The renaissance of vitamin D
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There is no doubt that vitamin D plays a crucial role in the maintenance of musculoskeletal system. But the function of this ancient molecule presumably ranges far beyond hormone-like regulation, as it could be generated by simple unicellular organisms. First, we are going to discuss the role of vitamin D as a global regulator of homeostasis from a historical perspective, but later we will focus on current views and its relevance to human physiology and pathology. Three milestones are defining the impact of vitamin D on science and humanity. Firstly, discovery that vitamin D is the cure for rickets, brought us supplementation programs and rapid irradiation of this devastating disease. Secondly, detail description of photoproduction of vitamin D, its subsequent metabolism and interaction with vitamin D receptor VDR, provided mechanistic background for future discoveries. Finally, recent large epidemiological studies provided indirect, but strong evidence that optimal level of vitamin D in serum has beneficial effects on our health and protects us from multiple diseases, including cancer. Furthermore, existence of alternative pathways of vitamin D metabolism and multiple intracellular targets broadens our understanding of its physiological activities and offers new and very promising tools for prophylactics and treatment of many diseases of civilization. Although vitamin D (and its derivatives) should not be regarded as a cure-all for every human disease, its beneficial effects on the human health have to be taken under consideration.

Key words: vitamin D, skin, vitamin D deficiency, vitamin D supplementation, vitamin D analogs

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HISTORICAL PERSPECTIVE

Vitamin D is probably one of the oldest hormone that exists on earth (Bikle, 2011). Some of the earliest life forms have the capacity to produce vitamin D₃, when exposed to the sunlight. Impressively, vitamin D₃ producing phytoplankton survived, unchanged in the Atlantic Ocean, for more than 750 million years. There are many speculations, why these organisms need such excessive amounts of vitamin D₃. One of the most probable is that ergosterol may acted as natural “sunscreen” protecting cells against an ultraviolet (UVA and UVB) radiation (Holick, 1989; Holick, 2003).

The modern history of vitamin D in human health began during Industrial Revolution, in the 17th century. City lifestyle and growing air pollution decreased an access to the sun resulting in massive outburst of rickets. In that time, the disease was recognized as a major health problem among children. Severe growth retardation, widening of the ends of the long bones, and bowing and bending of the legs are only a few clinical signs of rickets (Holick, 1994).

The importance of exposure to the sunlight and its association with the prevention and cure of this bone deforming disease in children was first recognized by Polish physician Jędrzej Śniadecki, in 1822. In his observations Śniadecki concluded that children living in the polluted, sunless centre of Warsaw (Poland), more often suffered from rickets than compared to children living in the sunny rural areas. He hypothesized, that lack of sufficient sun exposure was responsible for the development of rickets among children. What is more, he claimed that direct exposure to sunlight might be one of the most efficient methods to prevent and cure rickets. However, in the nineteenth century his studies were considered as incomprehensible and remained largely unnoticed. Of note, it was great Polish biochemist, Professor Włodzimierz Mozołowski, who brought back Śniadecki’s observations to the scientific community (Mozolowski, 1939).

Another scientist, who predicted the relationship between exposure to the sunlight and occurrence of rickets, was a British epidemiologist, Theobald Palm. In 1890, he combined notes from his travels with the opinions of colleagues and postulated that there is a negative dependence between latitude and occurrence of rickets. In his observations, he firmly highlighted that despite the poverty, in sunny, tropical areas there were significantly reduced number of rickets cases, than compared to “rich” urban countries. Similarly to Śniadecki, Palm was a supporter of the beneficial effects of the sun to bone health. He also strongly encouraged moving infants and children afflicted with rickets from large towns to sunnier rural areas (Palm, 1890). Once again, the observations and benefits arising from Palm’s findings remained unnoticed. It had taken another 30 years before significance of Śniadecki’s and Palm’s observations was explained.
In 1919, Huldschinsky showed that exposure to ultraviolet radiation from a mercury arc lamp resulted in regression of severe rickets. Furthermore, he demonstrated that the therapeutic effect of ultraviolet radiation was not limited to irradiate place, but had an equal effect on whole organism. For instance, the exposure to mercury arc lamp of just one arm resulted in the cure of rickets in both arms (Huldschinsky, 1919; Huldschinsky, 1928).

Two years after Huldschinsky findings, Hess and Unger conducted another valuable study. They exposed children suffering from rickets on a roof of a New York City hospital to sunshine for various periods. It resulted in significant improvement of the health of rachitic children as reported by X-ray examination (Hess & Unger, 1921). The results of above-mentioned studies prompted US government to establish an agency responsible for promoting an exposure of children to the sun in order to prevent rickets (Fig. 1). What is more, in the 1930s–1950s parents could buy ultraviolet lamps in local pharmacies to protect children from developing rickets (Hess, 1936; Eliot & Park, 1938). At that time, the popularity of UV irradiation was constantly growing. In 1924, Steenbock suggested that not only children and animals could be irradiated in order to prevent rickets but also irradiate food seems to be effective (Steenbock, 1924). This led to the UV irradiation of cows, their diet, and ultimately their milk to acquire food with antirachitic properties. Thanks to the fortification of milk with vitamin D rickets was very quickly eradicated in the United States and Europe. In the 1930s and 1940s in addition to milk, many other products fortified with vitamin D like bread, hot dogs, Twang soda, and even Schlitz beer were popular. Unfortunately, potential excessive consumption of vitamin D was blamed for the outbreak of hypercalcemia in Great Britain and US, in the 1940s. This resulted in tightening of the regulations concerning fortification of dairy products with vitamin D in Europe (Holick, 2006b). Interestingly, it seems now that the outburst of hypercalcemia may not be attributed to an excessive supplementation, but also could be explained by coexistence of relatively rare diseases, including: Williams’ syndrome (Wacker & Holick, 2013), primary hyperparathyroidism (Michels & Kelly, 2013) or even sarcoidosis (Nunes et al., 2007). It could be also caused by specific mutation of CYP24A1 coding the main catabolic enzyme for vitamin D (Jacobs, 2014), resulting in abnormally high level of vitamin D in serum.

Simultaneously to ongoing studies on the effect of the sun on bone health, another potential antirachitic agent was found — a cod liver. The effectiveness of cod liver oil in prevention of the disease has been particularly valued on the coastlines of the Scandinavian countries and the United Kingdom (Ibde, 1975). Nevertheless, Schutte was a first physician, who prescribed cod liver oil as specific agent preventing rickets, in 1824. From this time to the end of the century, German and French physicians have widely recommended cod liver oil as an antirachitic agent. Nevertheless, at the beginning of the 20th century, the usefulness of cod liver oil was questioned, probably due to a poor quality or impurity of prescribed cod liver oil (Guy, 1923). The first scientific approach to prove the anti-rachitic properties of cod liver oil was made by Edward Mellanby and Elmer McCollum. In classic, animal experiments, they accredited the antirachitic function of cod liver oil to fat-soluble vitamin A or other similar substance (Mellanby, 1919). However, in 1922, McCollum demonstrated that vitamin A do not possessed antirachitic properties. He was aware that oxidation destroys fat-soluble vitamin A, while similarly treated cod-liver oil preserved its protective action against the development of rickets. Thus, McCollum concluded that the antirachitic substance must be a distinct one from fat-soluble vitamin A. The newly discovered antirachitic factor from cod liver oil was named vitamin D, as it was fourth in the sequence of discovery of vitamins (McCollum et al., 1922).

In retrospect, the establishment of the fact that cod liver oil and sunlight were different but similar in their ability to prevent and treat rickets, was a significant advance in the study of vitamin D.

**NATURALLY OCCURRING VITAMIN D ANALOGS**

Although the idea of fat-soluble vitamin D as antirachitic factor became very clear at the beginning of the 20th century, the actual vitamin structure was not solved until 1932. First, Askew and co-workers succeeded in isolation of vitamin D\(_2\) (D\(_2\), or ergocalciferol) (Askew et al., 1931). Independently, a German group led by Windaus in 1935 had isolated 7-dehydrocholesterol (Windaus, Lettre & Schenck, 1935) and two years later vitamin D\(_1\) (Windaus & Bock, 1937). Interestingly, although Windaus was involved in discovery of vitamin D\(_1\) and its synthesis pathway, he received Nobel Prize in Chemistry on the account of his discoveries concerning structures of sterols and their relationship with vitamins, in 1928 (Woll, 2004). Interestingly, he passed his patent’s rights to the production of vitamin D by UV-irradiation of yeast derived ergosterol to Merek and Bayer companies. As a result, well known Viganol is on the market since 1927 (Haas, 2007).

It was however still not clear, whether the vitamin D is normally produced in the human body or could be found only in natural products. Henry Steen-
bock was one of the pioneers in vitamin D research, who in an addition to early experiments with food irradiation (Steenbock, 1924) was later focused on the physiological activity of this fat-soluble vitamin. After his retirement in 1955, Hector DeLuca took over his laboratory and similarly to his predecessor, vitamin D became the centre of his attention. In 1968, he isolated an active vitamin D metabolite and identified it as 25-hydroxyvitamin D₃ (25-OH D₃) (Blunt et al., 1968). A few years later, he demonstrated that previously identified substance was produced in the liver (Gray et al., 1971). Further collaboration of Hector DeLuca with Michael Holick resulted in numerous discoveries. They identified the major circulating form of vitamin D, 25-hydroxyvitamin D₃ (Holick et al., 1972a). Another a milestone achievement was the discovery of biologically active metabolite of vitamin D — 1α,25-dihydroxyvitamin D₃ (Holick et al., 1971). This was followed by the identification of other vitamin D metabolites, including: 24,25-dihydroxyvitamin D₃ (Holick et al., 1972b), 1α,23,25-trihydroxyvitamin D₃ (Holick et al., 1973) and 25,26-dihydroxyvitamin D₃ (DeLuca et al., 1970). Those key discoveries enable us to understand the mechanisms associated with production and metabolism of vitamin D.

THE SKIN — FINAL LINK BETWEEN SUN AND VITAMIN D

Since Sniadecki’s times it was speculated that sun is essential for the product of the antirachitic factor, which was later described as vitamin D. However, it was Michael Holick, who for the first time showed effective synthesis of vitamin D in the skin subjected to ultraviolet radiation (Holick et al., 1977; Holick et al., 1979). His subsequent studies also confirmed experimentally, that the latitude or seasonal changes affect production of vitamin D in the skin (Webb et al., 1988). Interestingly, the influence of skin pigmentation on the efficiency of vitamin D production is still under debate. In individuals with black skin phototype, the production of previtamin D₃ was found to be reduced to 20% of the white skin phototype (Fitzpatrick, 1988). More recent studies on the US population showed that mean serum concentrations of 25(OH)D₃ were approximately 25 nmol/L less in African-Americans than in Caucasian (Looker et al., 2008). Therefore, darker-skinned individuals require longer exposures to achieve the same plasma 25(OH)D₃ concentration. However, even people with highly pigmented skin can obtain relatively high 25(OH)D₃ concentrations in the serum, as it was observed among Gambia population (Prentice, 2008).

Interestingly, it was the production in the skin subjected to the sunlight not suplementation, that was found to be the most efficient source of vitamin D. The exposure of the skin to only 1 minimal erythmal dose (MED) of the sunlight results in production of at least 20000 Units of vitamin D (Holick, 2008). Furthermore, skin production of vitamin D does not cause the symptoms of an overdose, because the excessive exposition to UVB light leads to its photodegradation. The main products are 5,6-transvitamin D₃ and suprasterols I and II (Webb et al., 1989). Other photoproducts including 5,7,9(11)-triene were described recently (Chignell et al., 2006; Zmijewski et al., 2009).

Thus, almost 250 years after Sniadecki’s observations, it became obvious that beneficial role of the sunlight in rickets is attributed to skin production of vitamin D₃.

CLASSIC PATHWAY OF PRODUCTION AND METABOLISM OF VITAMIN D

It is well established that a biologically active form of vitamin D₃ is 1α,25(OH)₂D₃ (Fig. 2). It is produced in multistep process involving photochemical isomerisation of 7-dehydrocholesterol (cholesta-5,7-dien-3-ol, 7-DHC) followed by enzymatic hydroxylation of vitamin D. Initially, under the UVB radiation, the B-ring of 7-DHC is photolysed, what leads to formation of previtamin D (Holick et al., 1977). The reaction takes place in keratinocytes of the basal layer of the epidermis (Holick et al., 1977; Slominski et al., 2012c). Then, previtamin D isomerizes to vitamin D₃, tachysterol (T₃) and lumisterol (L₃). Vitamin D₃ can be released to the circulation, where it is transported by vitamin D-binding protein (DBP) (Lehmann, 2009). Circulating vitamin D is activated by subsequent hydroxylations. First hydroxylation to 25-hydroxycholecalciferol (25-OH D₃) takes place in the liver and is carried out by mitochondrial or microsomal 25-hydroxylases (CYP2R1, CYP27A1). Next, in the kidneys 25-OH D₃ is hydroxylated by mitochondrial 1α-hydroxylase (CYP27B1) to 1α,25(OH)₂D₃ (calcitriol) — the fully active form of vitamin D₃ (Takeyama et al., 1997). Additionally, a number of distinct tissues and organs, such as intestines, also have the ability to activate vitamin D by its hydroxylation (Hewison et al., 2004). It should be emphasized, that the skin is the only known organ equipped with complete machinery of vitamin D₃ production and metabolism including enzymes responsible for 25- and 1α-hydroxylation as well as the vitamin D receptor (Bouillon et al., 2008; Luderer & Demay, 2010). The level of 25-OH D₃ and 1α,25(OH)₂D₃...
in circulation and tissues is regulated by 24-hydroxylase (CYP24A1), which transforms them to 24,25(OH)₂D₃ or 1α,24,25(OH)₃D₃, respectively. Further catabolism results in formation of water-soluble calcitriol acid, which is excreted in urine (Reddy & Tsergg, 1989).

Vitamin D₃ is exclusively formed from ergosterol by fungi and phytoplankton subjected to UVB radiation (Holick et al., 1982). Some plants have also limited capacity to produce vitamin D₂ (Japelj et al., 2013). Similarly to 7-DHC, the photoisomerization of ergosterol results in formation of three main products: vitamin D₃, lumisterol, and tachysterol (Kalaras et al., 2012). Furthermore, acquired vitamin D₃ undergoes hydroxylation at position C₂₅ in the liver and C₁ in the kidney to produce biologically active 1,25(OH)₂D₃ (Holick, 2003; Zhu & DeLuca, 2012). It has to be added, that vitamin D₃ is a major form of dietary vitamin D in humans, especially in Western Europe and USA (Holick, 2003; Bikle, 2011). However, the question whether vitamin D₃ is an ideal replacement for D₃ is still open to debate (Leventis & Kiely, 2009).

ALTERNATIVE PATHWAY LEADING TO NOVEL VITAMIN D ANALOGS

Although classical pathway of vitamin D synthesis and metabolism was established long time ago, new class of vitamin D derivatives was recently described. Collaboration of Andrzej Slominski and Robert Tuckey (recent reviewed Slominski et al., 2013b) resulted in discovery of novel metabolic pathway for 7-DHC and vitamin D in animals (Fig. 2). The alternative route is initiated by the enzymatic action of cytochrome P450sc (CYP11A1) on 7-dehydrocholesterol (Slominski et al., 2004; Slominski, Kim et al., 2013a; Slominski et al., 2014). It was shown that cytochrome P450sc (CYP11A1) in analogy to the conversion of cholesterol to pregnenolone may also catalyse the transformation of 7-DHC to 7-DHP (7-dehydroprognenolone). This conversion requires hydroxylation of 7-DHC at the C22 and C20 positions, followed by cleavage of side chains resulting in formation of 7-DHP (Slominski et al., 2004). It seems that 7-DHP may be further modified by classical steroidal metabolic enzymes (17α-hydroxylase and 17, 20-lyase), leading to the formation of new steroidal 5,7-dienes with modified side chains (Slominski et al., 2009). All of those compounds can serve as precursors for the vitamin D-like derivatives after exposure to the UVB radiation (Zmięjski et al., 2008; Zmięjski et al., 2009; Zmięjski et al., 2011). Interestingly, not only 7-DHC, but also ergosterol, vitamin D₃, and vitamin D₄ can be metabolised by cytochrome P450sc, what results in formation of a new class of hydroxyderivatives (Slominski et al., 2005b; Slominski et al., 2005a; Slominski et al., 2006; Slominski et al., 2013a).

The CYP11A1 was shown also to act on C20 of vitamin D analogs (e.g. vitamin D₃ and D₄) generating family of novel vitamin D hydroxyderivatives (Slominski et al., 2005; Tuckey et al., 2008). Furthermore, it was shown that major product of hydroxylation of vitamin D₃, namely 20-hydroxyvitamin D₃ (20-OH D₃) (Guryev et al., 2003; Slominski et al., 2005b) can be hydroxylated by CYP11A1 to 20,23-dihydroxyvitamin D₃ (20,23(OH)₂D₃) (Slominski et al., 2005b; Tuckey et al., 2011). It has to be stress out that CYP11A1-initiated metabolism of vitamin D₃ was detected both, in vitro (Tuckey et al., 2008) and in vivo (Slominski et al., 2012a). Furthermore, several new studies showed that Cyp450sc generated vitamin D hydroxyderivatives are biologically active. Importantly, it was shown that they are less prone to induce hypercalcemia, therefore they are currently investigated as potential anti-leukemia (Slominski et al., 2010) and anti-melanoma factors (Slominski et al., 2012a). Moreover, 20-OH D₃ exhibits anti-proliferative and pro-differentiation activities in human epidermal keratinocytes, as it was shown recently (Zbytek et al., 2008; Slominski et al., 2011). Nevertheless, further research is needed in order to establish physiological role of alternative vitamin D metabolites and their potential applications in therapy (recent review: Szszska et al., 2012).

INTERCELLULAR MECHANISM ACTIVATED BY VITAMIN D AND ITS ANALOGS

Final puzzle in the studies on vitamin D was to establish, how it is possible that one, relatively simple molecule expresses such a variety of biological functions. It turns out that similarly to other steroid hormones, vitamin D activates its canonical nuclear receptor. Exploration of the classical pathway began in 1969, when Haussler and Norman discovered the nuclear receptor for 1,25(OH)₂D₃ (Haussler & Norman, 1969). Over the following years, scientists revealed expression of the vitamin D receptor (VDR) in many target tissues (Cavalier, 2009). More than twenty years later VDR expression was also shown in epidermal keratinocytes (Milde et al., 1991). According to well-established “genomic pathway”, vitamin D exerts its biological activity by binding with nuclear receptor — VDR, which after stimulation forms a dimer with 9-cis-retinoic acid receptor — RXR (retinoid X receptor). The complex is then translocated to the nucleus and acts as a transcriptional factor by binding to a VDR-responding element (VDRE). Now, it is well established that several co-activators or co-repressors interact with VDR-RXR complex and regulates its activity (Silvagno et al., 2013). Initially, VDRE was discovered in the promoter region of bone-specific osteocalcin gene (Morrison et al., 1989). It seems that this was symptomatic for the vitamin D history. Since then, the VDR action as transcription factor was extensively investigated by both mRNA and miRNA microarrays. For example, in squamous cell carcinoma cells over 900 genes was shown to respond to 1α,25(OH)₂D₃ (Wang et al., 2005). It was demonstrated that 1α,25(OH)₂D₃ can regulate genes controlling extracellular matrix structure and its remodelling, cell adhesion or inducing a basal keratinocyte phenotype (Lin et al., 2002).

Having in mind ancient origin of vitamin D, its interaction with VDR seems to be quite recent adapted pathway regulating its activity. In fact, so-called, non-genomic mechanism of rapid vitamin D response has been described recently. This mechanism does not directly affect gene expression or require additional protein synthesis. Rapid vitamin D response was shown to modulate intracellular calcium levels, affects activity of several intracellular signalling pathways, through activation of selected phosphatases and phosphatases. These activities take minutes and occur in the cytoplasm of the cell rather than in the nucleus. Potential mechanism of non-genomic response involves interaction of vitamin D to 1α,25(OH)₂D₃ membrane–associated rapid response steroid-binding protein (1,25 D-MARRSBP), also known as the protein-disulfideisomerase-associated 3 (PDIA3) or endoplasmic reticulum stress protein 57 (ERP57) (Nemere et al., 2004). PDIA3 activates phospholipase C in a G protein-coupled process and results in production of inositol trisphosphate (IP₃) and diacylglycerol. These two
cellular messengers mediate the rapid release of calcium from the cellular stores (Nemere et al., 2012).

Recently, new targets for vitamin D have been discovered. It was that secosteroids (such as 20-OH D$_3$ and 20,23(OH)$_2$D$_3$) can act as antagonists of retinoid acid-related orphan receptors $\alpha$ and $\gamma$ (ROR$\alpha$ and ROR$\gamma$) (Slominski et al., 2014). ROR$\alpha$ and ROR$\gamma$ are the members of the nuclear receptors ROR subfamily, which take part in the regulation of a number of physiological processes — affects several immune functions, metabolism, and cerebellar development (Jetten, 2009). RORs are expressed in a variety of tissues, including testis and kidneys (Jetten, 2009). Moreover, their presence was also confirmed in human skin cells (Slominski et al., 2014). Crystallography provided insightful structure of the ligand binding pockets of RORs (Stehlin et al., 2001). Those observations not only confirmed that RORs can function as the ligand-dependent transcription factors, but also imply that RORs might be new interesting therapeutic targets for vitamin D analogs. Especially if we take under consideration several reports indicating a potential role of RORs in osteoporosis, autoimmune diseases, asthma, cancer, and obesity (Jetten, 2009). Thus, it seems that our relatively simple model for vitamin D, shown on Fig. 2 is going to be modified in forthcoming years in order to explain complexity of vitamin D metabolism and its pleiotropic activities.

THE RENAISSANCE OF VITAMIN D$_3$

The classic physiologic function of vitamin D$_3$ is to maintain calcium and phosphorus homeostasis, ensuring proper metabolic functions of bone mineralization and neuromuscular transmission (Holick, 2006a). Until recently, vitamin D was considered as “the bone vitamin” and was used predominantly for the treatment of diseases such as rickets or osteomalacia. As a result of vitamin D discovery, rickets was successfully eradicated by proper supplementation (Holick, 2013). However, it has to be underline that vitamin D is also crucial for maintenance of nervous and cardiovascular and immunological systems, as well as plays important role in skin physiology, to name only a few. Recent 20 years brought us constantly increasing number of epidemiological studies indicating that maintenance of the optimal level of 25-OH D$_3$ in the serum is simply essential for our health. Amongst others, vitamin D was found to be a protecting agent against multiple types of cancer (Garland et al., 2006), bacterial infections (Bikle, 2008); autoimmune (Munger et al., 2006) or cardiovascular diseases (Wang et al., 2008; Tukaj et al., 2012). It seems that vitamin D affects at least in part all major human function at the cellular, organ and whole body levels (Fig. 3). Multiple epidemiological studies provide strong evidence that monitoring of vitamin D status is the key factor in proper supplementation. For instance, recent Polish study (Gdansk region) showed that amongst 448 volunteers only 2.5% had optimal concentration of 25-OH D$_3$ in serum (more than 30 ng/μL) in winter of 2012. Moreover, lack of proper supplementation and food fortification with vitamin D in Poland resulted in very low mean of 25-OH D$_3$ concentration (14.3 ± 6.6 ng/μL). Interestingly, only individuals with recent episodes of UVB exposure had sufficient concentration of vitamin D (Kmiec, 2014). This finding as many other, strongly suggested the necessity of proper supplementation (Webb et al., 2010; Trofimiuk-Muldner et al., 2012). Furthermore, routinely suggested 400–800 Units of vitamin D, per day may not be sufficient for efficient supplementation. Thus, higher doses up to 2000 U are recommended according to recently published guidance for Central Europe (Pludowski, 2013). This detail recommendation concerning supplementation for different groups was published recently in English (Pludowski et al., 2013a) and in Polish as well (Pludowski et al., 2013b). It has to be also mentioned that monitoring of 25-OH D$_3$ concentration in the serum is essential for optimal supplementation. It is especially important for several groups of individuals vulnerable to vitamin D deficiency, including pregnant woman, children, and el-

![Figure 3. Overview of biological functions of vitamin D.](image_url)
CONCLUSIONS

In spite of more than 100 years and thousands of published articles, the overall impact of vitamin D and its derivatives on human health is not fully understood. Having in mind its ancient origin, it is obvious that vitamin D regulates multiple pathways and has an impact on human physiology and internal homeostasis. Proper activity of multiple organs depends on optimal vitamin D level, thus it should not be a surprise that vitamin D deficiency is an important factor involved in development of multiple human diseases.

Recent studies revealing existence of alternative pathways of vitamin D metabolism and activity broaden our knowledge concerning pleiotropic impact of vitamin D and its derivatives on human physiology and pathology. Furthermore, newly discovered low-calcemic vitamin D analogs such as 20-OH D₃ or intracellular targets like PDIA3 or RORs, provide new opportunities for the therapy of multiple human diseases.

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REFERENCES


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