

Eduardo Tallon

**Can vitamin D levels influence bone metabolism and osseointegration of dental implants? – Umbrella Review**

Universidade Fernando Pessoa

Porto, 2023



Eduardo Tallon



**Can Vitamin D levels influence bone metabolism and osseointegration of dental implants? – Umbrella Review**

Universidade Fernando Pessoa

Porto, 2023

Eduardo Tallon

**Can vitamin D levels influence bone metabolism and osseointegration of dental implants? – Umbrella Review**

I certify the originality of the work,



---

Eduardo Tallon

(Signature)

Master's dissertation, presented to the Fernando Pessoa University as part of the requirements for obtaining the master's degree in Dentistry, under the guidance of Professor Paulo Macedo, in 2023.

## **ABSTRACT**

**Introduction:** Due to the large amount of scientific evidence on the subject and the limitations and incongruities in previous reviews, the primary aim of this umbrella review was to gather all the information regarding the importance of vitamin D levels in the osseointegration of dental implants.

**Methods:** The literature search was performed in PubMed, Web of Science, CINAHL Plus, Cochrane Library, and Academic Search Complete throughout the search expression ["vitamin D" AND ("dental implant" OR "dental implants")].

**Results:** The initial search yielded 351 results but at the end of the process only five Systematic Reviews were selected.

**Conclusions:** vitamin D seems to have a positive effect on the osseointegration of dental implants and on the reduction of dental implant failures, however it is recommended that future studies take into account the limitations mentioned in this study, in order to increase the validity and quality of scientific evidence on the subject.

**Keywords:** Bone metabolism; Dental implants; Dentistry; Osseointegration; vitamin D.

## RESUMO

**Introdução:** Devido à grande quantidade de evidência científica sobre o tema e às limitações e incongruências nas revisões anteriores, o objetivo principal desta revisão guarda-chuva foi reunir todas as informações sobre a importância dos níveis de vitamina D na osteointegração dos implantes dentários.

**Métodos:** A pesquisa foi realizada na PubMed, Web of Science, CINAHL Plus, Cochrane Library e Academic Search Complete, através da expressão de pesquisa ["vitamin D" AND ("dental implant" OR "dental implants")].

**Resultados:** A pesquisa inicial originou 351 resultados, no entanto, no final do processo, apenas cinco Revisões Sistemáticas foram selecionadas.

**Conclusões:** A vitamina D parece ter um efeito positivo na osteointegração de implantes dentários e na redução do insucesso dos mesmos, porém é recomendado que futuros estudos considerem as limitações mencionadas neste estudo, a fim de aumentar a validade e a qualidade da evidência científica sobre o tema.

**Palavras-chave:** Implantes dentários; Medicina Dentária; Metabolismo ósseo; Osteointegração; vitamina D.

## **ACKNOWLEDGEMENTS**

First of all, I would like to thank Professor Paulo Macedo, for his commitment, guidance and follow-up throughout this journey.

To Professor Paulo Gomes and Professor Elisa Gomes da Costa, for the availability they always demonstrated on all occasions.

To my wife, girlfriend and partner, Marta Pinto, who always believed and was tirelessly present in all the difficult moments of my entire academic career without ever letting me give up. I love you.

To my father, for all the hours we spent on the phone and for always making me believe that it would be "in an instant".

To my mother, for always believing in me.

To my brothers, for all the moments and efforts to shorten the distance.

To my friends and colleagues, Filipa Fonseca and Sofia Meneses, for all the affection, time and patience dedicated in the most complicated moments.

To my friend and colleague Nuno Macedo for all the laughs and sleepless nights.

To all other colleagues and Professors at this institution, as they all, in some way, contributed to this special day.

## INDEX

I. INTRODUCTION.....	1
II. MATERIALS AND METHODS.....	6
1. Study Design.....	6
2. Search Strategy .....	6
3. Eligibility Criteria.....	6
4. Study Selection .....	6
5. Methodological Quality Assessment .....	7
6. Data extraction and analysis .....	8
III. RESULTS.....	9
1. Study Selection.....	9
2. Methodological Quality .....	10
3. Characteristics of the Included Studies .....	11
4. Outcome Measure Analysis.....	19
IV. DISCUSSION .....	23
V. CONCLUSION.....	27
VI. BIBLIOGRAPHIC REFERENCES .....	28

## **INDEX OF TABLES**

Table 1: Characteristics of the excluded studies .....	10
Table 2: Methodological quality of the included SR.....	11
Table 3: Characteristics of the included SR .....	11
Table 4: Characteristics of the studies included in the 5 SR selected by this umbrella review .....	17

## **INDEX OF FIGURES**

Figure 1: Recommendations for prevention of vitamin D deficiency in adults .....	2
Figure 2: Recommendations for treatment of vitamin D deficiency in adults .....	2
Figure 3: Algorithm for vitamin D deficiency screening and treatment .....	3
Figure 4: Literature selection process, according to the PRISMA statement.....	9

## INDEX OF ABBREVIATIONS

<b>Abbreviation</b>	<b>Definition</b>
<b>BIC</b>	Bone-to-implant contact
<b>EDIF</b>	Early dental implant failure
<b>JBI</b>	Joanna Brigs Institute
<b>MA</b>	Meta-Analysis
<b>PRISMA</b>	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
<b>RCT</b>	Randomized-Controlled Trial
<b>SR</b>	Systematic Review

## I. INTRODUCTION

### *Vitamin D*

Vitamin D is a fat-soluble vitamin and its name refers to both vitamin D2 (Ergocalciferol) and vitamin D3 (Cholecalciferol). Vitamin D2 comes from the Ultra Violet-B irradiation of Ergosterol, a steroid found in some plants and, mainly, fungi (vegetable origin) and vitamin D3 is synthesized through Ultra Violet irradiation in the skin of animals and humans (animal origin) (Tripkovic et al., 2012). Furthermore, foods like egg yolks, fatty fish and fish liver oil are rich in vitamin D3 (Pludowski et al., 2018) however, nutrition is usually only a minor source of it (Pilz et al., 2018).

Both function as prohormones and are used identically by the body. They are transformed through two enzymatic hydroxylation reactions, in the liver and in the proximal renal tubule (Christakos et al., 2016), into their most active form – 1,25-dihydroxyvitamin D2 or D3 (Merchan et al., 2017).

In addition to other functions related to other systems, vitamin D regulates calcium phosphate homeostasis and bone mineral metabolism (Halfon et al., 2015), stimulating the production of osteoblastic bone matrix and optimizing bone remodeling (Kogawa et al., 2010). It increases intestinal calcium absorption, leading to a reduction in parathyroid hormone secretion and less systemic bone resorption, with a possible inhibition of osteoclastogenesis (Choukroun et al., 2014).

In this way, vitamin D is associated with cancer, heart disease, high blood pressure, diabetes, arthritis and others but is mainly crucial for musculoskeletal health. It's well recognized that prolonged vitamin D deficiency is detrimental to the skeleton and may lead to bone loss (Spiro and Buttriss, 2014).

Despite the existing knowledge regarding the importance of vitamin D, there are still a high inconsistency in the definition of vitamin D values. The US Institute of Medicine considers that people with a serum value  $< 12$  ng/mL (30 nmol/L) are at risk of vitamin D deficiency, considers serum levels between 12 and 20 ng/mL as corresponding to a risk of insufficiency, and levels above ( $\geq$ ) 20 as being sufficient (Ross et al., 2011; Duarte et al., 2020). The Endocrine Society, together with European Calcified Tissues Society, International Osteoporosis Foundation or American Geriatrics Society established the threshold of deficiency at  $\leq 20$  ng/mL (50 nmol/L) and designates levels  $\leq 10$  as severe deficiency (Holick et al., 2011; Bouillon, 2017; Lips et al., 2019; Duarte et al., 2020). The

Review

Endocrine Society determines that only levels  $\geq 30$  ng/mL are to be considered normal, designating levels between 21 and 29 ng/mL as insufficient (Holick et al., 2011).

In Portugal, the estimated national prevalence of vitamin D  $\leq 10$  ng/mL and  $< 20$  ng/mL is 21.2% and 45.4% respectively. Only 33.4% of the adult population presents values  $\geq 20$  ng/mL and no more than 3.6% present values  $\geq 30$  ng/mL (Duarte et al., 2020).

Figures 1 and 2 provide an overview of guideline recommendations, with a focus on Central and Eastern European countries, for prevention and treatment of vitamin D deficiency, respectively, put together by Pludowski et al. (2022).

Authority and/or Country or Region (Year)	Target Population	Age (Years)	Oral Vitamin D (IU)
Endocrine Society (2011) USA	General population	19–70	600–2000/day
	Pregnant and lactating women	>70	800–2000/day
	Obese individuals/Patients on anticonvulsants, glucocorticoids, antifungals, AIDS medications		600–2000/day
DACH (2012) Germany/Austria/Switzerland	General population	>18	800/day
EVIDAS (2013) Central Europe	General population	>18	800–2000/day
	Obese individuals and elderly		1600–4000/day
	Prevention of pregnancy and fetal development complications Night workers and dark skin pigmentation	>16	1500–2000/day
EFSA (2016) Europe	General population	>18	1000–2000/day
			600/day

Figure 1: Recommendations for prevention of Vitamin D deficiency in adults.

Authority and/or Country or Region (Year)	Target Population	Oral Vitamin D for Treatment (IU)	Treatment Duration	25(OH)D Target Concentration nmol/L (ng/mL)	Oral Vitamin D for Maintenance (IU)
Endocrine Society (2011) USA	General population	50,000/week or 6000/day			1500–2000/day
	Obese individuals/Patients on anticonvulsants, glucocorticoids, antifungals, AIDS medications	2–3 times more; at least 6000–10,000/day	8 weeks	75 (30)	3000–6000/day
EVIDAS (2013) Central Europe	General population	50,000/week or 7000–10,000/day	4–12 weeks	75–125 (30–50)	a maintenance dose may be instituted

Figure 2: Recommendations for treatment of vitamin D deficiency in adults.

Based on all guideline recommendations and on Pludowski et al. (2022)’s consensus statements, an algorithm for the prevention and treatment of vitamin D deficiency was developed (Figure 3).

Review

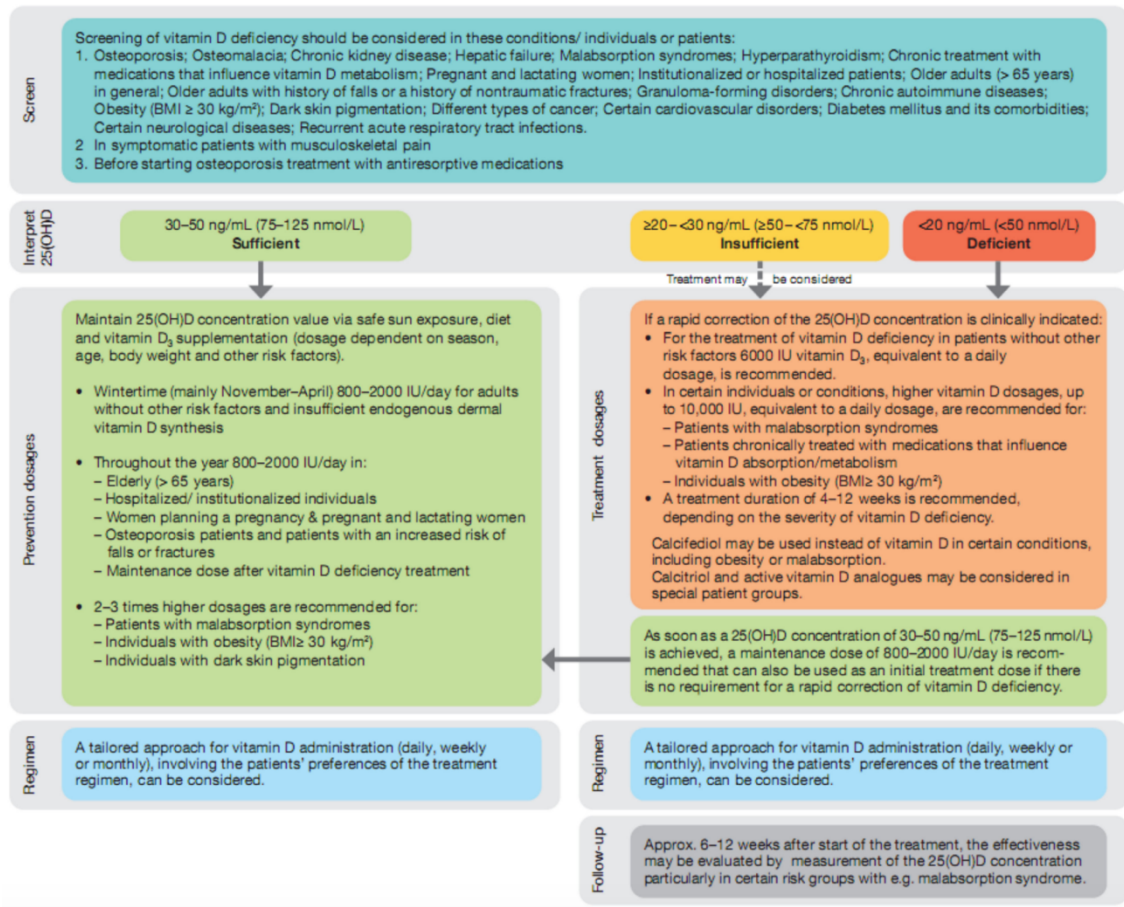


Figure 3: Algorithm for Vitamin D deficiency screening and treatment.

**Bone Metabolism**

Bone formation occurs through the processes of endochondral ossification and intramembranous ossification (Chen et al., 2012). During the first one, the mesenchymal cells differentiate into chondrocytes – chondrogenesis –, responsible for the formation of the cartilage growth plate that is gradually replaced by bone (Estrada et al., 2011). Most of the bones of the human skeleton (long, short and irregular bones) are formed through this process (Beederman et al., 2013). The remaining bones are formed by intramembranous ossification. In this process, mesenchymal stem cells differentiate directly into osteoblasts – osteoblastogenesis (Yang et al., 2012).

In order to preserve the strength and integrity of the bone, it must be constantly replaced. Bone formation, by osteoblasts, produces organic bone matrix, and bone resorption, by osteoclasts, dissolves bone mineral and extracellular matrix. In this way, osteogenesis and angiogenesis are two closely associated processes that are involved in bone growth, remodeling and repair (Crockett et al., 2011).

The success of the osseointegration processes largely determines the perceived bony and the state of bone remodeling plays a significant role in maintaining optimal quantitative and qualitative characteristics of the jaw bones (Yanushevich et al., 2014).

To date, the gold standard in the evaluation of bone microarchitectonics is with histomorphometric study (Mkrtumyan et al., 2020).

### ***Dental Implants***

The dental implant is made of alloplastic materials and is implanted in the oral tissues below the mucosa and/or periosteum and/or within the bone, with the aim of providing retention and support for a fixed or removable dental prosthesis (Gupta et al., 2022).

Currently, therapy with dental implants is a treatment option for total or partial edentulism (Aslan, 2018; Ogawa et al., 2022). Its performance is indicated in partially edentulous patients who have intermediate gaps or free-end edentulism; when a patient is not satisfied with the conventional, unstable, non-retentive full denture or in situations where it is intended to preserve the existing removable partial dentures (Grisar et al., 2017).

It has advantages over conventional fixed partial dentures. It has a high success rate (over 97%), low risk of developing caries and endodontic problems of adjacent teeth, better maintenance of bone in the edentulous site and less sensitivity of adjacent teeth (Gupta et al., 2022).

Over an observation period of 10 years, a survival rate of 85-95% can be estimated and in 5% the absence of primary implant integration results in implant failure (Staedt et al., 2020).

Dental implant failure can occur early – associated with impaired bone healing (Mohajerani et al., 2017) – or late – after a latency of six months (Lin et al., 2018). Early failure is due solely to biological complications that usually involve soft and hard tissue resorption (Do et al., 2020).

There are many risk factors that can be associated with DIF such as iatrogenic, material-associated, patient-related and systemic factors (Staedt et al., 2020).

Mainly in the last five years, the existing literature on the influence of vitamin D on the osseointegration of dental implants has been increasing, however, there are still studies that argue that there is not enough evidence to establish a correlation or causal relationship between the two factors (Schulze-Späte et al., 2016).

Considering the existence of inconsistent information and the increase in the publication of Systematic Reviews (SR) on the subject, this document aims to summarize all the

Review

information regarding the importance of vitamin D levels in bone metabolism and, consequently, in the osseointegration of dental implants, gathered by SR, identify the most common and significant failures found in them, present the respective conclusions and future suggestions, in order to guide and establish a new starting point in the development of future studies.

## **II. MATERIALS AND METHODS**

### **1. Study Design**

This document consists of an umbrella review that is a review and a qualitative analysis of all the information documented only in SR regarding the influence of vitamin D levels on bone metabolism and consequent success of osseointegration of dental implants.

This umbrella review was carried out from January to April 2023, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021).

Before the start of the review, its protocol was developed and registered in the Open Science Framework (DOI: <https://doi.org/10.17605/OSF.IO/EQVGD>).

### **2. Search Strategy**

The existing literature search was performed in five databases, PubMed, Web of Science, CINAHL Plus, Cochrane Library, and Academic Search Complete.

The entire search strategy was developed by two researchers, independently, and the search expression used was, ["vitamin D" AND ("dental implant" OR "dental implants")]. All terms used in the search expression correspond to Medical Subject Headings.

The "advanced search" method was selected, the fields defined in the search "All fields" in PubMed and Web of Science and "Full text" in the Cochrane Library, CINAHL Plus and Academic Search Complete.

No limitation was established on the year of publication of the studies.

### **3. Eligibility Criteria**

As inclusion criteria, the following were defined: (i) SR or MA; (ii) SR or MA of studies that assess the influence of vitamin D on bone metabolism and, consequently, on the osseointegration of dental implants; (iii) SR or MA of studies performed in humans or animals; (iv) SR or MA published in Portuguese, English or Spanish.

As exclusion criteria, the following were defined: (i) SR or MA of studies that only include humans or animals with pathology; (ii) abstracts and commentaries; (iii) irrelevant outcome; (iv) duplicated or incomplete data.

### **4. Study Selection**

The study selection was carried out by two researchers independently.

After searching all published studies corresponding to the established keywords, all duplicates were eliminated.

In the next phase, the remaining studies were analyzed, by reading the title and abstract, where most of them were eliminated.

Subsequently, the full texts of the SR selected and not eliminated in the previous phase were obtained and analyzed through their complete reading, always taking into account the established eligibility criteria.

At the end of the article selection process, an analysis of the lists of bibliographic references of the SR included so far was made in order to identify any additional SR that met the eligibility criteria.

This first phase was carried out in January 2023 and, in March of the same year, the entire process was repeated, in order to ensure that the umbrella review encompasses all published literature until its completion.

In each of these phases, meetings were scheduled to discuss the process and reach an agreement in situations of doubt and/or disagreement.

## **5. Methodological Quality Assessment**

The evaluation of the methodological quality of the included SR was carried out by two researchers independently, and it was used The Joanna Briggs Institute (JBI) instrument for Systematic Reviews (Joanna Briggs Institute, 2017; Aromataris et al., 2015).

The choice of instrument considered the fact that the SR included other study designs in addition to RCT.

The purpose of this critical appraisal is to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. This tool produces decision-making that considers the feasibility, appropriateness, meaningfulness, and effectiveness of healthcare practice. There are 11 questions to guide the appraisal of SR or MA and each one has to be answered as “yes”, “no”, or “unclear”. “Not applicable” is also provided as an option and may be appropriate in rare instances (Aromataris et al., 2015).

Meetings were scheduled to discuss the process and reach an agreement in situations of doubt and/or disagreement.

## **6. Data extraction and analysis**

This step was also carried out by two researchers.

Review

In a first phase, all main data were identified and placed in a table divided by author(s) and year of the SR, aims of the study, research strategy used, design and number of primary studies included (by the five included SR), number and characteristics of the sample of primary studies, risk(s) of bias, methodological quality and authors' conclusions (Table 2).

Subsequently, whenever possible, the remaining data were analyzed and compared, throughout the text.

### III. RESULTS

#### 1. Study Selection

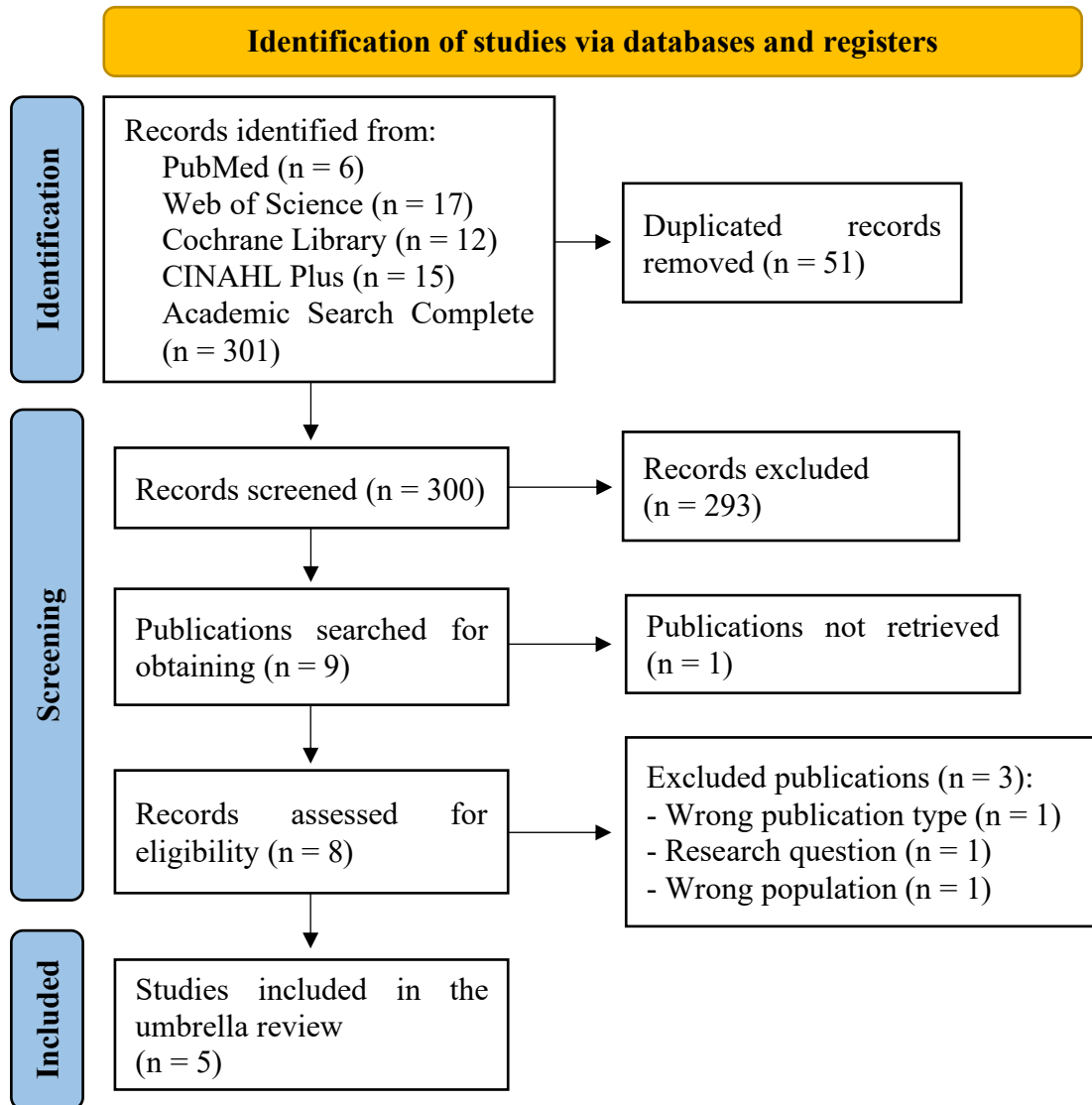


Figure 4: Literature selection process, according to the PRISMA statement.

The initial research, through the five databases, yielded 351 results but after removing the duplicates (51) it boiled down to 300 different studies.

In the second stage, after reading the titles and abstracts, most of the studies were eliminated (292).

In the third stage, only one study was eliminated due to impossibility of access.

In the fourth stage, through the full reading of the remaining studies, three more were eliminated.

In the last phase of the study selection process, no study was eliminated. Thus, five SR were included in this umbrella review.

Figure 4 represents the entire literature selection process (Page et al., 2021).

Table 1 shows the characteristics of the excluded studies in the last selection phase.

Table 1: Characteristics of the excluded studies.

Author, year	Exclusion criteria
<b>Javed et al., 2016</b>	The location of the implants does not correspond to the intended location in this study.
<b>Insua et al., 2017</b>	The SR does not answer the question of the present umbrella review.
<b>Blasco et al., 2019</b>	It is a Narrative Review and not a SR.

After analyzing all the bibliographic references of the five included SR, no additional SR was found. The SR included in this umbrella review were published between 2021 and 2022 (Hakim et al., 2021; Makke, 2022; Alsulaimani et al., 2022; Werny et al., 2022; Bazal-Bonelli et al., 2022).

## 2. Methodological Quality

The final score of the SR included varied between 4 (Makke, 2022) and 9 (Bazal-Bonelli et al., 2022), corresponding to low and high methodological quality, respectively. The other authors had moderate – 6 (Hakim et al., 2021) – and high – 7 (Werny et al., 2022); 8 (Alsulaimani et al., 2022) – methodological quality (Table 2 and 3).

The most frequently satisfied critical items were items 4, 8, 10 and 11, and the least frequently satisfied were items 6 and 7.

Item 6 can be related with “lack of a risk of bias assessment” bias and item 7 can be related with “selective outcome reporting” bias.

Item 9 is not applied in any of the SR since none of them performed a MA.

Table 2: Methodological quality of the included SR.

Authors/ Items	Hakim et al., 2021	Makke, 2022	Alsulaimani et al., 2022	Werny et al., 2022	Bazal-Bonelli et al., 2022	TY
1	N	N	Y	Y	Y	3 (60%)
2	Y	N	Y	Y	Y	4 (80%)
3	Y	N	Y	Y	Y	4 (80%)
4	Y	Y	Y	Y	Y	5 (100%)
5	U	N	Y	N	Y	2 (40%)
6	U	N	N	N	N	0 (0%)
7	N	N	N	N	Y	1 (20%)
8	Y	Y	Y	Y	Y	5 (100%)
9	NA	NA	NA	NA	NA	NA
10	Y	Y	Y	Y	Y	5 (100%)
11	Y	Y	Y	Y	Y	5 (100%)
<b>TY</b>	6 (54.5%)	4 (36.4%)	8 (72.7%)	7 (63.6%)	9 (81.8%)	

### 3. Characteristics of the Included Studies

Table 3: Characteristics of the included SR.

Author, year	Aims	Search Strategy	SR Included/ Sample	Risk of Bias	Authors' Conclusions	JBI Score
<b>Hakim et al., 2021</b>	To evaluate the associatio n between vitamin D and EDIF.	PubMed, Scopus, Web of Science, Cochrane and EMBASE. Study selection performed by two authors, independently. It's not mentioned by how many researchers the data extraction is performed. Referred keywords.	Nine human studies (cross- sectionals, case reports, case controls and one RCT) and three animal studies.	----	It is difficult to conclude the association between vitamin D and EDIF based on the current research in the literature because of the inconsistent findings. However, the authors hypothesize that the vitamin D may play a role in	6/11

Review

		Assessment of methodological quality not mentioned.			improving implant success through its effects on the immune system modulation.	
<b>Makke, 2022</b>	To investigate the available literature regarding vitamin D supplementation and dental implant osseointegration.	PubMed, Scopus, ResearchGate and Google Scholar. It is not mentioned by how many researchers the study selection and data extraction is performed. Referred keywords. Assessment of methodological quality not mentioned.	Five human studies (retrospective, case series and case reports) and six animal studies.	----	Additional prospective clinical studies and case reports such as studies with specific inclusion and exclusion criteria are required to determine the association between serum vitamin D levels and osseointegration and to isolate vitamin D levels as the only factor tested.	4/11
<b>Alsulaimani et al., 2022</b>	To investigate the relationship between low serum levels of vitamin D and EDIF and determine the amount of vitamin D that can	PubMed, Directory of Open Access Journals and Web of Science. It is not mentioned by how many researchers the study selection and data extraction is performed. Referred keywords. Assessment of methodological quality not mentioned.	Six human studies (case-controls, case reports and reviews).	----	It is difficult to find a direct relation or causality between the low serum vitamin D level and EDIF, however it may play an important role in its success because of vitamin D in modulating the immune system and healing process.	8/11

Review

	affect the implant survival rate.					
<b>Werny et al., 2022</b>	To review the available evidence to evaluate the efficacy of vitamin D supplementation or vitamin D depletion on the osseointegration of implants in animals and humans.	PubMed/Medline, Cochrane Library and Google Scholar. Study selection was performed by one researcher, but it is not mentioned by how many researchers data extraction is performed. Referred keywords. Assessment of methodological quality not mentioned.	Five human studies (case-controls, case reports and reviews) and 13 animal studies.	----	vitamin D deficiency seems to have a negative effect on the osseointegration of implants in animals and the supplementation appears to enhance it in animals with vitamin D. However, it does not appear clear evidence that supports the hypothesis that humans similarly benefit from vitamin D supplementation in terms of osseointegration.	7/11
<b>Bazal-Bonelli et al., 2022</b>	To investigate the relationship between serum vitamin D levels and dental implants in	PubMed/Medline, Cochrane Library, Scopus and Web of Science. Study selection and data extraction was performed by two researchers, independently. Referred keywords.	Four human studies (retrospective cross-sectional and RCT).	Clear Assessment of methodological quality of primary studies.	It appears that serum vitamin D levels in patients may play a relevant role in osseointegration, marginal bone loss and dental implant survival. In this way, it is advisable to determine	9/11

Review

terms of survival rates, marginal bone loss, and associated complications.	The Cochrane Handbook of Systematic Reviews and Interventions was used to assess the risk of bias of RCT, and the Newcastle-Ottawa scale was used to assess the quality of others.			the vitamin D level of each patient before placing dental implants and to provide vitamin D supplementation, when necessary.
--	--	--	--	--

As seen in the eligibility criteria and in the previous table, SR that analyzed studies with any type of study design were included, due to the small amount of RCT published on the subject, as perceived in the preliminary research.

The sum of primary studies, included in the five SR, corresponds to 51 studies, of which 22 are duplicates. Of the remaining 29, only eight primary studies, published between 2014 and 2021, met the eligibility criteria and therefore moved on to the qualitative analysis phase (Table 4). Makke (2022) and Bazal-Bonelli et al. (2022) included three of them, Hakim et al. (2021) and Werny et al. (2022), included four of them, and Alsulaimani et al. (2022) included five of the eight studies.

Hakim et al. (2021) and Bazal-Bonelli et al. (2022) included two cross-sectional studies (Mangano et al., 2016; Mangano et al., 2018), Hakim et al. (2021), Makke (2022), Alsulaimani et al. (2022) and Werny et al. (2022) included one case report (Fretwurst et al., 2016), Alsulaimani et al. (2022) included two reviews (Choukroun et al., 2014; Nastri et al., 2020), Hakim et al. (2021) and Bazal-Bonelli et al. (2022) included two RCT (Garg et al., 2020; Kwiatek et al., 2021) and Hakim et al. (2021), Makke (2022) and Werny et al. (2022) included one animal study (Salomó-Coll et al., 2016).

Through this analysis, it was noticed that none of the SR included all the existing primary studies on the literature. All of them included studies with main objectives not corresponding to our own (Pereira and Alvim-Pereira, 2019; Alvim-Pereira et al., 2008; Wagner, 2017), studies whose implants were placed in other parts of the body, such as in tibia (Cho et al., 2011; Akhavan et al., 2012; Dvorak et al., 2012; Zhou et al., 2012; Naito et al., 2014; Pimentel et al., 2016; Satué et al., 2017), femur (Nakamura et al., 2008; Kelly

et al., 2009; Wu et al., 2013; Liu et al., 2014) or abdominal region (Vandersteenhoven et al., 1988), studies only including subjects with pathology, such as diabetes mellitus (Akhavan et al., 2012; Wu et al., 2013), chronic kidney disease (Liu et al., 2014) or renal failure and secondary hyperparathyroidism (Flanagan and Mancini, 2015), studies that evaluate another variable in addition to vitamin D, not allowing its individual and isolated analysis (Schulze-Spate et al., 2016) or even inaccessible studies (Bryce and MacBeth, 2014; Vedururu et al., 2016; Boas et al., 2019; Tabrizi et al., 2021).

Furthermore, Werny et al. (2022)'s SR was the one that included the largest number of primary studies – 18 studies – and the one that included the least amount – four studies – is the most recent SR (Bazal-Bonelli et al., 2022). Clearly, methodological errors occurred in the latter since the objective of a SR is to include all existing studies about one subject on the literature.

Considering all the flaws identified and mentioned, it is not possible to guarantee that these five SR collected and analyzed all existing primary studies on the subject. In this way, the need to develop an umbrella review that gathered as much data as possible regarding the importance of vitamin D levels in osseointegration and the success of dental implants, and presented all the limitations of existing SR, was reinforced.

Even so, a clear homogeneity was observed in the rest of the SR' methodology. They all used the keywords “vitamin D” and “Dental Implant” or “Implant”, but most also used “vitamin D deficiency” and “Implant Failure”.

The most frequently used databases were PubMed, Scopus, Cochrane Library, Web of Science and Google Scholar.

Regarding the inclusion criteria, the most common ones were studies evaluating the effect of vitamin D deficiency on dental implants, and studies evaluating the effects of vitamin D serum levels on dental implants osseointegration or failure. In addition to these, some SR still established as inclusion criteria the intended study designs and studies publish in English. The most frequently established exclusion criteria were irrelevant topic, incomplete data and duplicated studies. Some SR still excluded in vitro and animal studies, letters to the editor, historic reviews and commentaries.

Only one of the SR included specific characteristics of the sample in the eligibility criteria. Although it was not very specific, Alsulaimani et al. (2022) included male-female human adult patients between 18 and 65 years of age.

All SR were conducted according to the guidelines of the PRISMA statement.

Review

Only two SR selected, as eligibility criteria, a specific experimental (EG) and control group (CG). Alsulaimani et al. (2022) defined as EG, patients with low serum vitamin D level and as CG, patients with normal serum vitamin D level, and Werny et al. (2022) defined as EG “the effect of vitamin D deficiency/supplementation on osseointegration” and as CG “osseointegration with adequate vitamin D serum level”. The remaining SR only defined the eligibility criteria in a general way, as indicated above however, all of them; evaluated either the effectiveness of optimal levels of vitamin D or the implication of a vitamin D deficit in dental implants, such as indicated in the main objectives of the SR and this umbrella review.

Four of the five SR defined "success of dental implants" and thus, as outcome measures, "survival rate and marginal bone loss of placed implants" (Bazal-Bonelli et al., 2022), "implant survival" (Hakim et al., 2021), "dental implant failure; peri-implant marginal bone loss; biological or mechanical complications reported at the implant or patient-level." (Alsulaimani et al., 2022), "bone to implant contact (BIC); new bone formation and/or implant resistance; bone volume/tissue volume around the implants with and without vitamin D deficiency/supplementation." (Werny et al., 2022). Makke (2022) was the only one who did not mention outcome measures.

According to Bazal-Bonelli et al. (2022), Alsulaimani et al. (2022) and Makke (2022), a serum vitamin D level < 10 ng/ml is considered deficient or inadequate, in the range of 10-30 ng/ml insufficient, and > 30 ng/ml sufficient/optimal serum level. According to Hakim et al. (2021), 25(OH)D or 25-hydroxyvitamin D less than 10 ng/ml is considered severe deficiency, 24-10 ng/ml, deficiency and 25-80 ng/ml, normal. Werny et al. (2022) did not mention vitamin D reference levels.

Table 4: Characteristics of the studies included in the 5 SR selected by this umbrella review's eligibility criteria.

Author, year	Aims	Study design	Sample size	Authors' main conclusions
<b>Choukroun et al., 2014</b>	Summarize the state of art of biological risk factors in bone grafting in implantology.	Narrative review	---	The vitamin D serum level plays a predominant role in bone metabolism. It is recommended to explore vitamin D serum level systematically in patients in a difficult case of implants and/or bone grafting.
<b>Salomó-Coll et al., 2016</b>	To evaluate the effect of topical application of Vitamin D over implant surface throughout analysis of peri-implant tissue.	Animal study	Six dogs <b>TG:</b> 12 implants supplemented with 10% of Vitamin D <b>CG:</b> no treatment	Topical application vitamin D during immediate implants treatment seems not having enhanced effect on dental implants osseointegration, although the supplemented implants exhibited less crestal bone loss and 10% more BIC.
<b>Mangano et al., 2016</b>	To investigate whether there is a correlation between EDIF and low serum levels of vitamin D.	Retrospective cross-sectional study	822 patients and 1625 implants	Although the incidence of early implant failures was higher in patients with low serum levels of vitamin D, the study failed in proving an effective link between both variables.

Review

<p><b>Fretwurst et al., 2016</b></p>	<p>Illustrate two patients with vitamin D deficiency and EDIF and demonstrate that implant placement was successful after supplementation.</p>	<p>Case-report</p>	<p>Two patients</p>	<p>Implant placement was successful after vitamin D supplementation in patients with vitamin D deficiency and EDIF.</p>
<p><b>Mangano et al., 2018</b></p>	<p>To investigate whether there is a relationship between low serum levels of vitamin D and EDIF.</p>	<p>Retrospective cross-sectional study</p>	<p>885 patients and 1740 implants</p>	<p>No statistically significant correlation was found, however, a clear trend toward an increased incidence of EDIF with lowering of serum vitamin D levels was reported.</p>
<p><b>Nastri et al., 2020</b></p>	<p>Summarize the role of dietary supplements in optimizing osseointegration after implant insertion surgery.</p>	<p>Scoping review</p>	<p>19 articles included</p>	<p>There is a clear association among vitamin D deficit, reduced osseointegration and increased EDIF incidence in both animal and human studies.</p>
<p><b>Garg et al., 2020</b></p>	<p>To evaluate the crestal bone level in patients having low level of vitamin D treated with dental implant with or without vitamin D3 supplements.</p>	<p>RCT</p>	<p>32 patients <b>EG:</b> VD3 supplements <b>CG:</b> no treatment</p>	<p>Cholecalciferol has systemic effects on accelerating bone formation around titanium implant.</p>
<p><b>Kwiatek et al., 2021</b></p>	<p>To assess what effect the 25-hydroxycholecalciferol concentration and vitamin D deficiency</p>	<p>RCT</p>	<p>122 patients <b>GA:</b> low level of vitamin D and no treatment</p>	<p>The correct level of 25-hydroxycholecalciferol on the day of surgery and vitamin D deficiency treatment have a</p>

Review

	<p>treatment have on changes in the bone level at the implant site during the process of osseointegration in the mandible.</p>		<p><b>GB:</b> low level of vitamin D and supplementation <b>GC:</b> normal level of vitamin D.</p>	<p>significant influence on the increase in the bone level at the implant site during the process of osseointegration.</p>
--	--	--	--	--

**4. Outcome Measure Analysis**

*i. Vitamin D deficiency and dental implants failure*

According to Hakim et al. (2021), six of the 12 investigated studies found a significant association between vitamin D deficiency and DIFs. Of these six, one is part of the eight primary studies considered relevant for this umbrella review (Mangano et al., 2018). This same conclusion, based only on Mangano et al. (2018)'s results, was also given by Werny et al. (2022) and Alsulaimani et al. (2022).

Bazal-Bonelli et al. (2022) observed that the patients, included in one of the studies reviewed (Tabrizi et al., 2021), presenting sufficient serum vitamin D levels, were found to undergo significantly less bone loss measured at one year compared with deficient serum vitamin D levels. However, the SR's authors defend that serum vitamin D level do not decrease early survival of dental implants since the long-term follow-up study of Mangano et al. (2018) did not find statistically differences between survival of dental implants in patients with deficient vitamin D serum level and in patients with sufficient serum levels of vitamin D. This same conclusion, related to Mangano et al. (2018)'s results, was also given by Makke (2022).

It is possible to observe that different authors drew different conclusions regarding the analysis of the same study. Through the specific analysis of the study, Mangano et al. (2018) observed a tendency for EDIF to increase in patients with vitamin D deficiency, although the difference was not statistically significant ( $p = 0.105$ ). We note that such statement does not mean that null hypothesis is the true one.

Despite Tabrizi et al. (2021)'s study, from reading the title and abstract, seem relevant for this umbrella review, due to the impossibility of accessing it, it was not possible to read

the study in its entirety. Therefore, only the information reported by Bazal-Bonelli et al. (2022) was taken into account.

***ii. Optimal level of vitamin D and success of dental implants***

The results of Hakim et al. (2021) showed some evidence of the association between vitamin D levels and the success rate in dental implantation. Of the five studies that reached these conclusions, two are part of the eight primary studies considered relevant for this umbrella review (Salomó-Coll et al., 2016; Fretwurst et al., 2016).

Alsulaimani et al. (2022) states that it is difficult to find a direct relation or causality between the low serum vitamin D level and EDIF and that vitamin D may play a role in dental implant success through its effects in modulating the immune system and healing process, however, it was based on only three included studies (Bryce and MacBeth, 2014; Mangano et al., 2016; Mangano et al., 2018). In the remaining discussion, the authors analyzed studies that were not included in the selection phase and took into account their results in the conclusions of the review. By contrast, they didn't discuss the results of the remaining three included studies, all being part of the eight relevant primary studies (Choukroun et al., 2014; Fretwurst et al., 2016; Nastri et al., 2020). Taking this information into account and through individual analysis of the four relevant primary studies included, it is possible to suggest that implant placement can be successful after vitamin D supplementation (Fretwurst et al., 2016), that vitamin D supplementation has beneficial effects on bone turnover and regeneration in patients with a deficit (Choukroun et al., 2014) and that there is a clear association among vitamin D deficit, reduced osseointegration and increased EDIF incidence in both animal and human studies (Nastri et al., 2020). Contrary to what the SR authors reported, it should have been mentioned that the other two studies didn't obtain statistically significant results (Mangano et al., 2016; Mangano et al., 2018).

Werny et al. (2022) states that the supplementation of vitamin D appears to enhance the osseointegration in animals with systemic diseases and that only slight evidence supports the hypothesis that humans similarly benefit from it. However, deleting information regarding animals with pathology and other studies with eligibility criteria that do not agree with those of this umbrella review, the literature suggests that local vitamin D supplementation enhances the BIC (Salomó-Coll et al., 2016) but also that systemic vitamin D supplementation reduces symptoms associated with vitamin D deficient, helps

patients with a disturbed mineral homeostasis (Fretwurst et al., 2016) and enhances new bone formation around dental implants in humans (Kwiatek et al., 2021).

According to Bazal-Bonelli et al. (2022), patients supplemented with vitamin D underwent less bone reduction than patients who were not supplemented. Of the three studies that led the authors to this conclusion (Garg et al. 2020; Kwiatek et al., 2021; Tabrizi et al., 2021), two of them (Garg et al. 2020; Kwiatek et al., 2021) are part of the relevant primary studies.

The findings of Makke (2022) are contradictory since, taking into account only the relevant primary studies, the author found one human study with favorable results (Fretwurst et al., 2016) and two human studies that found no significant relationship between vitamin D and dental implants (Mangano et al., 2016; Mangano et al., 2018).

### ***iii. Supplemented doses of vitamin D***

None of the SR, which included experimental or case-report studies, mentioned the supplemented dose of vitamin D. Analyzing each of the primary studies individually, of the four that were supposed to mention these data (Salomó-Coll et al., 2016; Fretwurst et al., 2016; Garg et al., 2020; Kwiatek et al., 2021), only both RCT did it (Garg et al., 2020; Kwiatek et al., 2021). In Garg et al. (2020)'s study the EG were supplemented with cholecalciferol sachet 60000 IU/month for three months and continued for six months depending on level of vitamin D. In Kwiatek et al. (2021)'s study the patients were instructed to take 8000 IU/daily for 12 weeks. It is clearly evident that the dosage differs greatly from one study to another, however, the results of both studies are concordant and conclude that vitamin D supplementation is an effective approach to improve the osseointegration of dental implants.

### ***iv. Vitamin D theories***

In addition to the direct influence of vitamin D on the success or unsuccess of dental implants, the included SR also presented some theories that may justify the relationship between these two factors.

The role of vitamin D in the calcium economy is extremely important. During osseointegration, calcitriol affects the processes of activation and differentiation of osteoblasts and osteoclasts (Hakim et al., 2021; Makke, 2022).

Vitamin D has also been found to be essential for the maturation and proper functioning of bone cells, for increasing osteoid mineralization, that can play an important role in the

Review

stabilization phase of the implant, seems to have potent anti-inflammatory effects and may be essential in modulating the innate and adaptive immune responses and for the antibacterial response (Hakim et al., 2021; Bazal-Bonelli et al., 2022). There was a significant correlation between infection rate and vitamin D levels < 20 ng/ml.

Therefore, the optimal vitamin D level might be one of the most critical systemic factors in preventing infection and providing an optimal environment for successful osseointegration (Makke, 2022).

Moreover, it has been observed that DIFs decrease threefold when dental implants are placed by digitally guided surgery compared with freehand placement (2.25% vs. 6.42%) (Bazal-Bonelli et al., 2022).

#### **IV. DISCUSSION**

An umbrella review, such as this one, has the main objective of analyzing and summarizing in the best possible way all the existing information in SR on a specific topic, considering certain eligibility criteria. In this way, it allows to present the state of the art of this same subject, up to the present time, to assist decision-making in clinical practice and to know the next steps that must be taken in terms of scientific research.

This umbrella review brought together five SR which, in turn, allowed the analysis and presentation of results from eight primary studies although, in all, they gathered 29 different studies. This was due to the fact that the SR did not elaborate specific eligibility criteria and to errors in the study selection process.

Generally, an umbrella review does not analyze the primary studies included by SR. However, in the present study, since numerous limitations were identified in the included SR, the need to individually analyze the studies included by them was felt. In this individual analysis of the 29 primary studies, it was noticed that the majority did not respond to the main problem of this umbrella review due to the various reasons already mentioned in the results.

Despite this major limitation, the analysis of the eight primary studies carried out by the five SR and by the present umbrella review is sufficient to present the state of the art of the subject, up to the present time, to identify the main limitations of the study of the subject and to guide future researchers.

In methodological terms, several flaws were found in the SR that, most likely, called their quality and internal validity into question and what that, in the future, should be avoided. For instance, in only one of the SR (Bazal-Bonelli et al., 2022) it is mentioned that literature search and/or data extraction were carried out by two researchers, independently, as it should be done. This made the five SR, whose main objective were to demonstrate the effect of vitamin D on dental implants, include studies where implants were placed in other limbs or studies where vitamin D was not even evaluated. In this way, knowing that the selection process of the studies of the five SR was not carried out correctly, this umbrella review does not guarantee that it brings together all existing studies in the literature, in Portuguese, English or Spanish, that evaluate the effect of vitamin D on the success of dental implants.

This same SR (Bazal-Bonelli et al., 2022) was also the only one that mentioned having evaluated the methodological quality of the primary studies. As the others do not mention

such information, it must be assumed that they did not carry out this phase of investigation. This phase is essential to understand how the results of primary studies may be negatively influenced by errors in the studies themselves.

Human studies were performed as a cross-sectional, case-report and RCT. These variations on the study design makes it difficult to come to a solid conclusion on the subject. As mentioned before, the most reliable studies after SR and MA are RCT because they can guide scientists accurately to resolve scientific gaps. Case-reports can help the researchers in case of lacking good sample size, and cross-sectional studies are performed to study deceptive aspects of a population in a specific time, however they cannot determine the relation or cause of something. The retrospective studies have just the possibility of analyzing the available information and data, with no possibility of manipulating the variables in the present (Ranganathan and Aggarwal, 2018).

Other observed limitations are related to the lack of characterization of the sample and of the EG and CG, resulting in a heterogeneous sample and a greater probability of non-significant results.

An inconsistency in the reference values of vitamin D was also observed, impairing the reliability of comparisons made between studies. In addition, none of the SR, which included experimental or case-report studies, mentioned the supplemented dose of vitamin D. Analyzing each of the primary studies individually, of the four that were supposed to mention these data, only both RCT did it (Garg et al., 2020; Kwiatek et al., 2021). This is a major failure of the SR, since it is important to relate the different supplemented doses and the different results obtained, in order to try to establish a relationship between them, helping future decision-making in clinical practice.

Although the main objective of all studies was to evaluate the effect that optimal levels of vitamin D have on dental implants, compared to low levels, some differences in the evaluation method were observed. Some of them looked at it through vitamin D supplementation and the others assessed how low levels of this hormone influence EDIF. Since five of the eight primary studies were included in more than one SR, an analysis and comparison of their conclusions was carried out in order to verify if there is any inconsistency or flaw in the presentation of results. According to this analysis, three differences were identified. Werny et al. (2022), when presenting Mangano et al. (2018)'s results, only mentions that a higher prevalence of EDIF was observed in patients with lower vitamin D levels, hiding that these results were not statistically significant. This

same author, as well as Hakim et al. (2021), when analyzing the results of Salomó-Coll et al. (2016), mention only the positive results, hiding the variables where the optimal levels of vitamin D did not prove to be significantly effective. Although the objective of most authors, when carrying out research studies, is to demonstrate the effectiveness of a variable, it is important that its development is as impartial as possible and that all results are presented, even when they are not favorable to research, in order to provide reliable data that can be extrapolated to clinical practice.

There are some important factors to consider that can influence the success of dental implants, such as age, diet, smoking, alcohol consumption or other drugs, stress, daily oral hygiene, among others (Raikar et al., 2017). However, it was observed that none of the analyzed studies took into account any of these and other related factors, with the exception of age (Alsulaimani et al., 2022).

In addition to the previously mentioned limitations, another one was detected related to the p-value. It is known that the threshold of statistical significance that is commonly used is a p-value of 0.05 and that the smaller the p-value the greater statistical incompatibility of the data with the null hypothesis. However, the p-value depends on other variables and its statistical significance does not automatically equate to scientific, human or economic significance, so a low or a high p-value is not the sole basis for a scientific claim (Yaddanapudi, 2016). In most of the SR included, an abuse was observed in the way the p-value was evaluated, since all results with a p-value greater than 0.05 were considered to be “no importance” or a “valueless”, ignoring the remaining factors such as inappropriate study design, imprecise measurement, erroneous statistical analysis or small sample size.  $P > 0.05$  only means “no evidence of difference” that does not mean “no difference between the groups” (Nahm, 2017). However, this abuse was not observed in the analysis of any of the primary studies considered relevant for this review.

Even so, when we say that, for example, Mangano et al. (2016) and Mangano et al. (2018) did not obtain statistically significant results, with a value of  $p = 0.15$  and  $p = 0.105$ , respectively, despite it is not an abusive conclusion, it is important to note that this does not mean that vitamin D does not influence, in any way, the osseointegration of dental implants. Although the results are not always statistically significant, the general trend of the results towards a positive relationship between vitamin D levels and the success of dental implants is clear, and this trend has great clinical relevance.

Despite the methodological differences between the SR, consistency was found in most of their conclusions.

It is difficult to find a direct relation or causality between vitamin D and implant failure based on the current research in the literature. The studies' findings were inconsistent, but some of this research showed a clear association between vitamin D and osseointegration, marginal bone loss, dental implant survival and EDIF (Hakim et al., 2021; Makke, 2022; Bazal-Bonelli et al., 2022).

The supplementation of vitamin D appears to enhance the osseointegration in animals with vitamin D deficiency although only slight evidence supports the hypothesis that humans similarly benefit from vitamin D supplementation in terms of osseointegration (Werny et al., 2022). Although this evidence may be superior in animals, this is how clinical research develops and, according to the data collected, we can conclude that research on the subject will increase and improve its quality in humans.

Vitamin D may play an important role on all the variables mentioned through its effects in modulating the immune system modulation and healing process (Hakim et al., 2021; Alsulaimani et al., 2022). The physiological processes that explain and justify the influence of vitamin D on osseointegration of dental implants is still unclear, but all theories mentioned by the SR are valid and should be tested in future studies.

Additional large-scale human prospective clinical studies and case reports are required to determine the association between serum vitamin D level and osseointegration and to approve the hypothesis that vitamin D may play an important role in improving implant success through its effect on the immune system modulation.

In patients with severely compromised vitamin D levels, the recommendation is to supplement with vitamin D to ensure optimal treatment outcomes.

## V. CONCLUSION

The development of this umbrella review allows to conclude that the publication of studies on the effect of vitamin D on the osseointegration of dental implants has been increasing a lot in recent years. The evolution found in these studies is clear, moving from pre-clinical to clinical studies, with ever greater methodological quality.

According to the available literature and data analyzed in this umbrella review, it is possible to state that vitamin D may have a positive effect and play an important role on the osseointegration, in reducing bone loss, dental implant survival and consequently on the reduction of EDIF, that is, on the success of dental implants.

However, there is still some inconsistency in the results and the study of this topic still has a lot to evolve.

As mentioned by the authors of the included SR and given the high percentage of patients with vitamin D deficiency, it may be advisable to determine the serum vitamin D level of each patient before placing dental implants. The development of further higher-level studies such as prospective clinical research studies and mainly RCT to investigate the correlation or causal relationship between serum levels of vitamin D and risk of EDIF is also recommended. It is imperative to develop studies with this study design with larger sample sizes and different follow-up periods.

In future studies, to complement the disadvantages of p-value, some statisticians recommend the supplementation or replacement of p-values with other statistical methods including confidence, credibility or prediction intervals, likelihood ratios, Bayesian statistics, and decision-theoretic modeling, focusing more on estimation than testing.

In the future development of SR, it is recommended that each of the phases is carried out by more than one researcher and that decisions are discussed between them, to ensure that all existing information is selected and analyzed and, consequently, made available to best scientific evidence.

## VI. BIBLIOGRAPHIC REFERENCES

- Akhavan, A. et alii. (2012). The effect of vitamin D supplementation on bone formation around titanium implants in diabetic rats. *Dental Research Journal*, 9(5), pp. 582–587.
- Alsulaimani, L. et alii. (2022). The relationship between low serum vitamin D level and early dental implant failure: A Systematic Review. *Cureus*, 14(1), pp. 1-8.
- Alvim-Pereira, F. et alii. (2008). Analysis of association of clinical aspects and vitamin D receptor gene polymorphism with dental implant loss. *Clinical Oral Implants Research*, 19(8), pp. 786– 795.
- Aromataris, E. et alii. (2015). Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *International Journal of Evidence-Based Healthcare*, 13(3), pp. 132-40.
- Aslan, S. (2018). Improved volume and contour stability with thin socket-shield preparation in immediate implant placement and provisionalization in the esthetic zone. *The International Journal of Esthetic Dentistry*, 13(2), pp. 172–183.
- Bazal-Bonelli, S. et alii. (2022). Influence of serum vitamin D levels on survival rate and marginal bone loss in dental implants: A Systematic Review. *International Journal of Environmental Research and Public Health*, 19(16), pp. 1-11.
- Beederman, M. et alii. (2013). BMP signaling in mesenchymal stem cell differentiation and bone formation. *Journal of Biomedical Science and Engineering*, 6(8A), pp. 32–52.
- Blasco, L. et alii. (2019). Influencia de la vitamina D en la osteointegración de implantes dentales. *Sanidad Militar*, 75(4), pp. 214–217.
- Boas, R. et alii., (2019). Analysis of the effects of vitamin D insufficiency on osseointegration of dental implants. *Clinical Oral Implants Research*, 30(19), p. 113.
- Bouillon, R. (2017). Comparative analysis of nutritional guidelines for vitamin D. *Nature Reviews. Endocrinology*, 13(8), pp. 466–479.
- Bryce, G. and MacBeth, N. (2014). Vitamin D deficiency as a suspected causative factor in the failure of an immediately placed dental implant: a case report. *Journal of the Royal Naval Medical Service*, 100(3), pp. 328-332.
- Chen, G., Deng, C. and Li, Y. (2012). TGF- $\beta$  and BMP signaling in osteoblast differentiation and bone formation. *International Journal of Biological Sciences*, 8(2), pp. 272–288.

- Cho, Y. et alii. (2011). Promotion of osseointegration of anodized titanium implants with a 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> submicron particle coating. *The International Journal of Oral & Maxillofacial Implants*, 26(6), pp. 1225–1232.
- Choukroun, J. et alii. (2014). Two neglected biologic risk factors in bone grafting and implantology: High low-density lipoprotein cholesterol and low serum vitamin D. *Journal of Oral Implantology*, 40(1), pp. 110–114.
- Christakos, S. et alii. (2016). Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. *Physiological Reviews*, 96(1), pp. 365–408.
- Crockett, J. et alii. (2011). Bone remodelling at a glance. *Journal of Cell Science*, 124(7), pp. 991–998.
- Do, T. et alii. (2020). Risk Factors related to Late Failure of Dental Implant-A Systematic Review of Recent Studies. *International Journal of Environmental Research and Public Health*, 17(11), p. 3931.
- Duarte, C. et alii. (2020). Prevalence of vitamin D deficiency and its predictors in the portuguese population: A nationwide population-based study. *Archives of Osteoporosis*, 15(1), p. 36.
- Dvorak, G. et alii. (2012). Impact of dietary vitamin D on osseointegration in the ovariectomized rat. *Clinical Oral Implants Research*, 23(11), pp. 1308–1313.
- Estrada, K. et alii. (2011). Smad6 is essential to limit BMP signaling during cartilage development. *Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research*, 26(10), pp. 2498–2510.
- Flanagan, D. and Mancini, M. (2015). Bimaxillary full arch fixed dental implant supported treatment for a patient with renal failure and secondary hyperparathyroidism and osteodystrophy. *Journal of Oral Implantology*, 41(2), pp. 36-43.
- Fretwurst, T. et alii. (2016). Vitamin D deficiency in early implant failure: Two case reports. *International Journal of Implant Dentistry*, 2(24), pp. 1-6.
- Garg, P. et alii. (2020). Comparative evaluation of crestal bone level in patients having low level of vitamin D treated with dental implant with or without vitamin D<sub>3</sub> supplements. *National Journal of Maxillofacial Surgery*, 11(2), pp. 199–206.
- Grisar, K. et alii. (2017). Retrospective analysis of dental implants placed between 2012 and 2014: Indications, risk factors, and early survival. *The International Journal of Oral & Maxillofacial Implants*, 32(3), pp. 649–654.
- Gupta, R. Gupta, N. and Weber, K. (2022). *Dental Implants*. StatPearls.

Hakim, L. et alii. (2021). *The possible role of vitamin D deficiency in early implant failure*. BioMed Research International.

Halfon, M., Phan, O. and Teta, D. (2015). *Vitamin D: A review on its effects on muscle strength, the risk of fall, and frailty*. BioMed Research International.

Holick, M. et alii. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: An endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, 96(7), pp. 1911–1930.

Insua, A. et alii. (2017). Basis of bone metabolism around dental implants during osseointegration and peri-implant bone loss. *Journal of Biomedical Materials Research Part A*, 105(7), pp. 2075–2089.

Javed, F. et alii. (2016). Efficacy of vitamin D3 supplementation on osseointegration of implants. *Implant Dentistry*, 25(2), pp. 281–287.

Joanna Briggs Institute. (2017). *Critical appraisal checklist for systematic reviews and research syntheses*. [In line]. Available in <[https://jbi.global/sites/default/files/2019-05/JBI\\_Critical\\_Appraisal-Checklist\\_for\\_Systematic\\_Reviews2017\\_0.pdf](https://jbi.global/sites/default/files/2019-05/JBI_Critical_Appraisal-Checklist_for_Systematic_Reviews2017_0.pdf)>. [Consulted in 11/02/2023].

Kelly, J. et alii. (2009). Vitamin D and bone physiology: demonstration of vitamin D deficiency in an implant osseointegration rat model. *Journal of Prosthodontics*, 18(6), pp. 473–478.

Kogawa, M. et alii. (2010). Osteoclastic metabolism of 25(OH)-vitamin D3: A potential mechanism for optimization of bone resorption. *Endocrinology*, 151(10), pp. 4613–4625.

Kwiatek, J., Jarón, A. and Trybek, G. (2021). *Impact of the 25-Hydroxycholecalciferol concentration and vitamin D deficiency treatment on changes in the bone level at the implant site during the process of osseointegration: A prospective, randomized, controlled clinical trial*. Journal of Clinical Medicine

Lin, G. et alii. (2018). A retrospective study of 30959 implants: Risk factors associated with early and late implant loss. *Journal of Clinical Periodontology*, 45(6), pp. 733–743.

Lips, P. et alii. (2019). Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: A position statement of the European Calcified Tissue Society. *European Journal of Endocrinology*, 180(4), pp. 23–54.

Liu, H. et alii. (2022). Efficacy and safety of eldecacitol for osteoporosis: A meta-analysis of randomized controlled trials. *Frontiers in Endocrinology*, 13, pp. 1-20.

- Liu, W. et alii. (2014). Vitamin D supplementation enhances the fixation of titanium implants in chronic kidney disease mice. *PLoS One*, 9(4), pp. 1-6.
- Makke, A. (2022). *Vitamin D supplementation for prevention of dental implant failure: A Systematic Review*. International Journal of Dentistry.
- Mangano, F. et alii. (2016). *Is low serum vitamin D associated with early dental implant failure? A retrospective evaluation on 1625 implants placed in 822 patients*. Mediators of Inflammation.
- Mangano, F. et alii. (2018). Low serum vitamin D and early dental implant failure: Is there a connection? A retrospective clinical study on 1740 implants placed in 885 patients. *Journal of Dental Research, Dental Clinics, Dental Prospects*, 12(3), pp. 174–182.
- Merchan, B. et alii. (2017). The role of vitamin D and VDR in carcinogenesis: Through epidemiology and basic sciences. *The Journal of Steroid Biochemistry and Molecular Biology*, 167, pp. 203–218.
- Mkrtumyan, A. et alii. (2020). Regulation of bone's metabolic process under dental implantation procedure. *Oral Rehabilitation and Dentistry*, 2019(1), pp. 1–4.
- Mohajerani, H. et alii. (2017). The risk factors in early failure of dental implants: A retrospective study. *Journal of Dentistry*, 18(4), pp. 298–303.
- Nahm, F. (2017). What the p values really tell us. *The Korean Journal of Pain*, 30(4), pp. 241–242.
- Naito, Y. et alii. (2014). The influence of 1 $\alpha$ .25-dihydroxy vitamin D<sub>3</sub> coating on implant osseointegration in the rabbit tibia. *Journal of Oral & Maxillofacial Research*, 5(3), p. 3.
- Nakamura, Y. et alii. (2008). Effect of preoperative combined treatment with alendronate and calcitriol on fixation of hydroxyapatite-coated implants in ovariectomized rats. *The Journal of Bone and Joint surgery. American Volume*, 90(4), pp. 824–32.
- Nastri, L. et alii. (2020). *Do dietary supplements and nutraceuticals have effects on dental implant osseointegration? A scoping review*. Nutrients.
- Ogawa, T. et alii. (2022). Effectiveness of the socket shield technique in dental implant: A systematic review. *Journal of Prosthodontic Research*, 66(1), pp. 12–18.
- Page, M. et alii. (2021). *PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews*. British Medical Journal.
- Pereira, T. and Alvim-Pereira, F. (2019). A complete physical mapping of the vitamin D receptor gene for dental implant loss: a pilot study. *Clinical Oral Implants Research*, 30(12), pp. 1165–1178.

- Pilz, S. et alii. (2018). Vitamin D: Current guidelines and future outlook. *Anticancer Research*, 38(2), pp. 1145–1151.
- Pimentel, S. et alii. (2016). Impact of micronutrients supplementation on bone repair around implants: microCT and counter-torque analysis in rats. *Journal of Applied Oral Science*, 24(1), pp. 45–51.
- Pludowski, P. et alii. (2018). Vitamin D supplementation guidelines. *The Journal of Steroid Biochemistry and Molecular Biology*, 175, pp. 125–135.
- Pludowski, P. et alii. (2022). Clinical practice in the prevention, diagnosis and treatment of vitamin D deficiency: A Central and Eastern European Expert Consensus Statement. *Nutrients*, 14(7).
- Raikar, S. et alii. (2017). Factors affecting the survival rate of dental implants: A retrospective study. *Journal of International Society of Preventive & Community Dentistry*, 7(6), pp. 351–355.
- Ranganathan, P. and Aggarwal, R. (2018). Study designs: Part 1 – An overview and classification. *Perspectives in Clinical Research*, 9(4), pp. 184–186.
- Ross, A. et alii. (2011). The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. *The Journal of Clinical Endocrinology and Metabolism*, 96(1), pp. 53–58.
- Salomó-Coll, O. et alii. (2016). Osseoinductive elements for promoting osseointegration around immediate implants: A pilot study in the foxhound dog. *Clinical Oral Implants Research*, 27(12), pp. 167–175.
- Satué, M. et alii. (2017). Titanium implants coated with UV-irradiated vitamin D precursor and vitamin E: in vivo performance and coating stability. *Clinical Oral Implants Research*, 28(4), pp. 424–31.
- Schulze-Späte, U. et alii. (2016). Systemic vitamin D supplementation and local bone formation after maxillary sinus augmentation—A randomized, double-blind, placebo-controlled clinical investigation. *Clinical Oral Implants Research*, 27(6), pp. 701–706.
- Spiro, A. and Buttriss, J. (2014). Vitamin D: An overview of vitamin D status and intake in Europe. *Nutrition Bulletin*, 39(4), pp. 322–350.
- Staedt, H. et alii. (2020). Potential risk factors for early and late dental implant failure: A retrospective clinical study on 9080 implants. *International Journal of Implant Dentistry*, 6(1), p. 81.

Tabrizi, R. et alii. (2021). Does the serum level of vitamin D affect marginal bone loss around dental implants? *International Journal of Oral Maxillofacial Surgery*, 51, pp. 832–836.

Tripkovic, L. et alii. (2012). Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: A systematic review and meta-analysis. *The American Journal of Clinical Nutrition*, 95(6), pp. 1357–1364.

Vandersteenhoven, J. et alii. (1988). Osteoinduction by implants of demineralized allogeneic bone matrix is diminished in vitamin D-deficient rats. *Calcified Tissue International*, 42(1), pp. 39–45.

Wagner, F. et alii. (2017). Does osteoporosis influence the marginal periimplant bone level in female patients? A cross-sectional study in a matched collective. *Clinical Implant Dentistry and Related Research*, 19(4), pp. 616–623.

Werny, J. et alii. (2022). Does vitamin D have an effect on osseointegration of dental implants? A systematic review. *International Journal of Implant Dentistry*, 8(1), p. 16.

Wu, Y. et alii. (2013). Vitamin D3 and insulin combined treatment promotes titanium implant osseointegration in diabetes mellitus rats. *Bone*, 52(1), pp. 1–8.

Yaddanapudi, L. (2016). The American Statistical Association statement on p-values explained. *Journal of Anaesthesiology, Clinical Pharmacology*, 32(4), pp. 421–423.

Yang, Y. et alii. (2012). The role of vascular endothelial growth factor in ossification. *International Journal of Oral Science*, 4(2), pp. 64–68.

Yanushevich, O. et alii. (2014). Qualitative assessment of jawbones in patients with complex antiosteoporherapeutic therapy. *Russian Dentistry*, 4, pp. 34-40.

Zhou, C. et alii. (2012). 1,25Dihydroxy vitamin D(3) improves titanium implant osseointegration in osteoporotic rats. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, 114(5), pp. 174-178.