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Review Article

The Role of Vitamin D in Bone Healing and Bone Integration

O Papel da Vitamina D na Consolidação e na Integração Óssea

El Papel de la Vitamina D en la Consolidación y la Integración Ósea

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Abstract
The historical quest for replacing lost teeth dates back to ancient civilizations, evolving into modern advancements in the field of implant dentistry. This article provides a literature review, highlighting the role of vitamin D in osseointegration and in the practice of implant dentistry. Firstly, a search was conducted in Capes/Cnpq databases, Virtual Health Library, PubMed, and Google Scholar-indexed databases using the following health descriptors (DeCS): Vitamin D, Osseointegration, and Dental Implants. Vitamin D emerges as a critical component in maintaining bone tissue homeostasis, influencing the absorption of calcium and phosphorus, essential for bone remodeling. Despite the clear importance of vitamin D in osseointegration, the shortage of longitudinal studies in humans is evident, emphasizing the need for further research in this area to fully elucidate its influence and optimize clinical outcomes in implant dentistry. This study underscores the need for an integrated approach in implant dentistry practice, considering not only the technical aspects of procedures but also systemic factors such as adequate vitamin D supplementation to promote osseointegration and ensure long- term success of prosthetic rehabilitations on implants.
Descriptors: Vitamin D; Osseointegration; Dental Implants.
Resumo
A busca histórica pela substituição de dentes perdidos remonta às civilizações antigas, evoluindo para os avanços modernos na área da implantodontia. Este artigo apresenta uma revisão da literatura, destacando o papel da vitamina D na osseointegração e na prática da implantodontia. Inicialmente, foi realizada uma busca nas bases de dados Capes/Cnpq, Biblioteca Virtual em Saúde, PubMed e Google Scholar, utilizando os seguintes descritores de saúde (DeCS): Vitamina D, Osseointegração e Implantes Dentários. A vitamina D emerge como um componente crítico na manutenção da homeostase do tecido ósseo, influenciando a absorção de cálcio e fósforo, essenciais para a remodelação óssea. Apesar da clara importância da vitamina D na osseointegração, a escassez de estudos longitudinais em humanos é evidente, enfatizando a necessidade de mais pesquisas nessa área para elucidar completamente sua influência e otimizar os resultados clínicos na implantodontia. Este estudo destaca a necessidade de uma abordagem integrada na prática da implantodontia, considerando não apenas os aspectos técnicos dos procedimentos, mas também fatores sistêmicos, como a suplementação adequada de vitamina D para promover a osseointegração e garantir o sucesso a longo prazo das reabilitações protéticas sobre implantes.
Descritores: Vitamin D; Osseointegração; Implantes Dentários.
Resumen
La búsqueda histórica de reemplazar los dientes perdidos se remonta a las civilizaciones antiguas, evolucionando hacia los avances modernos en el campo de la implantología dental. Este artículo presenta una revisión bibliográfica que destaca el papel de la vitamina D en la osteointegración y en la práctica de la implantología dental. En primer lugar, se realizó una búsqueda en las bases de datos Capes/Cnpq, la Biblioteca Virtual en Salud, PubMed y Google Scholar utilizando los siguientes descriptores de salud (DeCS): Vitamina D, Osteointegración e Implantes Dentales. La vitamina D emerge como un componente crítico para mantener la homeostasis del tejido óseo, influyendo en la absorción de calcio y fósforo, esenciales para la remodelación ósea. A pesar de la clara importancia de la vitamina D en la osteointegración, la escasez de estudios longitudinales en humanos es evidente, lo que subraya la necesidad de más investigación en esta área para dilucidar completamente su influencia y optimizar los resultados clínicos en implantología dental. Este estudio subraya la necesidad de un enfoque integral en la práctica de la implantología dental, que considere no solo los aspectos técnicos de los procedimientos, sino también factores sistémicos como la suplementación adecuada de vitamina D para promover la osteointegración y garantizar el éxito a largo plazo de las rehabilitaciones protésicas sobre implantes.
Descriptores: Vitamina D; Oseointegración; Implantes Dentales.

INTRODUCTION

The quest to replace lost teeth has been documented throughout history for millennia. Ancient civilizations sought various methods to restore the teeth of edentulous patients using a wide variety of materials. Dental implants made of gold, wood, platinum, silver, tin, and porcelain have been

found in the jawbones of our ancestors. Dental implantology, as we know it today, began in the 1950s in the city of Gothenburg, Sweden, where orthopedic surgeon Per Ingvar Bränemark and his team-initiated studies on osseointegration after noticing that titanium micro-implants placed in the tibia of rabbits, in a study on microvascularization, integrated with living bone tissue. Thus, the concept of osseointegration was defined as the process of direct connection between the surface of an implant and living bone tissue, both structurally and functionally, under occlusal load[1,2].

The maintenance of bone tissue homeostasis depends on systemic and local factors, the main ones being the parathyroid and thyroid glands, glucocorticoids, bone morphogenetic proteins, prostaglandins, cytokines, and certain micronutrients[3].

In addition to calcium and phosphate, many other micronutrients have been shown to influence the mechanisms of bone remodeling and formation, such as magnesium, zinc, fluoride, vitamin B6, and, most importantly, the focus of this study[4]: vitamin D.

Vitamin D can be obtained in its inactive form through skin exposure to ultraviolet rays emitted by the sun, through diet, and through supplementation. For it to become active, it must undergo two types of hydroxylation. The first occurs in the liver, where it is converted from its inactive form to calcidiol (25-hydroxy-cholecalciferol), and the second in the kidneys, which transform it into its final active form, known as calcitriol (1,25-dihydroxy-cholecalciferol)[5,6]. Vitamin D plays an important role in bone physiology by promoting calcium uptake and absorption, helping to maintain adequate serum levels of calcium and phosphorus in the tissue environment—minerals that are essential for bone tissue metabolism and bone remodeling[3,5]. Due to its direct relationship with bone homeostasis, cases of hypovitaminosis are commonly found in patients with impaired bone repair following accidental or surgical injuries, osteoporosis, osteomalacia, and also in periodontitis[7].

Peri-implant tissues play a key role in protecting and maintaining osseointegrated implants. The success and longevity of prosthetic restorations on implants also depend on the stability and health of these soft tissues. Calcitriol acts by regulating and reducing inflammatory processes in these tissues, in addition to helping cells promote better marginal sealing, which reduces the risk of peri-implant sulcus infection[4,8]. Poor or negative outcomes may be observed in these tissues following surgical intervention in patients with vitamin D deficiency[9].

In recent years, numerous studies have concluded that vitamin D is closely linked to the functioning of other physiological systems, such as the cardiovascular, nervous, immune, digestive, and musculoskeletal systems. Therefore, serum levels of this vitamin should be analyzed in patients undergoing bone reconstruction surgery and implant placement, particularly in immunocompromised patients and those with autoimmune and degenerative diseases[6,10].

As a result of its direct involvement in the homeostasis of the immune system and bone metabolism, the focus of this study is to conduct a literature review on the importance of Vitamin D for the practice of comprehensive implant dentistry with higher success rates.

MATERIAL AND METHOD

This literature review was conducted through a search of the Capes/Cnpq databases, the Virtual Health Library, PubMed, and databases indexed by Google Scholar, using the following health-related subject headings (DeCS): Vitamin D, osseointegration, and dental implants. Articles in English, Spanish, and Brazilian Portuguese were selected for the literature review. Initially, 89 results were found, of which 29 were selected after filtering. These include in vivo and in vitro experimental studies, clinical studies, and systematic literature reviews.

LITERATURE REVIEW

The complex events of the bone healing process around implants begin immediately after their placement in the previously prepared bone bed, through the onset of an inflammatory process. Through blood flow and blood content, platelets, red blood cells, monocytes, polymorphonuclear inflammatory cells, growth factors, and cell differentiation factors simultaneously reach the injured site via the action of signaling proteins and perform their functions. The fibrin matrix formed during these events facilitates osteoconduction, serving as a scaffold for the migration of osteoblasts and undifferentiated mesenchymal cells to the site. Osteoblasts drive osteoinduction, the final step for bone neoformation to begin[11].

Several factors are taken into account to ensure that osseointegration is achieved properly. These include: the surgical techniques and protocols employed; the surface treatment and design of the implant; the condition and quality of the bone bed; the patient's age and systemic and local health status; the choice of how to secure the fixed prosthesis to the implant—whether cemented or screw-retained—as well as its proper fit. Failures in implant dentistry can occur even when all the factors mentioned above are adhered to and favorable. These cases require greater attention to be resolved and are related to deficiencies in the production or absorption of important components of bone metabolism[12].

Implant-related failures can be classified as

early, when the implant never integrates with the living bone tissue and is lost before or during the placement of an abutment (prosthetic/healing abutments), and late, when implant loss occurs after the placement of the prosthetic crown and exposure to occlusal load[13].

Vitamin D is currently classified as an autocrine and paracrine fat-soluble steroidal prehormone that helps modulate the expression of more than 200 genes and actively participates in many pathological and physiological processes, with a large proportion of human cells possessing specific receptors for it[14,15]. It can be obtained naturally as Vitamin D3 (cholecalciferol) through skin exposure to ultraviolet B and C rays (UVB and UVC), which account for 90% of the amount required by the human body, and through the consumption of certain animal-based foods, such as fatty fish, liver, and egg whites. It is also available as Vitamin D2 (ergocalciferol), obtained through the consumption of plant-based foods such as certain mushrooms and plants[15,16].

For the process of absorbing and converting ultraviolet rays into vitamin D to occur properly and without causing tissue damage, the skin must be exposed to wavelengths of 290–315 nm for approximately 15 to 30 minutes. After its synthesis, it is found in an inactive form, to then be converted into its active form by the kidneys and liver[10,11,17]. Therefore, it can be understood that populations in countries with a higher number of sunny days and exposure to UVB and UVC levels considered adequate for good in vivo vitamin D production are theoretically less likely to develop hypovitaminosis[18]. Furthermore, it is a fact that individuals of African descent have greater difficulty obtaining vitamin D3 because they possess higher levels of melanin, a protein that is directly responsible for protecting the skin against solar radiation and consequently blocks a significant portion of the synthesis of this prohormone in the skin[19].

For an accurate assessment of vitamin D levels in the human body, it is recommended to request that the clinical laboratory measure serum 25(OH)D levels, a marker present in higher concentrations and with a long half-life. This test will be performed by collecting peripheral venous blood from the patient. Reference values will be analyzed in nanograms per milliliter (ng/mL). Generally, in initially healthy patients, values below 10 ng/mL indicate vitamin D deficiency. Levels between 10 and 30 ng/mL are considered low, while values above 30 ng/mL are considered optimal.

When serum levels exceed 100 ng/mL, toxicity may occur, resulting in hypercalciuria. At levels of 150 ng/mL or higher, hypercalcemia may be observed, which can lead to vascular calcifications and acute nephritis[20,21].

Although calciferol supplementation is justified in individuals with concentrations between 20 and 30 ng/mL, to date there is no consensus on the values considered ideal. Therefore, treatment should be individualized according to each patient's clinical presentation[21,22].

DISCUSSION

During the literature review, several in vivo studies were identified that examined the influence of vitamin D on bone and peri-implant tissue repair. However, it is a fact that few clinical analyses and comparisons have been conducted in humans. This is because animal studies are more numerous due to their greater accessibility and the ease of maintaining strict control over experimental protocols. Therefore, the reports will be organized, divided, and discussed into animal studies and human studies.

- *Animal Studies.*

Oxidative stress caused by hyperglycemia in patients with diabetes mellitus (DM) delays the osseointegration process and the healing of peri-implant tissues. The existence of a cross-relationship between DM and Vitamin D is well established in the literature, with an increased risk of developing this condition when 25(OH)D levels are insufficient[23].

Some authors then analyzed osseointegration in diabetic rats supplemented with vitamin D. The inclusion criteria for the study differed. Akhavan et al.[24] used rats with glucose levels between 130 and 200 mg/dL as a parameter, while Xiong et al.[23] used a value of 300 mg/dL. The first group of researchers conducted a simpler study and divided the rodents into two groups: control and supplemented. They concluded that there were no significant differences in bone tissue formation around the implants between the groups during the 3- to 6-week period following surgery. In contrast, the second group, in a study with a greater number of variables, divided the animals into five groups: control, diabetic, diabetic treated with insulin, diabetic treated with vitamin D3, and diabetic treated with both insulin and vitamin D3. They demonstrated that the group of diabetic rats treated with insulin and supplemented with calcifediol exhibited better osseointegration capacity compared to those treated with insulin alone.

They found that vitamin D supplementation reversed impaired bone healing by helping to maintain blood glucose levels and supporting the repair process.

Zhou et al.[25] observed through micro-CT analysis and histological examinations that vitamin D supplementation in rats induced to develop osteoporosis, compared to a control group of unsupplemented rodents, improved

osseointegration, increased bone volume percentage, and enhanced the quantity and quality of newly formed bone trabeculae around implants placed in the proximal tibia of these animals.

Liu et al.[26] demonstrated that vitamin D supplementation in rats with chronic kidney disease (CKD) helped correct the hyperparathyroidism secondary to the induced osteopenia. The cumulative benefits of $1,25(OH)_2D$ resulted in improvements in osseointegration and increased resistance during implant removal from the rodents' femurs.

Salomó-Coll et al.[27] in a pilot study involving 6 American Foxhound dogs, compared levels of bone formation and bone-implant interface contact between conical titanium implants immersed in a 10% vitamin D solution and implants with only the original factory surface treatment, using histomorphometric and histological analyses. Implantation was performed immediately after extraction of the distal roots of mandibular premolars. They concluded that topical application of vitamin D to the surface of the placed implants reduced alveolar bone crest loss and increased bone-implant contact by 10%. In 2018, they conducted another pilot study using a similar methodology, this time comparing the implants mentioned above with those treated with a topical application of 5% melatonin on their surfaces[28]. The results showed significant improvements in bone tissue formation around the implants treated with 10% vitamin D and 5% melatonin on their surfaces. In addition to helping reduce alveolar bone loss after 12 weeks of osseointegration.

- *Humans Studies.*

Kwiatek et al.[8] conducted a study involving 122 participants to compare cervical bone levels around dental implants using radiographic examinations taken at three different time points: immediately after implant placement, after 6 months, and after 12 months. The patients were divided into three groups based on their serum vitamin D levels. It was noted that the correct level of 1,25-dihydroxycolecalciferol (30 ng/mL) had a significant influence on the increase and preservation of peri-implant bone level.

Garg et al.[29] in turn, demonstrated that satisfactory serum vitamin D levels (>30 ng/mL) also influence the maintenance of the peri-implant alveolar ridge. The evidence for this finding was obtained through a prospective, randomized clinical trial involving 32 implants placed in the posterior mandibular region in 32 patients with vitamin D deficiency (<30 ng/mL), who were divided into two groups. Group 1 consisted of individuals supplemented with 60,000 IU/month of calcifediol, and Group 2 consisted of individuals without supplementation. At the 3-month follow-up after implant placement, periapical radiographs revealed statistically significant differences in bone levels of the distal alveolar bone crest, whereas at the 6-month follow-up, the differences found were insignificant.

Bawa et al.[12] conducted a study involving 100 individuals in good general health, aged 18 to 55, to investigate whether there is a link between early dental implant failure and vitamin D deficiency. The implants were placed in edentulous areas by the same surgeon using the same surgical standards. The groups were divided according to the standard 25(OH)D classification. The evaluation was performed three months after implant placement, during the second surgical phase, using periapical radiographs (assessment of peri-implant radiolucent areas) and reverse torque tests; implants with a value less than 30 N/cm were considered mobile. It was then noted that among the 100 implants placed, only seven were lost. In the final comparison between the groups, it was observed that there were no statistically significant differences between serum Vitamin D levels and early implant failure.

In a large-scale study involving statistical analyses of early failures, Mangano et al.[20] evaluated 822 volunteers between January 2003 and December 2015. A total of 1,625 implants were placed in regions with no history of prior guided bone regeneration, and 27 early failures occurred. The mean serum vitamin D level among individuals who lost their implants was 25.5 ng/mL. Furthermore, the data showed that the failure rate was nearly twice as high in individuals with low 25(OH)D levels (4.4%) and nearly four times higher in those with severe deficiency (11.1%), compared to those with serum levels considered ideal or optimal (2.9%). However, the authors consider that more rigorous studies are necessary to definitively establish the connection between the variables studied.

CONCLUSION

The importance of vitamin D3 in bone repair and formation processes is well established in the literature. This literature review shows that cases of vitamin D deficiency—whether or not associated with comorbidities such as diabetes mellitus, chronic kidney disease, and osteoporosis—directly and/or indirectly reduce the success rate of osseointegration.

As demonstrated in this study, to date there is a scarcity of studies on the proposed topic. Among those found, only four were conducted on human samples. Therefore, further longitudinal studies in humans are needed to truly understand the direct relationship between vitamin D and osseointegration.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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