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Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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abstract

Dental surgeons, maxillofacial surgeons and implantologists are increasingly interested in the effects of vitamin D on bone metabolism and the immune system. The correct concentration of this prohormone potentially correlates with success at each stage of osteointegration of endosseous implants.

A review of literature related to the topic of the paper.

A suitable level of vitamin D3 is crucial from the day of surgery. It influences the modulation of the immune system - increases the production of cathelicidin and defensin, and reduces the expression of proinflammatory cytokines. It also has a positive effect on bone metabolism in osteo-suppression via the induction of osteoblasts and osteoclasts and continuous bone remodeling around the implant after prosthetic restoration.

The prevalence of low vitamin D levels in the European population leads to the conclusion that a high deficit is not a factor directly responsible for failures in the process of osteointegration.

Key words: vitamin D3, calcitriol, osteointegration of implants.

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INTRODUCTION

Vitamin D3 was discovered in 1919 by Mellanbe, who for the first time showed that nutritional deficiencies can affect the occurrence of rickets [1]. A hundred years earlier, Polish researcher Jędrzej Śniadecki noticed that children living in urban areas, where extensive air pollution and narrow streets limited the access to sunlight, were more likely to suffer from rickets. He recommended exposure of the children's bodies to direct sunlight as the best method of preventing and treating this disease [2,3].

Along with vitamins A, E and K, vitamin D belongs to a group of four fat-soluble vitamins. Due to its properties and effect on more than 200 genes, it is now considered to be a steroid hormone with an auto- and paracrine action [4]. In addition to the most obvious function, i.e. regulation of calcium homeostasis and bone metabolism, it also affects the proliferation and differentiation of cells, the immune system, the nervous system, insulin secretion, and regulation of blood pressure.

Vitamin D is the name used for two biologically active compounds that differ in structure:

- vitamin D3 (cholecalciferol) synthesized in the skin under the influence of UVB radiation on 7-dehydrocholesterol in animal organisms,
- vitamin D2 (ergocalciferol) found in plants and fungi [5].

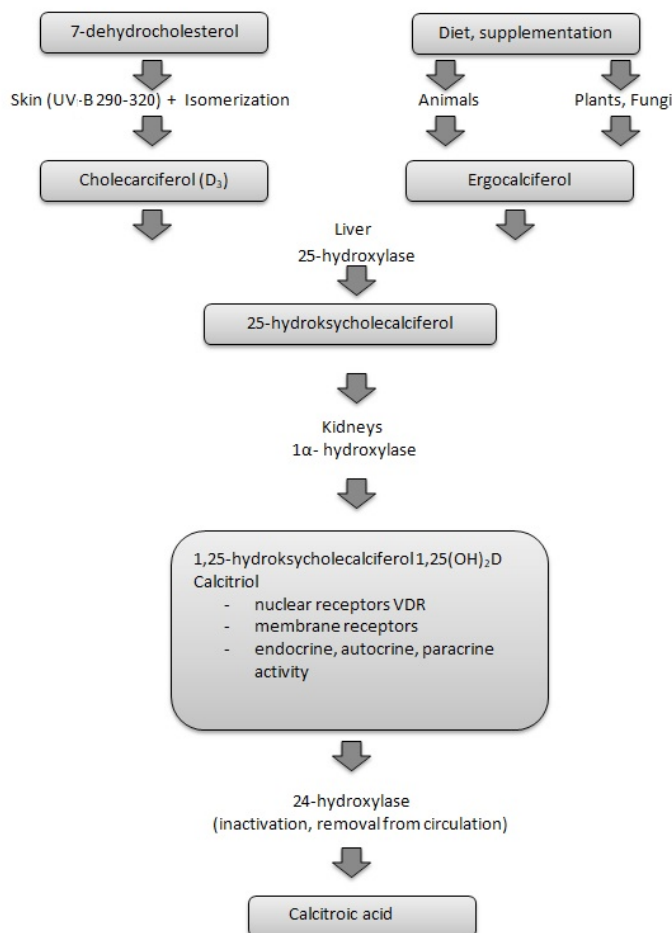


Fig. 1. The metabolic pathway of vitamin D

MATERIAL AND METHODS

The sources of the articles used in this manuscript were the PubMed database and Google Scholar. The effect of Vitamin D3 on the osteointegration of dental implants was searched. The key words used to search the PubMed and Google Scholar browsers included vitamin D3, calcitriol, osteointegration of implants. The work uses articles published in English and Polish.

Socio-demographic characteristics of all subjects and their families, their parents' education status, and their sibling's leisure activities were recorded. Information regarding the disability of the sibling of the study group was also noted. Physical fitness level, physical activity level, psychosocial status and quality of life of the included adolescents were then assessed.

THE ROLE OF VITAMIN D

Vitamin D is supplied to the human body along with food products (mainly fatty fish) and through synthesis in the skin. The key role here is played by UVB radiation (230–320 nm), with 295–300 nm (also referred to as UVD) considered the optimal wavelength range. This range of radiation is absorbed by the keratinocytes of the spinous layer and the basal epidermis, where the concentration of 7-dehydrocholesterol, the vitamin D precursor, is the highest. Due to the often limited supply of vitamin D in the diet, approx. 90% of its concentration is vitamin D derived from skin synthesis [5,6].

7-dehydrocholesterol is hydroxylated twice:

- first in the liver to 25-hydroxycholecalciferol D,
- then in the kidneys to the active form, 1,25-dihydroxycholecalciferol (also known as calcitriol). Thus, the process of vitamin D activation takes place in two stages. 1-alpha hydroxylation (renal hydroxylation) also occurs in monocytes, parathyroid cells, lungs, large intestine, mammary gland and prostate [1].

The transport of vitamin D in the body takes place with participation of the VDBP transport protein (vitamin D binding protein) belonging to the plasma gamma-globulin fraction [7]. Until the enzymatic conversion (hydroxylation), vitamin D is treated as a prohormone, and its hydroxylated derivatives 25(OH)D and 1,25(OH)₂D as hormones. Epidemiological studies have shown that the level of supply in the body with vitamin D is best reflected by the concentration of 25(OH)D [8]. Its concentration is given in nanograms per milliliter or in nanomoles per liter (1ng/ml = 2.5 nmol/l).

According to the hormonal theory of vitamin D, regulation of the level of 1,25(OH)₂D is based on the principle of negative feedback and takes place in two ways. First, 1,25(OH)₂D stimulates the synthesis of 24-hydroxylase, inactivating 1,25-dihydroxyvitamin D and 25-hydroxyvitamin D to biologically inactive calcitric acid, which is then removed in the bile [1]. Second, calcitriol regulates the secretion of parathormone (PTH), the parathyroid hormone responsible for the release of calcium from the bone in response to an insufficient concentration in peripheral blood. Sufficiently high levels of calcitriol in the body inhibit PTH synthesis at the genetic level. Thus, indirectly, through the inhibitory effect of vitamin D on PTH, hydroxylase activity is also regulated by an elevated concentration of Ca²⁺ in serum.

However, regulation of the activity of hydroxylases with the participation of phosphate ions takes place regardless of the parathyroid hormone [9].

It is estimated that in Poland, adequate skin synthesis of vitamin D in humans occurs only in the period from April to September, assuming an exposure of 18% of the body surface area to sunlight (minimum 15 minutes a day in the 10am–3pm interval) and the absence of protective filters [10]. Therefore, it seems reasonable to routinely assess the blood levels of vitamin D in the Polish population and include supplementation in case of deficiency. The measure of vitamin D3 supply is the concentration of 25(OH)D in blood (Table 1).

Table 1. Vitamin D supplementation based on the concentration of 25(OH)D in serum

25(OH)D LEVEL	CATEGORY	CLINICAL SYMPTOMS
0-10 ng/ml	Heavy deficiency	Secondary hyperparathyroidism, impaired calcium absorption, osteoporosis, osteomalacia
10-20 ng/ml	Moderate deficiency	Elevated PTH levels, reduced calcium intestinal absorption, reduced bone mineral density. Slightly elevated PTH levels, low vitamin D resources in the body
20-30 ng/ml	Light deficiency	Slightly elevated PTH levels, low vitamin D resources in the body
30-50 ng/ml	Recommended level	No disorders associated with vitamin D
>100 ng/ml	Toxic level	Hypercalcemia, hypercalciuria

Source: Guidelines of the Polish Society of Endocrinology for 2017.

Supplementing a deficiency of vitamin D at therapeutic doses, in the light of the latest guidelines for adults, should range from 4000 to 10,000 IU/24 h or 30,000–60,000 IU per week. Treatment is based on the analysis of laboratory measurements of blood 25(OH)D levels. The therapeutic dose should be applied for a period of 3 to 6 months. The first check-up should be performed after 6 weeks from the start of treatment and if its objectives have not been met, treatment should be continued [11]. The protocol of vitamin D supplementation depending on the serum concentration of 25(OH)D after 6 weeks of treatment is presented in Table 2.

Table 2. Supplementation with vitamin D3 depending on the concentration of 25(OH)D in serum after 6 weeks of therapy.

25(OH)D LEVEL	ACTION FOR CONSIDERATION
0-20 ng/ml	Deficiency therapy
20-30 ng/ml	Increasing/sustaining vitamin D supplementation
30-50 ng/ml	Sustaining vitamin D supplementation
50-100 ng/ml	Sustaining/lowering vitamin D supplementation
>100 ng/ml	Withdrawal of vitamin D supplementation until the optimal concentration of 25(OH)D is reached
>200 ng/ml	Treatment of potential toxic effects

According to the guidelines of the American Endocrine Society and the recommendations of the Team of Experts of the Polish Society of Endocrinology, serum levels of 25(OH)D below 30 ng/ml indicate a vitamin D deficiency [12].

A number of factors are mentioned as the causes of vitamin D deficiency. One of the most important is low skin synthesis due to insufficient exposure to sunlight. This can be related to the place of residence, using sunblock creams,

dark skin pigmentation, long-term stay in darkened rooms or cultural customs of covering the body, e.g. Arabian countries and India [13]. Other factors that cause vitamin D deficiency include inadequate supplementation, liver failure resulting in a reduced synthesis of 25(OH)D, renal failure causing a reduced synthesis of 1,25(OH)₂D and weak absorption of vitamin D caused by Crohn's disease, cystic fibrosis and celiac disease after surgical treatment of the gastrointestinal tract, e.g. the intestines or stomach. A reduced level of vitamin D may also be a consequence of obesity and associated sequestration of vitamin D in the adipose tissue. Demand for vitamin D also changes depending on the season and age, and highlights the need for increased supplementation in the autumn and winter as well as in later adult age [14]. Currently, according to epidemiological studies, vitamin D deficiency is common among both residents of Poland and the rest of Central Europe [12].

Undoubtedly, the most-known and studied function of calcitriol is its effect on calcium and phosphate homeostasis. Vitamin D deficiency results in bone and cartilage mineralization, resulting in rickets in children and osteomalacia in adults. Thanks to dynamic research in recent years, we have managed to define the effect of vitamin D on other tissues in which its active metabolite 1,25(OH)₂D binds to vitamin D receptor (VDR) present in most cells and tissues of the human body [15, 16]. The discovery of the widespread presence of VDR indicates the very wide range of vitamin D activity. Some cells, such as macrophages or keratinocytes, also have the ability to perform topical extra-regional synthesis of 1,25(OH)₂D. Local complexes 1,25(OH)₂D-VDR are responsible for the activation of over 200 genes affecting a number of major metabolic pathways. VDR works as a transcription factor and its activation occurs via a ligand - calcitriol. The VDR molecule plays the role of a gene transcription regulator, and the change in its spatial conformation allows binding to the promoters of the vitamin D-dependent genes [17].

Vitamin D is currently a very 'hot' topic in biology, biotechnology and medicine due to its broad role in metabolic processes that extend beyond bone tissue. In experimental, molecular and epidemiological studies, calcitriol has been shown to exert:

- modulation of cell growth and differentiation - anti-proliferative function, effect on cell differentiation;
- inhibition of angiogenesis and renin secretion;
- increase in the production of cathelicidin and defensin;
- modulation of lymphocyte activity and reduced production of anti-inflammatory cytokines;
- improved production / secretion of insulin [16, 18].

The classical roles of vitamin D, namely the regulation of bone metabolism and immunomodulation, are of particular importance for the osteointegration of implants.

THE ROLE OF VITAMIN D IN THE OSTEOINTEGRATION OF INTRAOSSEOUS IMPLANTS

The success of implantation depends on the course of osteointegration, i.e. the functional and direct structural connection between the structured live bone and the surface of the implant carrying functional loads [19].

Modern dentistry is increasingly based on the implantological rehabilitation of the masticatory system [20]. Most commonly used are titanium intraosseous implants whose biocompatible surface permits a persistent connection between the living bone tissue and the implant. The implantation procedure results in the formation of a post-operative wound within the soft and hard tissues. The relationship between the implant and the surrounding tissue is a continuous and dynamic process [21, 22].

In order to better understand the influence of vitamin D on the osteointegration of implants, its function can be divided into three phases that differ in terms of changes occurring in the tissues:

- wound healing period (up to a week after implantation),
- period of implant integration with bone tissue (from 1 to 3 months after implantation),
- period of stabilization and functional load of the implant with prosthetic reconstruction (from 3 to 6 months after the procedure).

At each stage, the activity of vitamin D is extremely important. In the first phase, the main goal is to heal the wound. Here, the influence of vitamin D is particularly important via a number of processes in the immune system, as shown by studies conducted over the last 20 years. Calcitriol plays an immunomodulatory role, stimulating innate and acquired responses. The innate immunity is modified by enhancing the function of macrophages, by intensifying chemotaxis and phagocytosis and by producing peptides such as cathelicidins and defensins. These natural antibiotics have a broad spectrum of bactericidal, antifungal and antiviral effects and are considered to be effector molecules, being one of the oldest evolutionary defense mechanisms. The role of $1,25(\text{OH})_2\text{D}$ in the induction of their production consists in binding to receptors in the genes coding for these peptides. The regulation of the production of cathelicidin and defensin through vitamin D is thus carried out at the genomic level. Vitamin D induced immune proteins can be found in monocytes, NK cells, mast cells, B lymphocytes, as well as intestinal enterocytes, epithelial cells and keratinocytes [23–26]. In studies on tuberculosis infection, it was confirmed that at low serum concentrations of $25(\text{OH})\text{D}$, i.e. below 20 ng/mL, macrophages and monocytes do not have the ability to initiate an innate immune response [27].

The immunomodulatory role of vitamin D also consists in stimulating the acquired response. Present in cells of the immune system, among others in macrophages, 1-alpha-hydroxylase participates in the local synthesis of calcitriol, which in turn enhances the antimicrobial function of these cells and also stimulates the action of interferon [28]. Studies have also shown the effect of calcitriol on the transformation of T lymphocytes from the Th1 phenotype to Th2 and a calcitriol induced decrease in the production of interleukin 2 (IL-2) resulting in the increased production of interleukin 4 (IL-4) [29]. Furthermore, the action of calcitriol in dendritic cells reduces their ability to present antigen, which in turn reduces allergic reactions [24].

The first period after implant surgery also crucially depends on the role of vitamin D in the induction of anti-inflammatory cytokines and a reduction in the level of proinflammatory cytokines, thus reducing the body's response to surgical intervention [30]. Susceptibility to bacterial and viral infections has been clearly established in patients with chronic kidney disease and a deficient concentration of $25(\text{OH})\text{D}$ in the blood. This indicates a clinically important role of vitamin D in the body's immune function [31].

During osteointegration of the implant, an adequate concentration of vitamin D is desirable due to the intensive processes of resorption and osteogenesis. Over the following few months, changes in the bone tissue lead to a direct connection of the implant with the bone.

The influence of vitamin D on the bone tissue depends on the regulation of the calcium and phosphate balance in the body. Maintaining an adequate level of calcium and phosphorus ions in the bone tissue as well as in extracellular fluid is necessary for proper bone and tooth mineralization. The function of vitamin D is primarily to intensify the active absorption of these ions in the intestine, which takes place in two ways. It directly involves the modification of the phospholipid membrane structure in the cells of enterocytes without the receptor participation. Such local modification increases its permeability to calcium ions [17]. The indirect mechanism of the action of vitamin D depends on the activating genes responsible for the synthesis of calcium binding protein – CaBP. This activation results in the synthesis of these de novo proteins and enables more efficient absorption of calcium ions from the intestines [32].

Reduced blood calcium, hypocalcemia, stimulates the secretion of the parathyroid hormone, which works by enhancing calcium resorption from the bones. This results in osteomalacia or osteoporosis [17]. Hence the regulatory role of vitamin D in calcium economy is extremely important. During osteointegration, calcitriol affects the processes of activation and differentiation of osteoblasts and osteoclasts. Vitamin D has also been found to be essential for the maturation and proper functioning of bone cells by the production of a factor stimulating osteoclast precursor fusion and stimulation of osteoblast differentiation. Vitamin D also increases osteoid mineralization [33]. This mechanism also plays an important role in the stabilization phase of the implant, after stabilization is achieved by loading it with a prosthetic crown. An adequate concentration of vitamin D is necessary for the maintenance of bone homeostasis, and hence the functional balance of osteoblasts and osteoclasts, as well as in the regulation of hormonal calcium-phosphate metabolism.

Of particular note is the function of vitamin D in reducing inflammation around the implant and local induction of immune cells by the production of 1-alpha-hydroxylase by monocytes [25]. According to current knowledge, the regulatory role of vitamin D is important in the process of tissue healing after implantation at all its stages [34].

Based on available literature, it can be concluded that there is a relationship between vitamin D concentration and the process of osteointegration of dental implants. These studies have been confirmed so far on animal models. Analyses conducted on rodent cultures also showed a relationship between vitamin D supplementation and increased bone contact with the implant, as well as impaired implant-to-bone integration in rats with a decreased vitamin D level [35, 36].

CONCLUSIONS

Vitamin D affects various stages of osteointegration of intraosseous implants. It has become an important field of knowledge in dental surgery and implantology through its role in the metabolism of the bone tissue and the immune system and has become a topic of interest in dental surgery and implantology. Considering the high percentage of patients with vitamin D deficiency, it seems appropriate

to determine blood levels of 25(OH)D before implantation and apply possible supplementation [37]. The prevalence of low vitamin D levels in the European population leads to the conclusion that a high deficit is not a factor directly responsible for failures in the process of osteointegration. Nevertheless, its synergistic effect with other risk factors seems to be well documented [38]. To sum up, a review of literature shows that there is a need for further research on the correlation between the osteointegration of implants and the concentration levels of 25(OH)D and to create a protocol of conduct when a deficit has been determined.

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