

## Review Article

# The role of vitamin D in dental implants osseointegration

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**Abstract**

Dental implants currently constitute a well-established solution for both functional and aesthetic restoration of complete and partial edentulism. Osseointegration, however, is a complex and multifactorial phenomenon bearing concerns as to its strong association to implant, prosthetics and surgical protocols, as well to patients themselves. This literature review aims to research into potential correlations linking the osseointegration process in dental implants to low levels of vitamin D in dental patients. A number of scientific articles were retrieved from PubMed and MEDLINE databases, using the following key words: “vitamin D deficiency”; “osseointegration”; and “vitamin D AND dental implants”. All retrieved studies were limited to those involving human and animal experimental models, and only articles written in English. Nine animal studies investigated the osseointegration process in dental implants that may be attributed to the effects of vitamin D; and five studies used human subjects. However, none of the said studies demonstrated statistically significant differences. A number of patients, especially those with severe deficiency, reported beneficial outcomes following vitamin D systemic administration prior the surgery. In such patients, is important to maintain vitamin D levels, as it ensures bone reconstruction around the implant.

**Keywords:** Dental implants, Implant failure, Osseointegration, Vitamin D, Vitamin D deficiency

**Introduction**

Rehabilitation with dental implants is a remarkably successful treatment option in the field of dentistry for partially/completely edentulous patients; their survival rates – accounting to more than 95%<sup>1-3</sup> – have been well documented as both evident and solid by several long-term clinical studies. Implant-supported prostheses demonstrate enhanced mastication experience<sup>4</sup> as well as a strong linkage to oral health-related quality of life (OHRQoL)<sup>5</sup>. Nonetheless, the achievement of long-term survival rates requires implants to osseointegrate, i.e. to directly connect between the bone and the implant surface, in absence of fibrous tissue formation<sup>6</sup>. Osseointegration is, however, a complex and multifactorial phenomenon affecting the implant (surface, material and macroscopic design), the surgical and prosthetic protocol and application thereof (surgical protocol and prosthetic loading), and, of course, the patient undergoing the whole procedure and not just the surgical/medical part of it (diseases, conditions and bone quality/quantity)<sup>6,7</sup>. To date, albeit dental implants are the treatment of choice, boasting a high level of survival rates, a number of unsuccessful attempts are still witnessed, in the

osseointegration stage of the implants inside the bone<sup>8,9</sup>. In particular, disruption of osseointegration and peri-implantitis hold a prominent place among the most common causes of premature implant loss<sup>2,8,9</sup>. Early failures manifest when either the quality or the quantity of bone proves insufficient, regardless of the material used or the surgical protocol observed<sup>8-10</sup>.

Vitamin D, a key component in bone metabolism<sup>11-13</sup>, is a fat soluble vitamin promoting calcium absorption and regulating phosphorus and calcium homeostasis in tissues. Being of fundamental nature to bones and teeth<sup>11,13</sup>, vitamin D is crucial to the circulatory system and the brain<sup>14,15</sup>.

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Additionally, studies have found that vitamin D is markedly beneficial to the cardiovascular<sup>16</sup>, immune and respiratory systems<sup>17,18</sup>. Even though the significance of vitamin D and its involvement in bone metabolism have been well documented<sup>19-31</sup>, limited studies have been conducted on the effects of osseointegration of implants in dental patients. Specifically, the majority of them have been performed in animal experimental models<sup>20-24,27-29,31</sup> and only a small number in humans<sup>15-18</sup>. This literature review aims to research into potential correlations linking the osseointegration process in dental implants to low levels of vitamin D in dental patients.

## Bone

Bone is a mineralized tissue, and it is the minerals that provide its hardness, which ensures the support frame, provides adhesion of muscles, ligaments, and tendons, and comprises four cell types: osteoblasts; lining cells; osteocytes; and osteoclasts<sup>32,33</sup>. Its hard composition properties facilitate the protection of the vital organs in the cranial cavity and the thoracic cavity. In its capacity as a considerably powerful organ, bone undergoes an ongoing absorption by osteoclasts combined with new formation by osteoblasts. The osteocyte elaborates in the course of remodeling, due to its mechanosensory activity<sup>34-38</sup>, while the function of lining cells is to connect to other bone lining cells via gap junctions, and send cell processes into canaliculi<sup>39</sup>. Bone remodeling is an outstandingly dynamic, preserving and high-powered process, anticipating the suitable balance conditions between bone resorption and bone deposition<sup>38</sup>, which translates into a 5-stage cycle: activation, resorption, reversal, formation and termination; all of which take place over a course lasting 120–200 days in cortical and trabecular bone<sup>40</sup>. Such process is owed to the concerted activities of osteoclasts, osteoblasts, osteocytes and lining cells that form the basic multicellular unit (BMU)<sup>41-43</sup>. The bone remodeling cycle is critical and indispensable for fracture healing and calcium homeostasis<sup>44</sup>. The applicable balance between bone resorption and osteogenic functions may well be considered as the crucial factor in maintaining ongoing bone mass. Any balance impairment may lead to a number of diseases and conditions in the bone, as in the case of marked absorption by osteoclasts resulting in bone loss and osteoporosis<sup>45</sup>; on the contrary, the opposite may well constitute the etiology of osteopetrosis<sup>46</sup>. Thus, this balance is action-dependent by certain localized and systemic factors encompassing parathyroid hormone (PTH), thyroid hormones, growth hormone, glucocorticoids, calcitriol, sex hormones, insulin-like growth factors (IGFs), bone morphogenetic proteins (BMP), tumor growth factor-beta (TGF-beta), prostaglandins, and cytokines<sup>47-49</sup>.

## Vitamin D

Over the last decades, the interest of researchers is particularly highly focused on vitamin D, as it displays numerous actions, notwithstanding those related to bone and metabolism of calcium (Ca)<sup>50</sup>. Vitamin D deficiency has been identified in numerous serious diseases and conditions, e.g. non-insulin-dependent (type II) diabetes, metabolic syndrome, obesity, and cardiovascular diseases<sup>51</sup>. High-risk groups for vitamin D deficiency include elderly and pediatric populations, expecting mothers, and institutionalized individuals<sup>52</sup>. Nutrition alone may cover only 10% of the Recommended Daily Intake (RDI) of vitamin D<sup>53</sup>, while the rest is produced from the synthesis of vitamin D by solar activity.

## Metabolism, transport and vitamin D receptor

Vitamin D is a fat-soluble vitamin which occurs in two forms, D2 (ergocalciferol) and D3 (cholecalciferol) as well as a significant, integral part in the metabolism of Ca and phosphorus (P). Its primary functions include intestinal absorption and renal reabsorption of Ca as well as unmediated involvement in the differentiation of chondrocytes and osteoblasts in the bone formation process. Vitamin D2 can be found in yeast and mushrooms, while vitamin D3 is ingested through nutrition or UVB radiation-composed<sup>54</sup>. Through the latter, the 7-Dehydrocholesterol (7-DHC) of the skin is converted to provitamin D3, which in turn is converted to vitamin D3 within 2-3 days by thermal isomerization<sup>55</sup>. In the liver, D3 is subject to hydroxylation in the C25 position of the side chain, assisted by the 25-hydroxylase enzyme (CYP2R1), and composes the 25-hydroxy-vitamin D [25 (OH) D], i.e. the primary circulatory form of the vitamin. The enzyme 25-hydroxylase belongs to the cytochrome P450 (CYP2R1 or CYP27A1) enzymatic superfamily. These proteins catalyze a good number of reactions participating in drug metabolism and cholesterol, steroids and other lipids production. It has been located in tissues other than the liver, such as testicles<sup>56</sup>, dermal fibroblasts and prostate cancer cells<sup>57</sup>. Next, the kidneys form the setting for its conversion, in the renal tubules, from cholecalciferol to calcitriol, which is the D-hormone responsible for all effects previously stated i.e. the highly engaging vitamin D3 attaching to the vitamin D receptor (VDR)<sup>56</sup>.

## Dietary intake sources

The action of vitamin D ingested from food does not differ from that synthesized in the skin from UVB radiation<sup>54</sup>. The main foods that contain vitamin D include salmon, tuna, egg yolk, beef liver, fish oils, and mushrooms; only a small number of foods are high in vitamin D, namely orange juice, breakfast cereals, and margarines<sup>54,55</sup>.

## UVB radiation

UVB radiation is an all-important factor for vitamin D production. The 7-DHC begins to absorb UVB radiation at 260 nm up to 315 nm, while maximum composition observed reaches 295 - 300 nm<sup>58</sup>. Such a small range of solar radiation can differentiate the production of vitamin D according to the geographical area, time of year and presence of clouds or sunshine. Moreover, the extent and type of skin exposed are determining constituents for the amount of vitamin D our body naturally makes. Conversion of 7-DHC to provitamin D3 is 6- to 10-fold more effective in light-colored skins, as melanin antagonizes 7-DHC in the absorption of UVB radiation. The body is protected from excessive vitamin D production, which could result from long-term exposure to sunlight, because only 10-15% of the 7-DHC is converted to provitamin D3. The remainder ends up in inert derivatives, such as tachysterol and lumisterol<sup>59</sup>. Additionally, lighter skin has the ability to produce vitamin D at a lower intensity of solar radiation<sup>60</sup>, because, considered a governing element, it establishes the initial physical vitamin concentration prior to exposure to sunlight. Following UV exposure, individuals with low initial vitamin D levels form vitamin D more rapidly. The use of sunscreen ranks high among the factors regulating the absorption process of vitamin D from the skin; UVBs cannot penetrate the skin to synthesize vitamin D, and exposure of large skin surfaces to sunlight is blocked<sup>61</sup>.

## Lack of vitamin D in the general population

A few trials estimate that people suffering from reduced or inadequate vitamin D uptake account for more than one billion worldwide<sup>62,63</sup>. Factors identified in cases of lack or depletion of vitamin D include age, obesity, educational attainment, race, drugs, and sedentary lifestyle combined with lack of exercise<sup>58</sup>. To date, there is no research consensus on the adequate concentrations of vitamin D, as some investigators set the lower limit at 50 nmol/l, while others at 75 or 100 nmol/l<sup>64</sup>. According to the Endocrine Society, "vitamin insufficiency" is established at concentrations of 25 (OH) D of 21-29 ng/ml, while "vitamin deficiency" is confirmed when concentrations are less than 20 ng/ml<sup>64</sup>. Concentrations of 25 (OH) D <25 nmol/l are considered as "clinical hypovitaminosis", a condition where patients experience pain, fractures, and muscle weakness. In terms of pediatrics, swelling of the joints is the clinical presentation. When the concentration of 25 (OH) D is <15 nmol/l, rickets and "soft bone" disease such as osteomalacia, other than genetically predisposed, may occur in children and adults, respectively<sup>62</sup>. In contrast, a toxic effect is observed when concentrations of 25 (OH) D are >500 nmol/l. This happens when the daily intake of vitamin D is greater than 10,000 IU. Hypervitaminosis not only sets the substrate, but also progresses to cause nausea, anorexia, vomiting, constipation, weight loss, weakness, hyperphosphatemia, and hypercalcemia<sup>55</sup>. According to the Endocrine Society,

concentrations of 25 (OH) D of 75 nmol are considered sufficient, with their "status of sufficiency" being maintained by a daily intake of 1,500 - 2,000 IU<sup>64</sup>. Based on the guidelines of the Institute of Medicine (IOM), concentrations of 25 (OH) D of 50 nmol/l are advised as sufficient, and the recommended daily intake of vitamin D ranges between 400 and 600 IU.

## Vitamin D and oral health

Vitamin D, due to its anti-inflammatory properties, is possibly beneficial both physical - and oral health-wide - it affects the pathogenesis of several diseases in the oral cavity, i.e. periodontitis, via immunomodulation, enhances bone mineral density (BMD), and limits bone resorption<sup>65</sup>.

The 1,25 (OH)<sub>2</sub>D / VDR is a crucial element in the oral epithelium and oral immunity, and is expressed by oral keratinocytes in which the function of the ligand is keratinocytes proliferation-independent. Vitamin D deficiency alone cannot be the sole etiology of precancerous transformation, however, synergistically with other factors, it may well increase the risk of developing oral squamous cell carcinoma<sup>66</sup>.

## Materials and methods

The search technique encompassed navigation through and diligent exploration of electronic databases. Applying the advance search option, i.e. from June 1993 up to May 2019, we conducted a search in MEDLINE, improving the accessed articles via Ovid interface. Our key words were primarily oriented towards a composite based on MeSH terms and text words. Our online search was conducted according to the PICO framework in the following fashion: "vitamin D deficiency"; "osseointegration"; and "vitamin D AND dental implants". The inclusion criterias were studies limited to those involving human and animal experimental models, and only articles written in English.

## Results

The search in the literature yielded 51 studies. After reviewing their title and summary, 46 of them were found to meet the inclusion criteria and, next, the full-text articles were reviewed. Of these, 37 studies were excluded, as they would no longer meet the inclusion criteria. A total of 14 studies were considered for the literature review, 9 were animal studies and 5 studies used human subjects. The literature review in animals demonstrated that administration of vitamin D can induce bone formation as well as strengthen and support the interaction between bone and implants<sup>29</sup>. Kelly et al. proved that osseointegration of Ti6Al4V implants in rats can be compromised due to low vitamin D levels<sup>20</sup>. Working on post-ovariectomy rats, Dvorak et al found that the deficiency may unfavorably affect bone formation around the implant<sup>24</sup>. Zhou et al. marked an increase in bone assimilation in osteoporotic rats that had been administered

synthetic vitamin D<sup>22</sup>; Wu et al., as well, demonstrated increased bone to implant contact in diabetic rats<sup>23</sup>. Liu et al. reported that in mice with chronic renal disease, receiving vitamin D could add to the firm fixation of dental implants<sup>27</sup>. Salomo-Coll et al. used dogs as models and studied how locally applied vitamin D acts on implant surfaces in postextraction sockets following a 12-week period<sup>31</sup>. Locally applied vitamin D may escalate the bone-implant contact percentage by 10%<sup>31</sup>. Cho et al. investigated how bone tissue reacts to anodized titanium implant surfaces coated with a poly(D,L-lactide-co-glycolide) (PLGA) solution mixed with 1 $\alpha$ ,25-(OH)<sub>2</sub>D<sub>3</sub> in rabbits, and they reported new bone formation at the implant spirals<sup>21</sup>. In an experimental study in rabbits, implant surfaces coated with 1,25-(OH)<sub>2</sub>D<sub>3</sub> were better osseointegrated compared to uncoated implants<sup>28</sup>.

Clinical dentistry has focused primarily on surgical-prosthetic protocols and implant surfaces for improving osseointegration, despite any patient-associated risk factors<sup>8-10,26,67</sup>.

In a clinical trial, Alvim-Pereira et al. 2008, found no association between vitamin D receptor and implant failure<sup>19</sup>. Bryce et al. 2014, studied the relation between vitamin D deficiency and immediate implant placement, where in this case report, the patient had severe deficiency and this may be related to the failure of the implant<sup>25</sup>. In a randomized, controlled, double-blind study, Schulze-Spate et al. examined the combination of vitamin D<sub>3</sub> (5,000 IU) and calcium (600 mg) in new bone formation following sinus lift procedure<sup>30</sup>. A ten-strong group of subjects received vitamin D and calcium, while a ten-strong group of controls were randomized solely to calcium; a 6-8 months post-surgery histology was conducted<sup>30</sup>. Although the administration of vitamin D<sub>3</sub> delivered increased vitamin D levels with possible favorable outcomes in terms of bone formation, the researchers concluded on the absence of statistically significant difference between the two groups<sup>30</sup>. According to Mangano et al. 2016<sup>67</sup>, a serious vitamin D deficiency may be related to early implant loss. In fact, implant loss was low (2.2%) in patients with normal vitamin D levels in the blood (> 30 ng/mL), almost twice as high (3.9%) in patients with inadequate serum levels (10-30 ng/mL) and high (9.0%) in patients with severe deficiencies. However, despite the tendency for an increased incidence of early failure in patients with deficiency, the differences between the three groups were not statistically significant ( $P = 0.15$ )<sup>67</sup>. The same study also confirmed that the serum levels of vitamin D in the general population were low: it was found that the rate of patients with insufficient levels was 49.4% and of that, severe deficiency was 2.7%. The number of patients with adequate levels was 47.9%. Administration of vitamin D in the weeks before a dental implant may be useful, especially in patients with severe deficiencies and vitamin D administration should be maintained until the required levels are achieved<sup>67</sup>.

In 2018, the same team of researchers<sup>68</sup>, in a retrospective study of 885 patients, confirms the data

from their previous study. Patients with satisfactory vitamin D levels (>30 ng / mL) reported low failure rates (12/410 patients, 2.9%). The incidence of early failures almost doubled (20/448 patients, 4.4%) in the group of patients with inadequate vitamin D levels (10-30 ng/mL) and was nearly four times higher in patients with severe vitamin D deficiency (<10 ng / mL), which had an early failure rate of 11.1% (3/27 patients). Once again, the study showed an increase in early implant failures in patients with insufficiency, although the difference between the three groups ( $P = 0.105$ ) were not statistically significant<sup>68</sup>.

## Discussion

Low counts of vitamin D have been linked to a high risk of insulin-dependent (type I) diabetes, cardiovascular conditions, cancers/tumor growths, mild cognitive impairment, mood disorders, complications occurring during gestation, immune system disorders, allergies, and even physical weakness<sup>69-72</sup>. It is well established that vitamin D acts on one of the “standard” tissue-targets; the bones. Vitamin D controls calcium homeostasis by interfering with the absorption of calcium by the intestines, renal calcium re-absorption, and bone calcium metabolism. It has been found that moderate to severe lack of vitamin D in adults has been commonly linked to limited bone mineral content<sup>12</sup>. Nowadays, the application of dental implants represents a treatment of choice with excellent outcomes, when it comes to restore function and aesthetics in dental patients<sup>73,74</sup>. In fact, it is a predictable treatment plan featuring remarkable survival rates that stands high in the decision-making process for the replacement of missing teeth with a fixed or a removable prosthesis<sup>10,75,76</sup>. According to Bosshardt et al., “osseointegration” is the formation of an unmediated bone-implant interface<sup>76</sup>. In the early healing period, dental implants should be completely homogenized in the bone and, over time, the outcome is a clinically asymptomatic fixation under functional load<sup>73,77</sup>. Osseointegration depends on several factors such as the surgical and prosthetic protocol, the surgeon’s experience and authority, the time of the prosthetic loading, the surface and the material of the implant, and, of course, other patient-related parameters, i.e. bone quality and quantity, and systemic factors<sup>76-78</sup>. Hong et al. investigated the favorable effects of calcium and vitamin D supplements on bone healing progress by closely monitoring the post-operative recovery of surgically created alveolar sockets in a dog model<sup>79</sup>. Only a few animal studies were identified that aimed to investigate the assimilation of dental implants to the bones and the correlation of vitamin D levels<sup>20-24,27-29,31</sup>.

## Conclusion

Vitamin D systemic administration weeks before undergoing dental implant surgery may be beneficial to patients, especially those suffering from serious lack of this



**vitamin. Nevertheless, further randomized clinical trials are required to confirm the correlation of vitamin D levels with osseointegration of dental implants.**

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