahead of the surgery showed enhanced CAL and decreased PD. Nevertheless, after the surgery, those with initial vitamin D deficiency showed a loss of clinical attachment. Significant differences in clinical results between participants with vitamin deficiency and sufficiency were observed beginning at six weeks after surgery. By twelve months, individuals with sufficient vitamin D levels experienced an enhancement in CAL and more noticeable reductions in PD compared to those who were vitamin D deficient. The radiological resolution of the infra-bony defect showed minimal differences, with no significant variation between the groups. Bleeding on probing (BOP) decreased in both deficient and sufficient participants, with no remarkable differences between the groups(18).

Outcomes for Teriparatide Group

In the teriparatide group, vitamin D-sufficient participants showed considerable recovery in CAL at six months and substantial reduction in PD from three to nine months. It is interesting to note that the vitamin D-sufficient patients at baseline have shown enhancement in radiographic infra-bony defect resolution than the vitamin D-deficient patients at baseline. On the other hand, the measurements of CAL and PD by one year for both vitamin D-deficient and -sufficient remained rather close. It was recorded that BOP of Vitamin D-deficient teriparatide patients at initial examination saw a 12% increase at twelve months, and vitamin D-sufficient teriparatide patients saw a 39% decrease. Consequently, the study emphasizes that constant sufficient vitamin D status

is required to obtain optimal periodontal healing and regeneration in periodontal surgery, whether teriparatide is used or not(18).

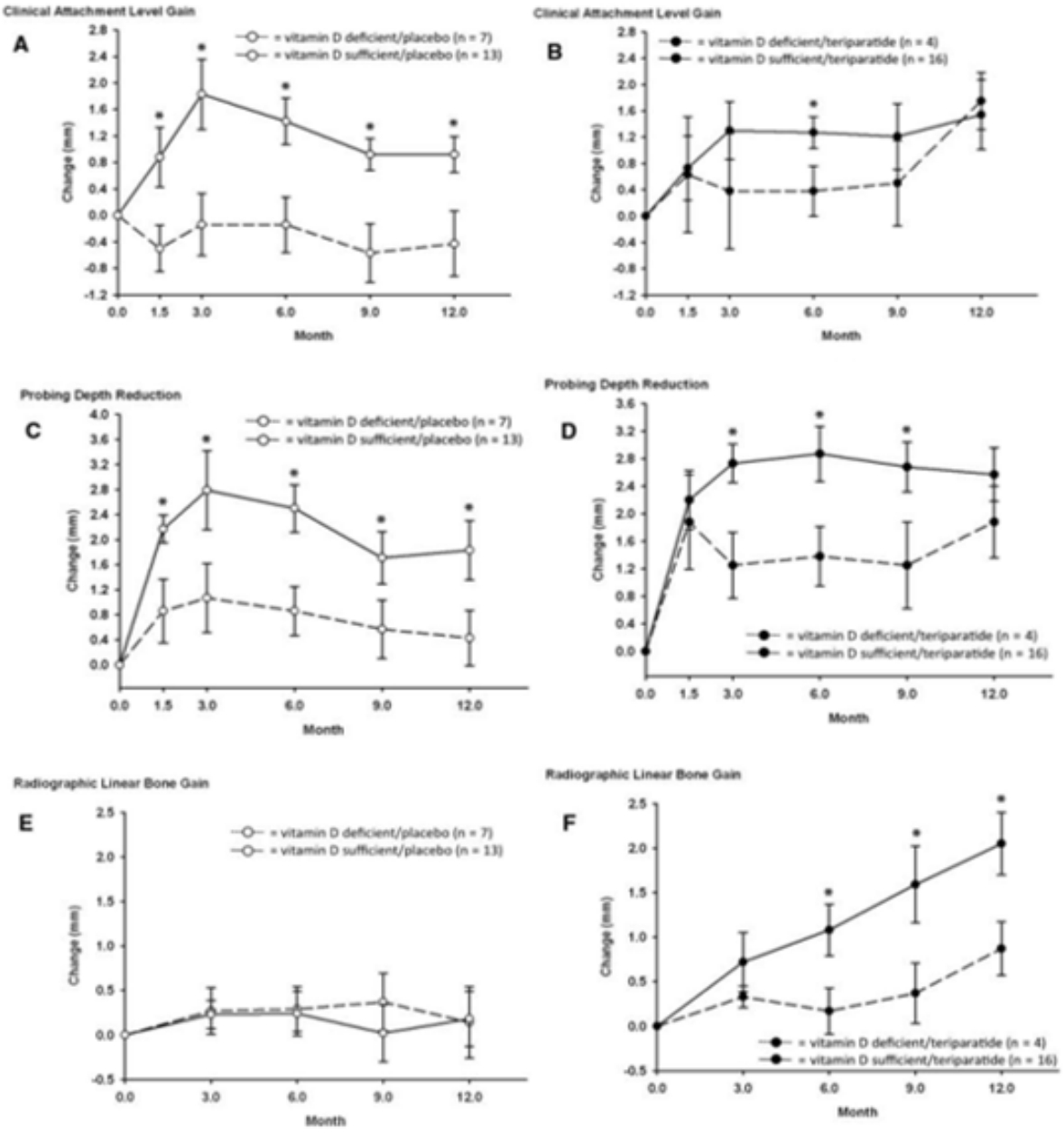

Table 6 (18)

4.2.3 Vitamin D and Dental Implant Placement

4.2.3.1 Maxillary Sinus Augmentation

A sinus augmentation is often performed on patients with limited bone height to increase dental implant stability(31). Bone replacement grafts will then be metabolized and ideally replaced with the patient's own bones(31). In this process, remodeling and bone formation play a crucial role(31).

Horwood et al.(32) have shown that increasing serum vitamin D directly influences the RANKL mechanism(32). This then stimulates osteoclastogenesis hence stimulating bone resorption(32).

Schulze-Späte et al.(33) conducted a randomized, double-blinded, placebo-controlled study with 20 individuals on whom they performed maxillary sinus augmentation. They have divided the patients in two groups, one group was instructed to take 5000 IU vitamin D3 orally and the other to take placebo medication for the timeframe beginning with the surgical procedure performed till harvesting of the bone core during implant surgery. Additionally, patients were guided to take antibiotics postoperatively: either 500mg amoxicillin three times per day for seven days or 300mg clindamycin four times per day for those who are allergic or sensitive to penicillin. They were also advised to rinse their mouth twice daily with chlorhexidine digluconate mouthrinse for three weeks(33).

Blood samples were taken at the patients' baseline visits, after two weeks, twelve weeks, and finally at the implantation surgery. During the study, other than two patients who decided to exit, none of them experienced any negative side effects from the surgical procedure or the medications and showed similar compliance(33).

During the implant surgery, a bone sample was taken, which was then processed and prepared in slides for histological examination. Under light microscopy, where both the host bone cells and graft material were visible, it did not show any significant differences (33).

Nevertheless, it is worth pointing out that more osteoclasts surrounding the bone graft material were observed in the bone cores obtained from the vitamin D3 group compared to the other group. This indicates more active bone metabolism, hence encouraging the promote bone turnover, as approved by some studies mentioned above(33).

However, considering the sample size of this study, it would not be justified to assume that there is a direct benefit of vitamin D3 and calcium supplementation for surgical bone augmentation therapy(33).

4.2.3.2 Implant and Simultaneous Alveolar Bone Augmentation

The study conducted by Ahmed Elsayed(34) included 14 patients between the ages of 28 and 40, who required single implant placement in the upper anterior region. All patients had minimal buccal-lingual bone dehiscence but sufficient bone height. None of the patients had any systemic diseases, as confirmed by the Burket's oral medicine health history questionnaire(35). However, the baseline vitamin D levels of the patients were not reported(34).

Preparation before surgical procedures

Prior to the surgical procedure, all patients underwent comprehensive clinical and radiographic examinations to measure the baseline alveolar ridge dimensions(34). Patients were then divided into a control group and a study group(34). All patients received preoperative antibiotics (36).

Surgical procedures

For the alveolar ridge augmentation, xenogeneic bone graft material and titanium mesh were used to stabilize the graft(34). In the study group, the bone graft material was mixed with vitamin D3 gel before placement (37). After implant placement, implant stability was measured using a magnetic resonance frequency device, then a healing abutment was placed (38,39). At the 4-month follow-up, radiographic measurements and another implant stability measurements were taken(34).

Outcomes of the study

The results showed that the initial bone levels between the two groups were not statistically different (p=0.25). However, the bone levels at the recall visit demonstrated a significantly higher mean value in the study group (group 1) compared to the control group (group 2) (p=0.00). Similarly, the implant stability quotient (ISQ) values showed higher mean values in the study group without statistical significance at the initial measurement (p=0.73), but with a statistically significant difference at the second measurement (p=0.00)(34).

In conclusion, adding vitamin D3 to the xenogeneic bone graft material during alveolar ridge augmentation performed simultaneously with dental implant placement resulted in a significantly increased measurements in both the buccolingual ridge width and the implant stability quotient than the control group(34).

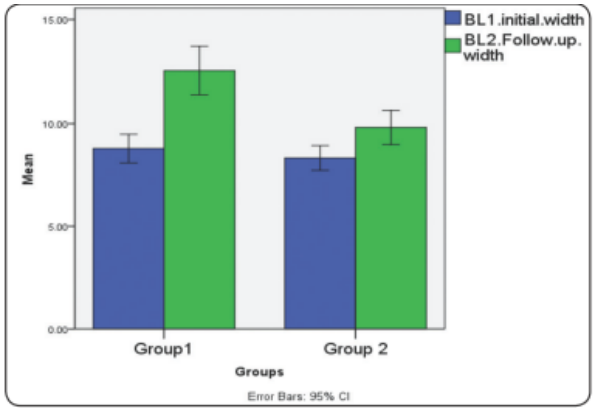

Figure 6:Bone level measurements in group 1 and 2(27)

4.2.3.3. Vitamin D and Success of Dental Implant Osseointegration

A clinical trial involving 122 participants was conducted by Kwiatek et al.(40) to examine the relationship between 25-hydroxycholecalciferol concentration, vitamin D deficiency, and the success of dental implant osseointegration(40).

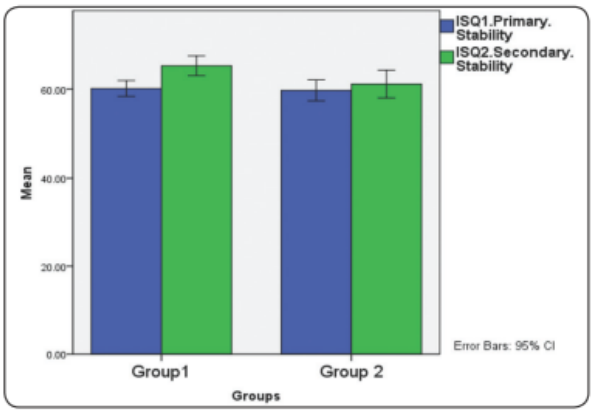

Figure 7 Implant stability quotient in group 1 and 2 (27)

Patient Selection and Grouping

The study included patients needing dental implants in the premolar or molar regions of the lower jaw. Eligible participants were free of diseases, healthy, who had no medical history of allergies to medication or implants. Another important criterion was to select patients who were not getting medications or supplements consistently. The participants were then divided into three groups(40):

- Study Group A (n=43): Serum 25(OH)D levels <30 ng/mL, did not receive vitamin D supplementation.
- Study Group B (n=48): Serum 25(OH)D levels <30 ng/mL, were administered 8000IU of vitamin daily per os for the entire duration of the study.
- Study Group C (n=31): Serum 25(OH)D levels ≥30 ng/mL, within the physiologically acceptable range.

Evaluation and Surgical Procedure

At the initial visit, the patients' medical history, physical examination, and radiographic data (including cone-beam computed tomography) were collected to assess the bone quantity for the surgical procedure as shown in Figure 8,9 and 10. Throughout the study, a single operator performed the surgical implantation. On the day of the implant placement, a separate individual conducted the initial assessment of implant stability and 25(OH)D blood serum levels(40).

Follow-up and Outcome Measures

A radiographic image was taken at the 6-week follow-up visit, and the 25(OH)D blood serum levels were measured again. Twelve weeks after the surgery, the success of osseointegration was evaluated through a comparative measurement of implant stability. The healing abutment was then inserted, and another radiographic image and 25(OH)D blood serum measurements were performed(40).

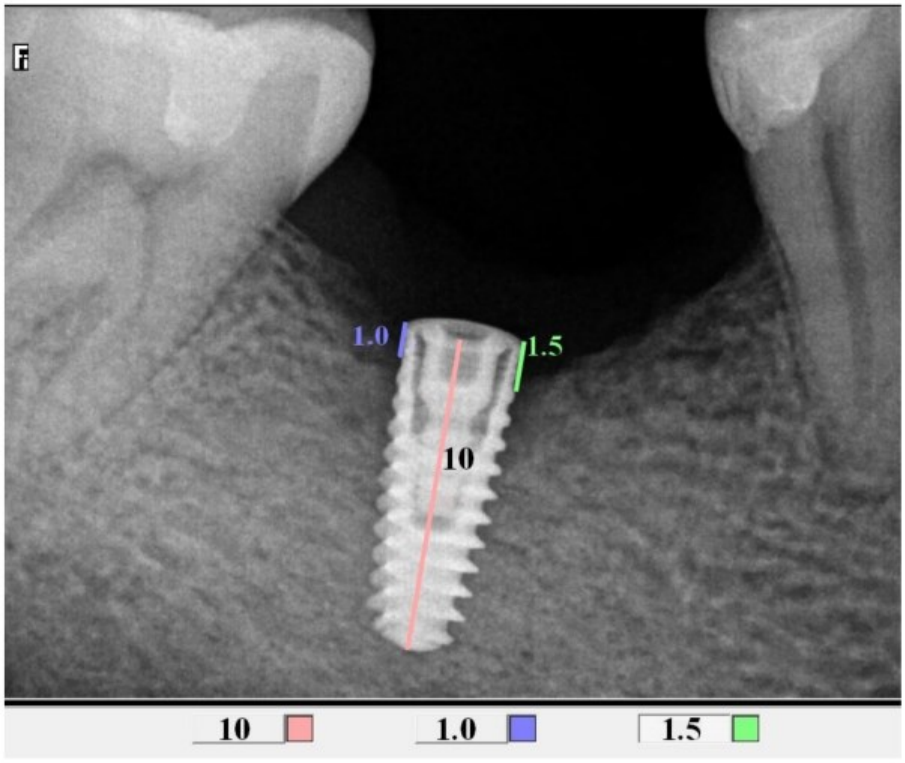

Figure 8: Bone quantity loss in the site of the implant insertion (40)

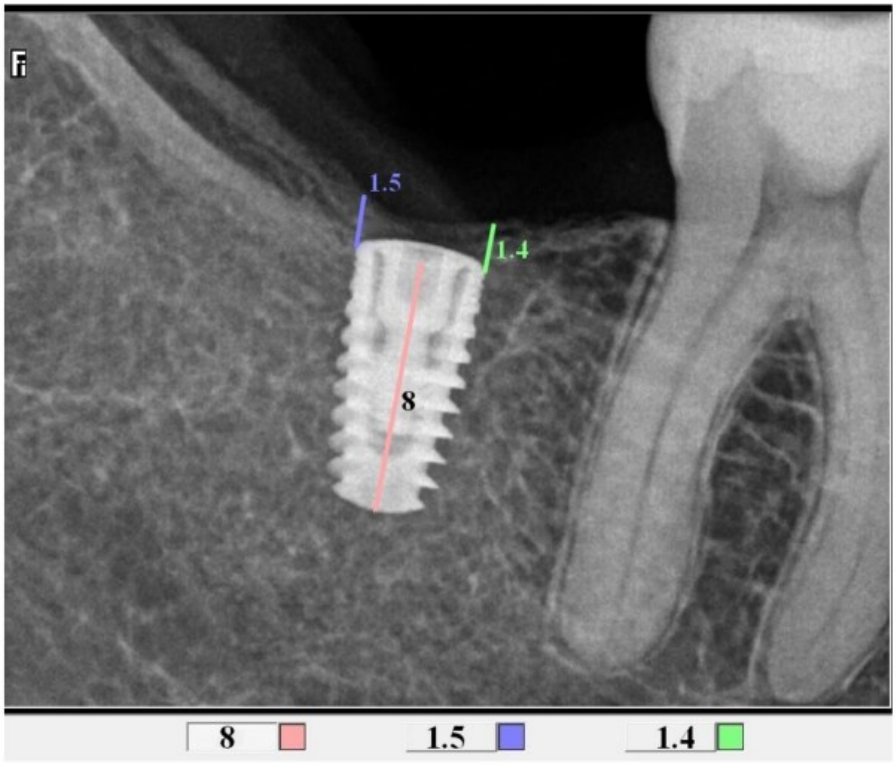

Figure 9: Bone quantity gain in the site of the implant insertion (40)

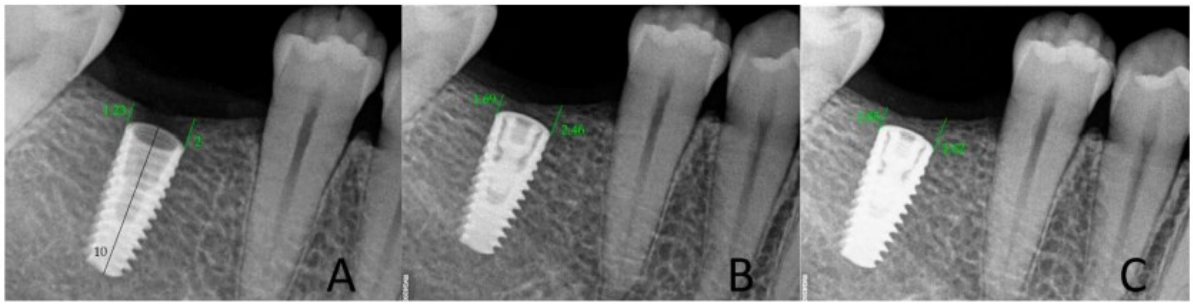

Figure 10: Bone quantity gain in the site of the implant insertion (A) At the time of surgery; (B) After six weeks; (C) After twelve weeks in study groups (40)

During the Study, 5 patients from group A were removed because they missed the control tests, and it might influence accuracy, because they relied on the patients to take the vitamin supplements regularly at home(40).

The results of the study revealed statistically significant ($p = 0.05$) differences in bone loss/growth at the implant site across the participant groups (Table 7)(40):

The data showed that the bone levels at the implant site were significantly higher in Group B and Group C compared to Group A(40).

Bone Level (mm)		After 6 weeks	After 12 weeks	p *
Study group A	Mean ± SD	0.06 ± 0.48	0.08 ± 0.92	0.232 NP
	Median	0	0.2	
	Quartiles	0–0.3	–0.05–0.65	
Study group B	Mean ± SD	0.25 ± 0.51	0.53 ± 0.77	<0.001 NP
	Median	0.25	0.65	
	Quartiles	0–0.6	0.1–1.02	
Study group C	Mean ± SD	0.29 ± 0.53	0.48 ± 0.74	0.008 P
	Median	0	0.3	
	Quartiles	0–0.55	0–0.9	

P, normal distribution of differences, Student's *t*-test for dependent (repeated) measurements; NP, deficiency in normality of distribution of differences, Wilcoxon test for dependent (repeated) measurements; * p significance; level.

Table 7: Difference of the bone quantity at the implant sight after six and twelve weeks in the study groups A, B, and C (40)

4.2.3.4 Early Dental Implant Failure

The key to successful osseointegration of dental implants is multifaceted. Factors influencing implant osseointegration are as follows:

- Surgical and prosthetic factors: These are influenced by the operator's experience, surgical techniques, and protocols, as well as the timing and type of prosthetic loading(41,42).
- Implant-related factors: These include the surface characteristics, material, and design of the implant(43,44).
- Patient-related factors: These encompass the patient's bone volume, bone quality, and immune response(41,45,46).

In the past, the primary focus in improving implant survival rates has been on enhancing prosthetic loading and the characteristics of the implant itself. While these advancements have been valuable, there are still cases of Early Dental Implant Failure (EDIF) and Late Dental Implant Failure (LDIF) that remain challenging to resolve(44).

When a dental implant is inserted, the first point of contact is the immune cells within the surrounding bone. The manner in which the immune system responds to this new implant material can significantly influence the outcome of the implantation procedure(47).

Given the significance of the immune system and bone metabolism in dental implants' success, ensuring that the patient's vitamin D levels are optimized before the implantation procedure is highly advantageous. By boosting vitamin D levels, the body's immune response and bone health can be improved, increasing the chances of a successful implant outcome(45).

In a retrospective clinical study, Mangano et al.(44) examined the connection between vitamin D status and EDIF in a cohort of 885 patients and 1,740 implants(44).

EDIF refers to failures that occur from the surgical implantation procedure up to 4 months after the operation until the restoration is placed. This type of failure indicates a failure in the osseointegration process, suggesting hindered bone healing(44).

LDIF, on the other hand, is defined as failures that happen after the prosthetic loading of the implant. This type of failure is caused by losing the previously established osseointegration(48,49)

Patient Selection and Data Collection

The study (42) began by carefully selecting eligible patients and excluding those with:

- Poor oral hygiene
- Systemic diseases
- Alcohol and/or drug abuse
- History of radiotherapy or chemotherapy

- Pregnancy
- Incomplete medical records

The data collection process included gathering information about each patient's:

- Missing tooth region
- Tooth location
- Implant details

Patients were asked to undergo blood tests to measure their vitamin D levels two weeks before the implantation procedure(44).

Tracking Implant Failures

After the surgical implantation, the researchers meticulously recorded any failures that occurred within the first 4 months up until the placement of the restoration. These early failures were categorized as EDIF. Additionally, any failures that happened after the loading of the prosthetics were recorded as LDIF(44).

Implant Placement and Postoperative Care

An experienced clinician with 25 years of expertise performed the dental implant placements. Patients were prescribed antibiotics and pain medications for the surgical procedure. Detailed oral hygiene instructions were provided, and patients were asked to use a medicated mouthwash twice daily for two weeks(44).

Follow-up Protocol

The first recall appointment was scheduled 10 days after the surgery, during which the sutures were removed. The implants were then allowed to heal in a submerged state for 4 months. The implants were uncovered at the second recall visit, and preparations were made for temporary restorations. These temporary restorations were maintained for 3 months to allow for further monitoring of the implant's response. After the 3-month period, the definitive restorations were finally loaded(44).

All patients who participated in the study were followed up with at least two annual checkups in accordance with the established protocols. This approach to implant placement, postoperative care, and long-term monitoring ensured that the researchers could thoroughly evaluate the outcomes and identify any potential complications or failures(44).

The outcome of the study

While this retrospective study did not yield statistically significant results overall, several notable trends are worth highlighting(44).

The vitamin D sufficient group (>30 ng/mL) exhibited a relatively low occurrence of EDIF at 2.9%. In the group of patients with insufficient vitamin D levels between 10-30 ng/mL, the EDIF rate almost doubled to 4.4%. Patients with severe vitamin D deficiency (<10 ng/mL) experienced an EDIF rate of 11.1% - nearly four times higher than the sufficient group. These findings suggest a clear trend of increasing EDIF rates as vitamin D levels decrease. While not statistically significant ($p = 0.105$), the dramatic differences observed across the three groups are compelling and warrant further investigation. As this was a retrospective study, the research design inherently limited the ability to draw more definitive conclusions from the results(44).

Interestingly, the same authors had previously conducted a clinical study in 2016, which showed similar findings regarding the association between vitamin D status and EDIF (50):

- Participants with vitamin D levels >30 ng/mL experienced 9 failures (2.2%)
- Subjects with levels between 10-30 ng/mL had 16 failures (3.9%)
- Individuals with levels <10 ng/mL experienced 2 failures (9.0%)

While the authors were unable to demonstrate a statistically significant connection between low serum vitamin D levels and increased EDIF rates, the data still revealed compelling differences in the number of failures between the sufficient and deficient groups(50).

4.2.3.5 Systemic Review of the Success of Implants

Garg et al. (2020)(51) conducted a randomized study involving 32 patients who underwent dental implants were separated as follows(51):

- Group I (n=16): Serum vitamin D levels <30 ng/mL, supplemented with 6000 IU of cholecalciferol per month.
- Group II (n=16): Serum vitamin D levels <30 ng/mL, not supplemented with vitamin D.

The study found the following (51):

Group I (Vitamin D Supplementation)

- At the time of surgery, the mean marginal bone level was 1.386 mm mesial and 1.310 mm distal.
- After 6 months, the mean marginal bone level decreased to 0.832 mm mesial and 1.085 mm distal.
- This reduction in marginal bone loss was statistically insignificant ($p < 0.05$).

Group II (No Vitamin D Supplementation)

- At the time of surgery, the mean marginal bone level was 1.179 mm mesial and 1.065 mm distally.
- After 6 months, the mean marginal bone level decreased to 0.229 mm mesial ($p<0.01$) and 0.285 mm distally ($p=0.05$).
- This reduction in marginal bone level was statistically significant ($p < 0.05$).

Importantly, no implant losses were reported in either group during the follow-up period. These findings suggest that vitamin D supplementation may help mitigate marginal bone loss around dental implants in patients with insufficient vitamin D levels (<30 ng/mL). However, the difference between the supplemented and non-supplemented groups did not reach statistical significance(51).

A prospective study conducted by Tabrizi et al. (2021)(48) examined the relationship between serum vitamin D levels and marginal bone loss around dental implants. The study involved 90 patients with 90 dental implants, divided into the following three groups(51):

1. Group I: Vitamin D <10 ng/mL, measured at the time of prosthetic loading and after one year.
2. Group II: Vitamin D between 10-30 ng/mL, measured at the time of prosthetic loading and after one year.
3. Group III: Vitamin D >30 ng/mL, measured at the time of prosthetic loading and after one year.

The findings from this study were consistent with the outcomes of a previous study which showed, while increased marginal bone loss showed a close correlation to vitamin D deficient probands, the other groups showed physiological bone loss around implants(51).

- In Group I (vitamin D <10 ng/mL), the peri-implant bone loss observed 1.38 mm ± 0.33 mm.
- In Group II (vitamin D 10-30 ng/mL), the peri-implant bone loss was 0.89 mm ± 0.16 mm.
- In Group III (vitamin D >30 ng/mL), the peri-implant bone loss was 0.78 mm ± 0.12 mm.

These differences were statistically significant ($p < 0.001$), indicating a clear correlation between vitamin D status and peri-implant bone loss around dental implants(51). Importantly, at the recall visits, no probands reported any implant losses(48).

Bazal-Bonelli et al.(52) explored the influence of serum vitamin D levels on dental implants regarding longevity peri-implant bone quality and common long-term complications(52). The basis of this review (52) consists of four large-scale studies aforementioned as shown in Table 8(40,44,48,50,51,52).

1129 edentulous and partially dentulous patients who received 1984 dental implants took part in these studies. The follow-up period ranged from 20 months to 20 years. Serum vitamin D levels are typically categorized as follows: <10 ng/mL is considered deficient, 10–30 ng/mL is insufficient, and >30 ng/mL is physiologically acceptable. The studies examined 1129 patients aged 20 to 57.3 ± 14.4 years, with most participants older than 40. This is significant because vitamin D deficiencies tend to manifest more commonly in older adults. The patient population consisted of 529 women and 568 men, with one study not specifying the participants' gender. The male-to-female ratio of 1.07 indicates a balanced representation of both sexes, suggesting that gender did not significantly influence the findings. The vitamin D status of the patients was as follows: 57 patients had vitamin D status <10 ng/mL, 478 patients had vitamin D levels ranging from 10-30 ng/mL, and 471 patients had vitamin D status >30 ng/mL. Additionally, a group of patients received vitamin D supplementation: 59 patients had vitamin D status <30 ng/mL, and 64 patients had vitamin D status <30 ng/mL. The review concluded that the group with decreased vitamin D blood status presented slightly more marginal bone loss around their dental implants. However, to fully assess the long-term effects of vitamin D on implant survival rates and osseointegration, longer follow-up periods are required(52).

Due to the limited number of studies conducted on the bone formation during osseointegration, implant survival, marginal bone loss and the small number of participants only a summary of the studies involved was constructed(52).

Author and Year	Study	Patients (Number)	Gender (Male/Female)		Mean Age (Years)	Vitamin D Serum Level (Patients)	Timing of Vitamin D Sampling	Implants (Number)	Implants Location	Implants Survival (%)	Marginal Bone Loss (mm)/DM	Bone Remodeling during Osseointegration (mm)/DM	Mean Follow-Up (Months)
Mangano et al., 2018 [28]	Retrospective study. Three cohorts	885	455	430	57.3 ± 14.4	G1: <10 ng/mL: 27 G2: 10–30 ng/mL: 448 G3: >30 ng/mL: 410	Two weeks prior to surgery	1740	-	G1: 88.9 G2: 95.6 G3: 97.1	-	-	168
Garg et al., 2020 [30]	RCT	32	-	-	20–40 (range)	G1: <30 ng/mL (supplement): 16 G2: <30 ng/mL: 16	At the time of diagnosis. The subsequent blood samples were taken at 3-month and 6-month follow-up period from G1 patients	32	Mandibular posterior teeth	100	-	G1: M: 0.832 D: 1.085 G2: M: 0.229 D: 0.285 RVG	6
Kwiatek et al., 2021 [31]	RCT	122	57	65	43.8 ± 12.15	G1: <30 ng/mL (supplement): 48 G2: <30 ng/mL: 43 G3: >30 ng/mL: 31	On the day of surgery, after six weeks, and after twelve weeks.	122	Premolar and molar mandible	100	-	G1: 0.08 ± 0.93 G2: 0.53 ± 0.77 G3: 0.48 ± 0.74 RVG	3
Tabrizi et al., 2021 [32]	Prospective study. Three cohorts	90	56	34	G1: 41.50 ± 10.13 G2: 45.03 ± 11.16 G3: 40.73 ± 9.95	G1: <10 ng/mL: 30 G2: 10–30 ng/mL: 30 G3: >30 ng/mL: 30	At the time of loading and 12 months later	90	Molar mandible	100	G1: 1.38 ± 0.33 G2: 0.89 ± 0.16 G3: 0.78 ± 0.12/RVG	-	12

RCT: Randomized clinical trial; G: group; DM: Diagnostic method; M: mesial; D: Distal; RVG: radiovisiography.

Table 8: Comparison of different studies involved(52)

The studies reviewed in this systematic review provide the following key insights(52):

Vitamin D Supplementation and Bone Loss

- Patients with blood vitamin D status <30 ng/mL during the osseointegration phase (bone integration with the implant) who were supplemented with vitamin D showed decreased levels of marginal bone loss around their dental implants(40,48).
- Supplemented patients with vitamin D deficient levels (<30 ng/mL) even exhibited lower bone loss than probands who had sufficient blood vitamin D status (>30 ng/mL)(48).
- The findings align with existing animal research, which has shown increased bone formation around implants with vitamin D supplementation(53–55).

- The group who had sufficient (>30 ng/mL) or insufficient (10-30 ng/mL) vitamin D status seemed to obtain less profits vitamin D supplements compared to the group with deficient vitamin D status (<30 ng/mL)(56).

Implant Survival Rates

- Three of the four studies examined in the systematic review reported no implant loss during the 6-12 months follow-up period (57).
- However, the 14-year study by Mangano et al.(50)provided more long-term insights(50):
    - Probands who showed satisfactory blood vitamin D status (>30 ng/mL) had higher implant survival rates than those with insufficient (10-30 ng/mL) or deficient (<10 ng/mL) levels.
    - Patients with vitamin D levels <30 ng/mL had higher long-term implant survival rates (97.1%) compared to an up-to-date research (96.4%).
    - This was not the case for patients with vitamin D 10-30 ng/mL (95.6% vs. 96.4%) or vitamin D <10 ng/mL (88.9% vs. 96.4%).

It was also found in a study that utilizing digitally guided surgery showed a three times better prognosis than implant placement was conducted without any digital guidance(57).

The failure rate for digitally guided implant placement was 2.25%, while the failure rate for freehand placement was 6.42%. This difference was statistically significant ($p = 0.0004$), indicating that using digital guidance technology for implant placement can significantly improve implant success rates(57).

This finding suggests that the surgical technique employed for dental implant placement is an important factor to consider in addition to the patient's vitamin D status. Utilizing digitally guided surgery appears to be a valuable approach to minimize implant failures, potentially providing better long-term patient outcomes(57).

Another systematic review by Shah et al.(58) provides the following insights on the relationship between vitamin D and dental implant success as shown in Table 9 and 10(58).

Implant Outcomes in Osteoporosis Patients

Studies have investigated ways to increase the success rate of dental implant placement for osteoporosis patients with particularly poor bone density. The results of these studies are mixed. Some studies show an increased success rate for osteoporosis patients who undergo bisphosphonate therapy for their condition. However, other studies do not find a significant correlation between bisphosphonate therapy and improved dental implant success (59,60).

- Merheb et al.(61) observed no implant loss in patients with osteoporosis. They also found a reasonable correlation between bone quality and implant stability when comparing osteoporosis and osteopenia patients to a control group(61).

Influence of Vitamin D Supply

- A retrospective study done by Wagner et al.(62) on 30 postmenopausal women proved that vitamin D supplementation has an advantage on peri-implant bone-remodeling(62).
- Several studies(45,46) indicate an increased incidence of premature implant loss in patients with vitamin D deficiency and improved osseointegration with supplementation(45,46).

Positive Osseointegration with Vitamin D Supplementation

- Three studies by Garg et al., Al-Rawee et al. and Piccolotto et al. (51,63,64) described positive osseointegration after vitamin D supplementation. The two latter studies reported no implant loss in the vitamin D deficient group, while the first reported implant loss in the comparison group(51,63,64).

Vitamin D Deficiency and Implant Healing

- Al-Rawee et al. and Piccolotto et al.(63,64) divided their subjects into a vitamin D-deficient group that received supplementation and a control group with normal vitamin D levels. They concluded that low vitamin D levels had a negative influence on healing after implantation(63,64).
- Piccolotto et al.(64) suggested that by supplying patients with vitamin D for eight weeks only increased serum levels without significant changes in clinical parameters(64).

Local Vitamin D Application

- A study using local application of vitamin D during a xenograft procedure showed better ridge augmentation and significantly higher implant stability quotient values in the test group(34).

Vitamin D's Role in Calcium Homeostasis

- An additional reason for the importance of vitamin D is its role in maintaining calcium homeostasis, which indirectly supports bone remineralization and, thus the osseointegration of dental implants(65).

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 and control group (vitamin D <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 (mBI), 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, Agarwal 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%

Table 9: (58)

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, Temmerman A, Rasmusson L. *et al.*[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, *et al.*[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, *et al.*[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.	-

Table 10: (58)

5. Discussion:

This narrative review aims to synthesize and analyze findings from multiple studies on the connection between vitamin D status and outcomes in various oral surgical procedures. By examining these diverse surgical interventions, this review seeks to provide a comprehensive understanding of vitamin D's role in oral surgical outcomes. The analysis considers how vitamin D status may influence factors such as wound healing, postoperative complications, and overall treatment success. This comprehensive approach allows for a broader perspective on the potential impact of vitamin D in oral surgery, offering insights that may be valuable for both clinical practice and future research directions. By consolidating evidence from various oral surgical procedures, this review aims to highlight patterns and consistencies in the relationship between vitamin D and surgical outcomes, potentially informing future treatment protocols and patient care strategies in oral surgery.

The review encompasses several types of oral surgeries, including:

- Third molar extractions
- Periodontal surgeries
- Bone augmentations,
- Simultaneous bone augmentations with dental implants
- Osseointegration of dental implants

5.1 Summary of Results

Third Molar Extraction

Studies examining the benefits of vitamin D on wound healing following third molar extractions are scarce. However, two notable studies researched this relationship further, however showed mixed outcomes(26,27).

Oteri et al. (26) investigated the effect of large quantity intake of vitamin D on post-extraction wound healing after surgical removal of third molars. While their results

showed minimal improvements in most clinical parameters, they did observe a statistically significant reduction in cheek edema at the T3 measurement point. More importantly, the study revealed significant differences in inflammatory indexes. The control group demonstrated reduced levels of inflammatory markers TNF-alpha, IL-1-Beta, and IL-6, which are closely associated with the rate of tissue healing. These findings suggest that vitamin D supplementation might enhance tissue healing after minor surgical procedures, aligning with the objectives of this review(26).

In contrast, Mameledzija et al.(27) failed to demonstrate significant differences in the clinical parameters they measured. However, their study did reveal a slight statistical interaction when comparing edema and trismus measurements between groups with insufficient and deficient vitamin D levels. This suggests that vitamin D status may still play a role in post-operative recovery, even if the effects are subtle (27).

Both studies included subjective pain measurements, quantified by tracking patients' painkiller consumption(26,27). However, these pain assessments may not be directly relevant to the wound healing process due to their subjective nature and the difficulty in establishing a clear correlation. The self-reported and subjective nature of pain levels in these studies make direct comparisons challenging(26,27).

Periodontal Surgery

The study by Bashutski et al. (18) imparts valuable understanding into the role of vitamin D in periodontal surgery outcomes. Their observations indicate that sustaining sufficient vitamin D status in patients might be crucial for optimizing the results of periodontal surgeries. While temporary vitamin D supplementation showed positive effects, patients with adequate vitamin D levels at the start of the study demonstrated superior recovery and regeneration of infrabony defects(18).

In this study(18), patients who received vitamin D supplementation alongside teriparatide treatment exhibited a gradual increase in serum 25(OH)D levels, eventually reaching and maintaining sufficient levels. These patients also showed improved clinical outcomes. However, it's important to note that at the one-year follow-up, vitamin D status did not appear to significantly modify clinical measurements in patients receiving

teriparatide. Nevertheless, there was a trend suggesting slightly less improvement in clinical findings among vitamin D-deficient patients who received teriparatide(18).

This observation raises an interesting question: Is this result due to the limited sample size of the study or does teriparatide treatment potentially mitigate the negative effects of vitamin D deficiency(18)? This research not only supports the hypothesis that vitamin D significantly influences recovery after oral surgeries but also introduces the possibility that its effects may be modulated or enhanced when combined with other supplements or medications. These findings pave the way for future studies to explore optimal supplementation strategies that could potentially improve outcomes in oral surgery.

Future studies with larger patient cohorts may help clarify whether teriparatide can indeed compensate for vitamin D deficiency in the context of periodontal surgery outcomes, or if the observed trend is merely a statistical artifact due to the small sample size.

It is crucial to emphasize that throughout the literature review conducted for this thesis, the study by Bashutski et al.(18) stands out as the sole research explicitly examining the relationship between vitamin D status and periodontal surgery outcomes (18).

The scarcity of research in this specific area highlights a critical need for further investigation. While this single study by Bashutski et al.(18) presents meaningful conclusions, it also raises numerous questions that remain unanswered. In order to find out the broader implications of vitamin D in periodontal surgery, more evidence is required.

This knowledge gap also raises several discussions such as: whether the findings of Bashutski et al. (18) can be validated, if the results resemble in various types of periodontal surgeries, potential interactions between vitamin D and other factors influencing surgical outcomes (experience of the operator, patient selection, dental hygiene, aftercare, patient compliance etc.) and if vitamin D has positive long-term effects periodontal health post-surgery.

Bone Augmentation

Schulze-Späte et al.(33) demonstrated that although there was no significant difference in volume and amount of bone graft material with vitamin D-sufficiency patients, they observed a notable distinction in cellular activity. Specifically, patients with sufficient vitamin D levels exhibited a higher number of osteoclasts surrounding the bone graft material compared to those with vitamin D deficiency(33).

It's important to note that this study utilized a combination of β-tricalcium phosphate and autogenous bone as graft materials. The choice of graft material is a crucial consideration, as β-tricalcium phosphate has a lower biodegradation rate compared to autogenous bone(33). This difference in material properties could potentially influence the bone turnover process and, consequently, the study outcomes and the research question of this review.

Simultaneous Bone Augmentation with Dental Implants

Ahmed Elsayed(34) conducted a clinical trial to find out the effects of vitamin D3 supply in bone graft material used for alveolar ridge augmentation during dental implant placement. The results demonstrate that the study group, which received bone graft material enriched with vitamin D3, exhibited significantly higher mean values for both buccolingual ridge width and implant stability quotient compared to the control group(34).

In contrast to the methodology employed by Schulze et al.(33), Ahmed Elsayed(34) utilized preformed and pretrimmed titanium mesh to stabilize the xenograft material mixed with vitamin D3. The author also emphasized the importance of using such specially prepared titanium mesh, as it minimizes the risk of sharp edges that could potentially irritate the surgical site and impede the wound healing process(34).

It's crucial to note that Ahmed Elsayed(34) specifically focused on patients undergoing simultaneous alveolar augmentation with dental implant placement(34). This targeted approach underscores the significance of careful patient selection, material selection and highlights the importance of having an experienced operator to ensure optimal outcomes.

Ahmed Elsayed also claimed in his study(34) that the combined single surgery, where the alveolar augmentation and implant placement was performed at once, not only helps the patients to avoid having to go through 2 surgeries, but also shows better prognosis. He mentioned that the majority of graft resorption happens shortly after the grafting procedure and the bone surrounding functional dental implants tends to be preserved better(34). Whereas Schulze-Späte et al.(33) chose to perform separate surgeries and focused more on exploring detailed insights. However, it is worth noting that the indications must be examined individually in choosing the surgical methods in order to aim for optimal outcomes.

Furthermore, it's crucial to recognize that Schulze-Späte et al. (33) administered vitamin D to patients systemically, whereas Ahmed Elsayed(34) focused on local cellular activity around the graft site. The research does not directly address the systemic effects of vitamin D levels on bone augmentation procedures(34). This localized perspective, while valuable, leaves open questions about how overall vitamin D status might influence broader aspects of bone healing and regeneration throughout the body. The author chooses to directly incorporate vitamin D3 into the bone augmentation procedure, rather than assessing pre-existing vitamin D levels in patients(34). This methodology shifts the focus from systemic vitamin D status to the local application of vitamin D3 as a potential enhancer of bone augmentation outcomes. This might be advantageous to benefit from the positive effects of vitamin D without having to increase the serum vitamin D levels of participants which usually takes longer time.

The study also explores the potential correlation between bone density, bone quality, and implant stability(34). The author mentioned that superior bone density might not necessarily contribute to enhanced implant stability, a relationship that has been suggested in different research, suggesting that vitamin D might have a positive influence in tissue healing, but might not result in better implant stability(53).

Osseointegration of dental implants

Kwiatek et al.(40) revealed that the patients who had sufficient baseline vitamin D levels without any supplementation demonstrated even better outcomes in terms of bone levels at the implant site. This suggests that having an adequate vitamin D status from the

outset may be more beneficial for alveolar bone health around dental implants compared to providing vitamin D3 supplementation only during the procedure. The study highlights the importance of considering the patient's baseline vitamin D levels when planning and executing alveolar ridge augmentation procedures in conjunction with dental implant placement. Ensuring sufficient vitamin D status before the surgery may lead to optimal bone formation and implant integration(40).

The study(40) in question, while informative, raises several important points of discussion regarding its methodological validity. Two key issues merit particular attention. Firstly, the administration of vitamin D supplementation relied entirely on patient compliance. Participants were provided with vitamin D supplements to take at home, without direct supervision or a reliable method to verify adherence. This approach introduces a potential source of variability and uncertainty into the study's results, as the actual intake of vitamin D could not be accurately controlled or measured. Secondly, the timing of the study presents another consideration. The research was conducted after the period when patients would typically have had maximum sun exposure. While this timing might have been intentional to establish a baseline, it introduces a confounding factor. The varying status of UV contact among participants in the preceding months could have significantly influenced their serum vitamin D levels at the time of the study(40).

These factors highlight the complex nature of vitamin D research in clinical settings. Sun exposure, a natural source of vitamin D, is challenging to standardize across participants due to individual lifestyle differences, geographical location, and seasonal variations. Moreover, the reliance on self-administered supplementation without direct oversight introduces an element of uncertainty regarding dosage consistency. Future studies in this area might benefit from more rigorous controls, such as supervised vitamin D administration or more frequent check-ins to ensure compliance, detailed documentation of participants' sun exposure habits, conducting the study over a longer period to account for seasonal variations in sun exposure and utilizing more frequent serum vitamin D level measurements to track changes over time.

While the retrospective study of Mangano et al.(44) failed to demonstrate a statistical significance between vitamin D deficiency and EDIFs, it did suggest a tendency in higher EDIFs in vitamin D deficient patients(44).

It's important to acknowledge the inherent limitations of retrospective studies, which typically cannot draw as definitive conclusions as prospective investigations. However, this study's strengths lie in its rigorous patient selection criteria and precise definition of early implant failure. By defining EDIFs as those occurring within four months of implant placement and before prosthetic loading, the researchers effectively minimized potential confounding factors. Several methodological aspects enhance the study's reliability such as consistent use of implant materials across all cases, all procedures performed by the same operator and exclusion of patients with conditions that could affect outcomes, such as diabetes mellitus, immunodeficiencies, bleeding disorders, or history of radiotherapy and chemotherapy(44).

Despite these strengths, some limitations persist. The study(44) did not examine the effects of vitamin D supplementation on bone quality and did not differentiate between the patients who received single or multiple implants, which might show a different rate in EDIF(44). Furthermore, the research(44) did not explore the aspect of patient compliance with post-implant care and dental hygiene routines across the large sample size of 885 patients(44).

5.2 Limitations of Included Studies

The decision to focus exclusively on human-based research significantly narrowed the pool of relevant studies, underscoring the need for more comprehensive clinical investigations in this field.

Mameledzija et al.(27) and Oteri et al.(26), with their comparable methodologies, exemplify the strengths and challenges inherent in clinical studies. The prospective study design offers distinct advantages, primarily the ability to conduct close monitoring and precise observations of participants. This approach allows researchers to gather real-time, directly relevant data on the effects of interventions or treatments. The findings

derived from these clinical studies hold relevance due to their direct observation of outcomes in a controlled setting. They provide conclusions into the immediate and short-term effects of the interventions under investigation. This real-world applicability is a key strength of the clinical study model.

Nevertheless, the design also presents limitations, particularly when considering long-term follow-ups and large-scale cohort studies. The intensive nature of clinical studies makes it challenging to maintain consistent monitoring and data collection over extended periods or across large participant groups. These constraints can restrict the scope of the research and limit the generalizability of findings to broader populations or longer time frames.

However, in comparison of these two studies, Oteri et al.(26) stand out for their larger sample size with 72 patients, which is more than triple number of probands studied by Mameledzija et al.(27). Moreover, Oteri et al.(26)'s investigation demonstrates a more comprehensive approach by incorporating both clinical and biochemical parameters in their assessment. This allows for a deeper exploration of the physiological processes underlying the observed clinical outcomes than the study conducted by Mameledzija et al.(27).

Bashutski et al.(18), Ahmed Elsayed and Schulze-Späte et al.(33) share common strength and limitations as aforementioned studies. However, in these studies, it is worth mentioning that the surgical procedures done in these studies, such as periodontal surgery, maxillary sinus augmentation and alveolar bone augmentation, might benefit more from long-term follow-ups than third molar extractions.

Kwiatek et al.(40) and Mangano et al.(44) have chosen the retrospective type of study to explore the influence of vitamin D in surgical procedures. They were therefore able to go through a much bigger number of cohorts without the logistical difficulties and resources. However, in retrospective studies, it is difficult to control confounding variables, such as close and frequent patient observations and examinations. It is also difficult to conclude the direct relationship between the cause and effect definitively.

A notable challenge encountered was the widespread prevalence of vitamin D deficiency, even in areas with abundant availability of UV contact, such as southern Italy(26). Consequently, majority of studies have been done on initially vitamin D-deficient or insufficient individuals who received supplementation during the study period. This approach has resulted in a shortage of data on surgical outcomes in individuals maintaining sufficient serum vitamin D levels over extended periods(26,27).

It's worth noting that the studies reviewed in this work employed diverse approaches to vitamin D administration. These ranged from merely measuring serum vitamin D levels without supplementation to administering high preoperative doses, applying vitamin D locally at the surgical site, or providing supplementation over six weeks. This variability introduces additional complexity, as results may differ between local and systemic administration and across different supplementation durations. Furthermore, to achieve unbiased outcomes, it's crucial to monitor various factors influencing vitamin D levels, including patients' sun exposure habits, seasonal variations, medications, and maybe even dietary habits that affect vitamin D absorption. More precise and frequent monitoring could also help mitigate these variations and enhance the reliability of results.

There is also a notable scarcity of research examining vitamin D's influence across different types of oral surgeries. For instance, Bashutski et al.(18) focused on periodontal surgery, using a single surgical technique(18). In order to be able to explore the influence of vitamin D on oral surgeries, more sample collection in various surgeries is needed.

Moreover, it is crucial to consider patients' general health, as pathologies and systemic diseases may influence vitamin D absorption or bone metabolism. Patients undergoing or who underwent chemotherapy, radiotherapy, or taking medications that pose risks for jaw necrosis may not yield valid results in such studies.

Lastly, some studies combine vitamin D supplementation with other medications, such as teriparatide (18,33). In these cases, further research is needed to determine whether concomitant medications might overshadow the effects of vitamin D on surgical outcomes.

6. Conclusion

After reviewing numerous literatures, the consistent emphasis on the critical role of vitamin D in wound healing across various surgical procedures has been reiterated. However, the initial challenges faced in this work were manifold, such as the limited number of human studies in different surgical procedures other than implantations and the general high prevalence of vitamin D deficiency throughout the population worldwide.

Furthermore, exploring the possible synergistic influence of vitamin D with other supplements or medications would be highly informative, as suggested in one of the studies reviewed(18). This could provide valuable insights into optimizing the benefits of vitamin D in surgical contexts. Despite the overwhelming evidence supporting the importance of vitamin D, it appears that the dental community has not fully embraced its significance. Vitamin D plays a crucial role, starting in the early days of life and odontogenesis in children, preventing caries in permanent dentition. It might even have a more detrimental impact than smoking on osseointegration after implantation(18).

While not definitive, this review's results highlight the potential importance of considering vitamin D status when planning and executing dental implant procedures. Ensuring patients have satisfactory vitamin D status from diets, supplements, or increased contact with UV radiation may help reduce the risk of early implant failures and promote successful osseointegration. Incorporating vitamin D screening and optimization into standard implant treatment protocols could be a simple yet impactful way to improve patient outcomes. Further research with larger sample sizes and more robust study designs is needed to confirm these findings and establish clear guidelines for incorporating vitamin D considerations into different oral surgical procedures and general dental care.

To conclude, further research with larger participant cohorts is required to obtain more definitive and unambiguous results. Additionally, to improve overall oral health, dentists must embrace vitamin D's vital role and guide patients on optimizing their vitamin D status for better treatment outcomes.

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