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ORIGINAL ARTICLE

Influence of vitamin D in bone healing

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Abstract:

Introduction: Vitamin D is an hormone whose function is to maintain calcium and phosphorus homeostasis in order to ensure bone mineralization. Vitamin-D deficiency can lead to severe diseases, including an atypical mineralization of bone, because it decreases osteoblasts activity. It has become increasingly common and it has been mainly observed in obese people who avoid direct sunlight exposure to their skin and have a vitamin D-deficient diet. **Objectives:** Due to the high incidence of hypovitaminosis D in the world population, this study sought to provide an analytical and minute literature review associating vitamin D deficiency with bone healing. **Methods:** To accomplish this, a bibliographic research was conducted in the following database: Medline (PubMed), Science Direct, Scielo, Periódicos CAPES (Brazilian database), and Bireme (Latin-American database). **Results:** From the main longitudinal and meta-analytic studies, as well as the main studies conducted on animals, published between 1995 and 2015, 20 articles were selected according to the inclusion criteria. **Conclusion:** From this review, it was concluded that vitamin D influences the cellular process of bone healing and that the exact mechanism of this influence is still unclear.

Keywords: 25-Hydroxyvitamin D 2; Vitamin D Deficiency; Bone Diseases, Endocrine; Bone Regeneration.

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INTRODUCTION

Vitamin D deficiency is a common scenario in almost all continents and has been predominantly observed among people of African descent, since their skin pigmentation functions as a barrier to UV radiation. Cases of vitamin D deficiency also occur in obese people, since the adipose tissue stores vitamin D.

This phenomenon can also be observed in countries whose inhabitants have a vitamin D-deficient diet, as well as in countries where wearing clothes that cover most parts of the body is a cultural practice that prevents the skin's direct exposure to the sunlight[1]. In addition, vitamin D deficiency or insufficiency can be a result of anticonvulsant medication usage or metabolic disorders such as chronic liver diseases, chronic kidney disease, and metabolic acidosis[2].

Disorders or abnormalities in vitamin D activation and absorption mechanisms can lead to serious diseases. Since vitamin D is responsible for maintaining the metabolic balance of calcium, low levels of this ion can cause atypical bone mineralization and can also lead to a decrease in osteoblast activity. In children, this decrease manifests as rickets; in adults, it is seen as osteomalacia (bone demineralization) or as other diseases related to hypovitaminosis D[3–5].

Bone tissue has the ability to heal after an injury or surgical treatment. This healing mechanism involves complex cell integration, growth factors, and an extracellular matrix[6]. The healing process consists of restoring the continuity of damaged tissues without necessarily increasing bone volume. During the phases of the healing process, biological events are regulated by signaling molecules that can be categorized into the following groups: (1) proinflammatory cytokines; (2) members of the transforming growth factor-beta superfamily (TGF-β); and (3) angiogenic factors. Each of these cytokine and other protein groups are involved in biological activities that promote overlapping biological processes and interactions among the different types of cells[7].

Due to the high incidence of hypovitaminosis D in the world's population, this literature review has proven pertinent. This review considers the main studies conducted on animals, as well as the main longitudinal studies and meta-analyses that address the influence of vitamin D in bone healing.

MATERIALS AND METHODS

To identify the studies included in this review, a detailed search was conducted in the Medline (PubMed), Science Direct, Scielo, Periódicos CAPES, and Bireme databases. It included articles published from 1991 to 2015. The research was limited to the most recent articles written in English and Portuguese. The following keywords were used in different combinations: vitamin D, vitamin D deficiency, bone healing, and dental implant.

The inclusion criteria were scientific research conducted on animals and/or humans and/or systematic reviews. Clinical cases were excluded. After these criteria were applied, 22 articles were selected. The data were analyzed, compared, and discussed to produce this review.

LITERATURE REVIEW

Vitamin D

Vitamin D is an essential steroid hormone. It can be found in two forms: vitamin D2 (ergocalciferol) and vitamin D_3 (cholecalciferol)[3]. The major source of vitamin D, and of vitamin D_3 in particular (which is endogenous in origin), is its storage in the cutaneous tissue after exposure to ultraviolet-B (UV-B) radiation, a process which leads to vitamin D synthesis. Over 90% of vitamin D is endogenous in origin, and the other 10% to 20% is provided by diet. Vitamin D is indispensable and extremely important, especially for elderly populations with temperate climates[8,9].

Vitamin D_3 is absorbed through the consumption of animal products and is primarily found in deep-water, oily fish. Meanwhile, vitamin D2 can be ingested through the consumption of plants and is most commonly produced by fungi. It is important to note that exposure to UV-B radiation through the skin is responsible for activating vitamin D by converting 7-dehydrocholesterol to pre-vitamin D_3, which, in turn, is quickly converted to vitamin D_3, also known as cholecalciferol, in the dermis[9].

Vitamin D-binding protein, a carrier protein, is responsible for transporting vitamin D from the skin or intestine to the liver, where it is metabolized and yields 25-hydroxyvitamin D, or $25(OH)_2D$. Next, $25\ (OH)_2\ D$ will produce the active form of vitamin D in the kidneys: 1.25-dihydroxyvitamin D, also known as $1.25(OH)_2D$ or calcitriol, which is responsible for binding to the vitamin D receptor (VDR)[4].

It is known that $1.25(OH)_2D$ is one of the main regulators of calcium metabolism. Though it does not originate from an endocrine gland, it is the only vitamin thought to have a hormonal function, since its pathway of molecular modification yields active metabolites and its mechanism of action is similar to

that of steroid hormones. Vitamin D is important to bone mineralization, and a vitamin D insufficiency or deficiency can increase the chances of certain diseases (in addition to bone diseases), such as cardiovascular diseases, neoplasms, diabetes, multiple sclerosis, dementia, infectious diseases, and rheumatoid arthritis[10].

Castro[9] states that the crucial action of vitamin D consists of maintaining calcium and phosphorus homeostasis in order to ensure bone mineralization, which is essential to all stages of life. (Vitamin D *does* play other roles and is active in up to 3% of the human genome). According to Murray et al.[4], this homeostasis can be produced by the regulation of intestinal calcium absorption, reduced excretion through renal calcium reabsorption, and bone mineral mobilization. Moreover, vitamin D is involved in other events such as insulin secretion, differentiation of monocytic precursor cells, synthesis and secretion of parathyroid hormone and thyroid hormones, and inhibition of interleukin and immunoglobulin synthesis.

When consumed concomitantly with vitamin D-rich food, some substances can increase or decrease the bioavailability of vitamin D in the body. Milk, for instance, increases vitamin D bioavailability; when it is concomitantly consumed with natural sources of vitamin D, it maximizes vitamin D absorption by a factor of 3 to 10 due to the lactalbumin in its composition. Long-chain fatty acids also support the absorption of this vitamin. Alcohol and fiber, on the other side, contribute to calciferol loss through the bile, which reduces vitamin D bioavailability in the body[11].

Synthesis of 1.25(OH)2D

In humans, the skin is considered the sole site able to metabolize 7-dehydrocholesterol. Both the dermis and the epidermis already contain provitamin D (7-dehydrocholesterol) in their natural composition. Upon direct exposure of the skin to UV-B radiation at a wavelength of 290-315 nm, provitamin D (7-dehydrocholesterol) produces pre-vitamin D_3, which turns into vitamin D after 24 hours[5].

This synthesis is determined by several factors, which vary depending on latitude, season of the year, skin pigmentation, clothing type, use of sunscreen, and the amount of sunlight. Therefore, 1.25$(OH)_2$D levels are influenced by environmental, hormonal, nutritional, and genetic factors[10].

When these metabolites are consumed as vitamin D_2 and vitamin D_3, they are simultaneously absorbed by the small intestine and incorporated into chylomicrons, which are directed to the lymphatic system and the blood system and finally reach the hepatic portal system. In the liver, the cytochrome P450-like enzyme will guide hydroxylation by converting 1.25$(OH)_2$D into 25(OH)D, which has a greater concentration in the blood system.

Levels of 25(OH)D are directly proportional to the amount of vitamin D produced in the skin. The last phase of synthesis takes place in the kidneys through 1α-hydroxylation, which occurs mainly in the proximal tubule cells. This stage produces 1.25$(OH)_2$D, which is the biologically active substance[12].

The figure below illustrates vitamin D metabolism (Figure 1).

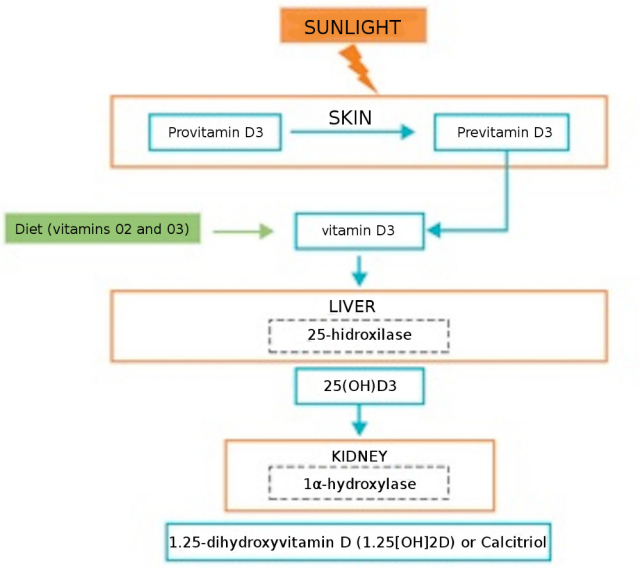

Figure 1. Vitamin D Metabolism. Source: Alves et al., 2013[10].

The concentration of 1.25$(OH)_2$D represents nearly 0.1% of the prohormone 25(OH)D. Its formation is influenced by parathyroid hormone (PTH), and its inhibition is triggered by the fibroblast growth factor 23 (FGF-23), which is synthesized in the osteocytes and osteoblasts. Therefore, a reduction in 25(OH)D stimulates PTH production, maintaining homeostasis via a negative feedback mechanism[13].

The action of 1.25$(OH)_2$D is initiated through this compound link to VDRs, which are nuclear and which have a greater affinity for calcitriol than for 25(OH)D. These receptors trigger the formation of a complex with the retinoic acid X receptor (RXR), resulting in a heterodimeric binding to calcitriol, which will finally bind to DNA.

This interaction enables transcription, which is the synthesis of messenger RNA that involves certain proteins (namely alkaline phosphatase in the osteoblasts, osteocalcin, and the specific protein, whose affinity for calcium at the level of intestinal cells increases the absorption of this mineral[3].

Therefore, intestinal VDR concentrations intimately interfere in calcitriol efficacy. Such phenomenon is observed in the elderly, who have a reduced quantity of VDR, resulting in a resistance to calcitriol, which, in turn, reduces calcium absorption[3].

Vitamin D Levels

The level of vitamin D that determines its efficacy is obtained by measuring the serum concentration of 25(OH)D. This plasma dosage also contributes to the evaluation of endogenous intoxication. Considering 1 ng/mL as 2.496 nmol/L, values of 25(OH)D ≤ 20 ng/mL indicate vitamin D deficiency, while values ranging from 21-29 ng/mL indicate vitamin D insufficiency, and values ≥ 30 ng/ mL indicate normal levels[13].

The biologically active compound 1.25(OH)2D is not usually measured for this purpose, since (OH) D plasma levels are approximately one hundred times higher and have a much greater half-life than $1.25(OH)_2D$[14].

Measurements of 1.25(OH)2D serum levels are indicated in patients with chronic kidney disease, rickets influenced by vitamin D levels, and granulomatous disease caused by hypercalcemia[13].

An optimal concentration of 25(OH)D would be able to maintain adequate levels of parathyroid hormone. Therefore, this association produces improved definitions of calciferol deficiency and insufficiency that the use of increased serum PTH. When 25(OH)D levels are reduced to a level lower than 30 ng/mL or 75 nmol/L, serum calcium decreases, stimulating parathyroid gland to release parathyroid hormone. This change increases PTH levels and results in calcium reabsorption in the kidneys and bones[15].

Vitamin D Properties

The biological effects of $1.25(OH)_2D$ are numerous and are not exclusive to the skeletal system. They begin when the active form of vitamin D binds to the VDRs in the kidneys, intestine, parathyroid glands and bones, in which a complex is formed. The kidney is considered one of the prime sites for 1α-hydroxylation of vitamin D; however, other sites, such as the breasts, prostate, colon, pancreas, and immune cells, also perform the same function in the presence of CYP27B1 and VDRs, exerting local autocrine and paracrine effects[14].

Thus, certain functions are triggered by calcitriol in the regulation of intracellular calcium as part of the pancreas's insulin release process, as well as in the release of prolactin by the pituitary gland, in the control of the skeletal muscles, and in its involvement in creatinine clearance. Calcitriol also generates a paracrine effect on the skin, preventing fibroblast and keratinocyte proliferation but contributing to the terminal differentiation of keratinocytes[5].

In the immune system, calcitriol performs many tasks. It induces the differentiation of T cells and B cells, thus decreasing T cells' capacity to produce interleukin-2 and increasing the percentage of cells that are required to produce interleukin-6 and interleukin-12. It blocks immunoglobulin production through lymphocytes. It stimulates monocyte differentiation into macrophages, thus inducing the production of interleukin-1. It adjusts and activates CD4 lymphocyte differentiation. It increases the quantity of regulatory T (TREG) cells and stimulates their function. It also reduces the synthesis of IFN-g, IL-2 and TNF-a cytokines through the stimulus of Th1 cells and Th2 cells, and it inhibits NKT cell signaling and IL-17 synthesis by the Th17 cells[5,12].

The role of vitamin D in cancer is often unclear. The articles divide the choices between vitamin D and have a protective role in various types of cancer. The protection pathway is understood as follows: in the cell cycle, calcitriol binds to VDR and modulates the G0 / G1 phase, which interferes in several other phases, such as differentiation, multiplication, and apoptosis. This modulation interferes in the amount of vascular endothelial growth factor (VEGF), inhibiting tumor angiogenesis. Thus, it is not agreed that reduced 25(OH) D levels necessarily lead to cancers such as breast, prostate, colorectal, and pancreatic cancer. The most commonly studied type of cancer is skin cancer (non-melanoma and melanoma)[9].

Among the many functions performed by calcitriol, its primary functions involve intestinal calcium reabsorption, interference of renal calcium reabsorption in the proximal convoluted tubule, and regulation of *parathyroid hormone* (PTH). Therefore, a long-term vitamin D deficit may contribute to the occurrence of rickets in children and osteomalacia in adults. It may also contribute etiologically to osteoporosis, which produces a risk of fractures in the elderly[12].

Other activities have a positive impact on bone formation. These activities include the stimulation of osteocalcin and receptor activator of NF-kappaB ligand (RANKL) synthesis, which triggers the maturation of osteoclast precursors and thus mobilizes calcium deposits in the bone structure. In doing so, the process maintains a balanced concentration of this mineral in the body. Another function that contributes positively to bone formation is the stimulus of *in vitro* differentiation of the precursors of monocytes-macrophages into osteoclasts[12].

Vitamin D Deficiency

Bone Healing

An *in vivo* study was performed by Sun et al.[16] in order to evaluate bone healing with the use of vitamin D in cases of vitamin D defects created in rats. To conduct the evaluation, the researchers performed a radiographic analysis, histological staining, and epifluorescence microscopy for a 9-week period. The defect groups received 1 x 10^6 of mononuclear bone marrow cells delivered using a gelatin sponge with or without 10 µg of DBP (referred to as the BM and BM-DBP-10 groups, respectively). Another group received 50 µg DBP, and three defects of the BM group were found to be completely filled with bone tissue. In all the other defects, pseudarthrosis occurred. Although the histological and epifluorescence observations confirmed that the addition of bone marrow mononuclear cells did not resolve the defect, enhanced or accelerated bone ingrowth was observed.

Bee et al.[17] conducted a retrospective study in orthopedic trauma patients who underwent fracture repair surgery to determine serum levels of vitamin D during the winter and the summer. The results showed a high incidence of vitamin D deficiency in serum levels in orthopedic trauma patients in both seasons, though these levels did not influence bone healing. The authors confirm that no consensus has been reached regarding how to quantify serum levels of vitamin D and that there may therefore be laboratory errors in this measurement. They encourage further studies to confirm bone healing after the normalization of vitamin D serum levels.

Other authors performed a systematic literature review[18] to determine the role of vitamin D in human bone healing and concluded that vitamin D supplementation produces a beneficial effect among vitamin D-deficient patients. However, clinical studies addressing the effects of vitamin D deficiency and supplementation on bone healing are scarce and remain inconclusive.

Allison et al.[19] developed a questionnaire for male athletes with questions on country of origin, involvement in sports activities, skin type, amount of daily sun exposure, and the use of sunscreen, food supplements and/or medications. They used this questionnaire to determine whether there is an association between vitamin D deficiency and bone health markers in athletes. The authors performed bone densitometries and X-ray densitometries, and also measured serum levels of vitamin D. Their study demonstrated that there is no association between vitamin D and bone health markers that can be based on age, ethnicity, or the extent of sports activity.

Periodontium

Bashutski et al.[20] conducted a study in humans to evaluate the influence of vitamin D on the periodontium. The subjects were monitored to determine bone alkaline phosphatase levels in serum during the drug administration phase (teriparatide with insufficient vitamin D, teriparatide with sufficient vitamin D, and placebo with sufficient vitamin D, and placebo with insufficient vitamin D).

The study demonstrated that vitamin D deficiency after periodontal surgery negatively affects the results of treatment for up to 1 year. These findings suggest that vitamin D levels may be critical for postoperative healing. Vitamin D supplementation during surgery is not able to ensure appropriate levels of vitamin D and achieve the best possible results. Therefore, supplementation is recommended well in advance of periodontal surgery so that the best possible results may be obtained.

Osseointegration

Regarding the influence of vitamin D on osseointegration, Kelly et al.[21] performed a study on vitamin D-deficient rats. The results suggest that vitamin D insufficiency significantly affects the osseointegration of implants. In addition, these unsuccessful implant results may be confused with the prevalence of vitamin D deficiency.

Akhavan et al.[22] evaluated the influence of vitamin D supplementation on osseointegration in diabetic rats. One group received oral supplementation of vitamin D_3, and the other did not. The authors concluded that vitamin D has no effect on the osseointegration of implants in diabetic rats after three- and six-week periods.

Osteoporosis

In order to evaluate the effect of vitamin D deficiency on osteoporosis, Melhus et al.[15] performed a

study on ovariectomized Wistar rats on a diet deficient in vitamin D. A closed midshaft tibial fracture was performed, and serum levels of 25(OH)D and estradiol, dual energy X-ray densitometry and histomorphometric analyses were performed. The analyses suggested that systemic effects on estrogen and vitamin D deficiency are not critical for bone healing or the mechanical properties of the fracture repair area. In light of these findings, the low scarring may not have been caused by the decrease in or lack of estrogen or vitamin D, but instead by the fracture or osteosynthesis procedure.

Diabetic

Mao et al.[23] conducted an *in vivo* study to analyze the role of vitamin D in bone healing in diabetic female rats. The results confirm that vitamin D deficiency associated with diabetes decreases bone mineral density; however, it does not affect bone healing. The authors also concluded that vitamin D supplementation may be useful as a complement to treatment for osteoporosis and fractures, particularly in diabetic patients.

DISCUSSION

Research on vitamin D and its effects on bone healing is still scarce, but even with the small number of studies available in the literature, it was possible to see consistencies in the information provided by the scientific community and to emphasize the importance of vitamin D in bone healing (Table 1).

Vitamin D deficiency has a significant influence on bone healing mechanisms, and most of the authors considered herein emphasized the important role of vitamin D in bone mineral density and the need to maintain adequate vitamin D levels in the body. Studies have proven that vitamin D has an anabolic effect on osteoblasts, meaning that it has the ability to increase bone growth. However, other authors have suggested that bone regeneration may be explained by the effects of inhibited osteoclast function[2,13,16-19].

As modern lifestyles have shifted from agricultural activities to urban activities, the amount of exposure to ultraviolet B to has plummeted, and vitamin D deficiencies have increased. This is even more common during the winter months, especially in countries in which dietary supplementation is not consistently performed[21]. This situation has also been observed with increasing prevalence in individuals of African descent, whose skin functions as a barrier to UV radiation. It has also become more common in obese individuals, since adipose tissue is able to store vitamin D. These factors favor and explain the worldwide prevalence of vitamin D deficiency.

Calciferol deficiency triggers a decrease in osteoconduction, which compromises the osseointegration of bone implants[21,24]. Finkelman et al.[24] analyzed growth factors (TGF-β) present in the bone matrices of rats and found that a vitamin D deficiency reduces TGF-β deposits in the bone matrix. This finding is consistent with the theory that vitamin D and the TGF-β derived from bones are necessary for the successful osteoinduction and osteointegration of bone implants. However, Akhavan et al.[22] reported that the osseointegration of implants in diabetic rats is not influenced by vitamin D. Thus, more complex studies on the role of vitamin D in bone implants are required for any conclusions to be reached.

Mao et al.[23] found that, in the presence of diseases such as diabetes, vitamin D has an influence on bone tissue: a vitamin D deficiency further aggravates the bone demineralization caused by the disease itself. Given this result, other authors 20 have suggested the importance of vitamin D in the clinical treatment of osteoporosis and bone regeneration, as well as in the increase in chondrogenesis at the site of injury, and they argue that vitamin D is useful whether is endogenic or acquired via supplementation.

The presence of a fracture or bone defect was also considered in studies conducted by Melhus et al.[15], Sun et al.[16] and Gorter et al.[18]. These studies demonstrated that vitamin D affects bone healing through effects on inflammatory cells, cytokines, growth factors, osteoblasts, osteoclasts, and the mineralization process; however, this effect is considered insufficient to achieve complete repair. Furthermore, the details of this mechanism of action have not been clearly elucidated, especially in terms of the exact role of vitamin D on healing human bone fractures[15,18].

Sun et al.[16] argue that the biologically active form of vitamin D_3 has been emphasized not only because of its influence in bone metabolism, but also because it triggers immunomodulatory activities that may impact bone formation and resorption. However, it is not known whether calciferol has a direct effect on the proliferation, differentiation, or anabolic function of osteoblasts. Therefore, *in vitro* studies are essential to determine whether this hormone has the potential to produce such effects.

Bashutski et al.[20] concluded that individuals with periodontal disease and who had undergone surgical

Table 1. Research regarding vitamin D and its effects on bone healing.

Author/Year	Experimental Model	Groups	Analyses	Perlods	Conclusion
ALLISON et al., 2015	Humans	1. Control 2. Athletes	Densitometry of bone Dual energy X-ray densitometry. Serum levels of vitamin D	-	There is no association between 25 (OH) D. BMD and T-score for any place analyzed, of male athletes after adjusting for age, ethnicity and sports activity.
MAO et al., 2014	Rats	1. Control 2. Diabetics	Computed tomography, Bone densitometry, PCR, Histological analysis, Serum levels of 25 (OH) D, calcium, phosphorus, parathyroid hormone and alkaline phosphatase..	04 weeks	The vitamin D deficiency aggravates the decline in bone mineral density of female rats in the diabetic state, although vitamin D deficiency does not affect bone repair delayed by the diabetic state.
BEE et al., 2013	Human	1. Serum vitamin D leveis in winter; 2. Serum vitamin D levels in the summer.	Serum levels of vitamin D 25 (OH) levels	3 months	There was a high incidence of serum deficiency of vitamin D levels in the group of patients with orthopedic trauma in all age groups and in both summer and winter months.
AKHAVAN et al., 2012	Rats	1. Control 2. vitamin D3	Histological analysis	3 and 6 weeks	Vitamin D has no effect on osseointegration of implants in diabetic rats.
BASHUTSKI et al. 2011	40 subjects with severe periodontal disease who received periodontal surgery	1. Teriparatide 2. Placebo 3. Vitamin-D-sufficient 4. Vitamin D deficient 5. Placebo and vitamin D deficiente 6. Teriparatide with vitamin D-sufficient	Monitored levels of serum alkaline phosphatase Loss of clinical insertion; Weld depth evaluation: Evaluation of linear bone gain	6 weeks and at 3, 6, 9 and 12 months	Vitamin D deficiency at the time of periodontal surgery adversely affects treatment results for up to 1 year.
JAMES, et al.,2009	Rats	1. Control; 2. Vitamin D deficient	Scanning electron microscopy, Histology not decalcified Histomorphometric evaluation of osseointegration Push-in test	14 days	The effect of vitamin D insufficiency on osseointegration of implants.
SUN et al., 2009	Rats	1. Local application 2. Simulated operation group.	Radiographic Evaluation Fluorescence Microscopy Histological Analysis	9 weeks	Only one specimen of the BM--PAD-10 and DBP-50 and three BM group specimens were solidly cured; Pseudo-arthrosis occurred in all other
MELHUS et al., 2007	Rats	1. Control 2. Vitamin D deficient.	Serum levels of 25 (OH) D and estradiol Dual energy X-ray densitometry Histomorphometry.	12 weeks	The systemic effects of estrogen and vitamin D deficiency are not crucial for bone healing or mechanical properties of callus.
FINKELMAN, et al., 1991	Rats	1. Vitamin D sufficient 2. Vitamin D deficient	Colorimetric test Chromatography Absorption spectroscopy	08 weeks	The vitamin D and bone derivatives TGF/ 3 are required for normal skeletal repair.

procedures, obtained unsatisfactory results due to reduced levels of calciferol. Their results suggest that vitamin D supplementation should be provided before periodontal surgery, since serum levels take time to become established after supplements are ingested. Their study therefore associates the importance of the role of calciferol with the periodontal post-surgical healing.

According to Bee et al.[17], a contributing factor to bone fractures in humans is a low serum concentration of vitamin D, regardless of age or season. However,

Alisson et al.[19] analyzed the relationship between vitamin D serum levels and bone health in an ethnically diverse athletic population, and they concluded that the osteogenic effect of weight-bearing exercise is enough to provide satisfactory bone health, regardless of the serum level of vitamin D. Therefore, no association between calciferol and bone maintenance was found.

CONCLUSION

Based on the evidence from the studies included in this review, it is possible to affirm that vitamin D influences the cellular process of bone healing; however, the exact mechanism of this influence has not yet been defined.

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