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Physiological study of prednisolone and dexamethasone and their effect on calcium and vitamin D metabolism in laboratory animals

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Abstract
In recent years, there has been a significant amount of focus research on the deficiency of vitamin/hormone D, a thorough examination has been carried out regarding recommendations, guidelines, and treatments. Furthermore, vitamin D has been firmly established as a hormone in numerous enzymatic, metabolic, physiological, and pathophysiological processes that impact various organs and systems within the human body. The growing attention to this topic is due to the common occurrence of mild to severe vitamin D deficiency on a global scale. It is widely acknowledged that maintaining optimal vitamin D levels is crucial for the health of bones, muscles, overall well-being, and the effectiveness of treatments aimed at preventing bone loss and promoting bone formation. Currently, vitamin D, along with vitamin D supplementation, is being used to increase vitamin D levels and correct deficiencies. This review delves into the established and emerging principles regarding the metabolism of vitamin D/hormone D, sources in the diet, concerns about deficiency, as well as the various types of vitamin D supplements available in the market and
the optimal strategies for their use. Moreover, research involving knockout and transgenic mice has offered fresh perspective on the biological function of vitamin D in traditional target tissues, in addition to showcasing the possible non-skeletal impacts of 1,25(OH)2D3 such as hindering cancer advancement, influencing the cardiovascular system, and modulating the immune response in specific autoimmune conditions. Several discoveries on a molecular level in mouse models have mirrored results seen in human subjects. The recognition of comparable pathways in humans holds the potential for the creation of innovative treatments for disease prevention and management.

Keywords: Vitamin D, metabolism**,** calcium, phosphate, mineral actions

Introduction

In the past few decades, there has been a significant rise in the attention given to vitamin D, especially due to its connection with various diseases [1-3]. At present, the confirmed role of vitamin D as a hormone in various physiological and pathophysiological processes within the human body encompasses diverse organs and systems [4]. Although there is significant evidence on the influence of vitamin D hormone on the skeletal system across all age groups, there are ongoing debates surrounding the potential non-skeletal advantages of vitamin D supplementation. Additionally, there is speculation about the potential risks associated with high doses of vitamin D [5]. Despite varying viewpoints, the consensus among researchers is that individuals with insufficient levels of vitamin D should undergo treatment to support bone health and general well-being. This is especially vital for high-risk individuals, including elderly individuals Patients with conditions such as individuals with diabetes, chronic kidney disease, and malabsorption residing in extended care facilities. [6]. Multiple recommendations discourage the utilization of vitamin D supplements in the initial prevention of fractures among postmenopausal women residing in the general population [7]. This step is necessary to enhance the efficacy of the treatments while also preventing the occurrence of hypocalcemia [8]. The awareness of the ramifications of a lack of vitamin D is increasing, yet there remains ambiguity and insufficiency in the information regarding this deficiency. Despite its prevalent occurrence, ease of detection, and the availability of straightforward, efficient, and cost-effective methods for remedying it, there is a prevailing lack of concern for vitamin D deficiency. This narrative review aims to outline the principles related to the metabolism of vitamin D/hormone D and its sources in food, as well as to delve into the existing knowledge on vitamin D deficiency and the protocols and substances utilized for treating it.

Vitamin D Sources and Metabolism

At first, studies primarily concentrated on the impact of vitamin D on bone metabolism and its essential function in maintaining calcium balance. The identification of 25-hydroxyvitamin D in 1968 represented a pivotal moment in the study of vitamin D [9], The initial focus of the research was on 1,25-hydroxyvitamin D [1,25(OH)2D], but it eventually expanded to include a range of topics, including immune-mediated conditions, infectious diseases, cancer, and cardiovascular disorders [10]. Vitamin D is essential for maintaining and regulating the immune system by influencing suppressor T lymphocytes, cytokine synthesis, and cellular apoptosis [11]. Vitamin D is recognized for its ability to enhance the absorption of phosphate in the intestines and prevent its excretion by the kidneys. The precursor known as 7-dehydrocholesterol, also called provitamin D, is converted into previtamin D3 in the skin upon exposure to ultraviolet sunlight within a specific range of wavelengths (290-320 nm). This procedure entails a reorganization of the triene structure of the molecule through isomerization, leading to the synthesis of vitamin D3 (cholecalciferol) [12] (Fig. 1). Exposure to ultraviolet (UV) radiation at a level equivalent to 25% of the minimum erythema dose (MED) over approximately 25% of the skin, encompassing regions such as the face, hands, and arms, can result in the synthesis of approximately 1000 international

units (IU) of vitamin D [13]. During the summer season, receiving sunlight for a duration of fifteen minutes around midday while ensuring complete coverage of the entire body can result in the absorption of approximately 10,000 IU (250 μg) of cholecalciferol. Exposing the arms, hands, and face to sunlight to a degree that causes slight tanning equivalent to one-third to one-sixth of the minimal erythemal dose (MED) has the potential to provide an intake of 200 to 600 IU of cholecalciferol. [14]. Numerous variables have the potential to impact the effectiveness of this process. These include factors such as age, skin pigmentation (melanin levels), time of year, weather conditions, geographical location, elevation, time of day, clothing choices, extent of skin exposure, vacation behavior, sunscreen usage, and individual skin type (with aging potentially diminishing the skin's ability to produce vitamin D) [15].

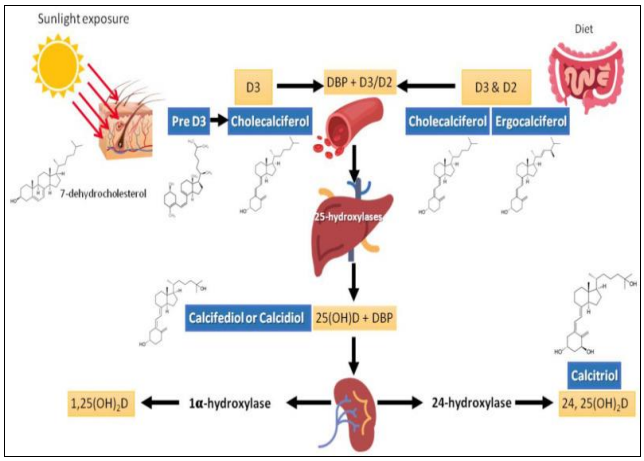

Fig 1

A uniform agreement has not been reached regarding the definition of safe and beneficial levels of sunlight exposure for the public at large. It is not advisable to offer definitive recommendations on this matter. In particular, the biologically beneficial rays from sunlight are diminished during winter months by as much as four times, with peak intensity occurring around midday. The thinning of the Earth's ozone layer may result in enhanced production of vitamin D in the body, but it also heightens the likelihood of skin cancer [15]. It has been forecasted that the ozone layer at a global scale will begin to replenish itself by the end of the 21st century if nations uphold the Montreal Protocol, despite earlier beliefs. This potential restoration could result in unanticipated outcomes [16]. However, despite evidence showing that even minimal exposure to simulated solar UV radiation can increase Variability in individual response to 25(OH)D concentrations is significant and influenced by various factors. The use of sunscreen and increased skin pigmentation can greatly reduce cutaneous vitamin D3 synthesis by nearly 90% by elevating levels of melatonin. In older individuals, synthesis of vitamin D through the skin can decrease by as much as 75%, especially in winter and regions with higher latitudes. Additionally, there is a decrease in renal hydroxylation as individuals age. It is therefore important to acknowledge that a patient with adequate vitamin D levels in the summer may become deficient during the winter months. Extended exposure to sunlight does not lead to excessive levels of vitamin D as previtamin D3 transforms into lumisterol and tachysterol, which lack defined endocrine roles, and vitamin D3 converts to suprasterols I and II via photoconversion [17]. The presence of melanin in the skin has the ability to diminish the production of vitamin D3 from sunlight by absorbing UV radiation. This phenomenon may be a contributing factor to the lower levels of 25(OH)D found in individuals of African and Hispanic descent residing in regions with temperate climates. One possible explanation for this disparity is that increased melanin production in response to sunlight exposure serves as a protective mechanism against excessive vitamin D3 synthesis. Nevertheless, extended exposure to UVB and UVA rays can result in sunburn and harm to DNA [17]. The Vitamin D levels in food tend to remain consistent, however, its potential impact is limited due to the infrequent consumption of Vitamin D-rich food items. Fatty fish, eggs, mushrooms exposed to sunlight, liver, and other organ meats are considered key dietary sources of Vitamin D. In some areas, fortified foods such as milk (from cows or plant-based sources), Butter, margarine, and breakfast cereals are frequently fortified with either ergocalciferol or cholecalciferol to act as the main sources of Vitamin D in the diet. While fortifying food with Vitamin D appears to be a beneficial option, consumption levels vary significantly, leading to uncertainty regarding its effectiveness in combating Vitamin D deficiency [17]. A recent investigation devised a food frequency and lifestyle questionnaire (FFLQ) for the purpose of evaluating vitamin D consumption among athletes. The study was conducted throughout all seasons, utilizing the FFLQ to approximate vitamin D intake in comparison to estimates based on food records. The findings revealed that levels of 25-hydroxyvitamin D [25(OH)D] in the blood were not correlated with the vitamin D intake estimates derived from the FFLQ or from food records. However, researchers did observe a noteworthy connection between serum 25(OH)D levels and the use of in spring, the utilization of tanning beds, supplements in autumn, and monitoring body mass index (BMI) throughout the year were examined. These findings underscore the influence of different factors, aside from dietary patterns, on calcifediol levels in the blood [18].

Metabolism

Vitamin D is a comprehensive term encompassing a group of fat-soluble compounds characterized by a shared primary cholesterol ring structure. Among these compounds, 25(OH) D, also referred to as calcifediol or calcidiol, is the most abundant in the bloodstream, with a half-life of two to three weeks. In contrast, another compound, 1,25(OH)2D, known as calcitriol, has a much shorter half-life of four to eight hours and is the active form of vitamin D. This dynamic form engages with the vitamin D/hormone D receptor (VDR) to perform its physiological roles and controls its own levels via a negative feedback loop [19]. The synthesis of vitamin D has been an integral function of plants and animals since the dawn of life on Earth. The mechanism by which this essential nutrient is transformed and dispersed into its more biologically active variants has undergone evolutionary adaptation in various organism have become more intricate and their cellular functions have become more specialized. In more advanced animals, the presence of the vitamin D receptor (VDR) is pervasive across various cell types, and the capacity for producing 1,25(OH)2D is also widespread [19].

The Vitamin D Receptor belongs the protein family under discussion is broad and includes receptors for a variety of substances such as steroid hormones, thyroid hormone, retinoids, cholesterol metabolites, bile acids, isoprenoids, fatty acids, and eicosanoids are all encompassed within this category of compounds. The identification of the Vitamin D Receptor (VDR) can be traced back to the year 1969 when it was initially identified as a binding protein for an unidentified metabolite of vitamin D, later recognized as 1,25(OH)2D). Subsequently, VDR was cloned and sequenced in 1987 [20]. Experimental models lacking VDR displayed symptoms the investigation revealed a significant lack of vitamin D, affirming VDR's role as the chief controller of vitamin D's impacts. VDR can be found in various tissues within the human body to differing extents, with 1,25(OH)2D governing gene transcription [20].

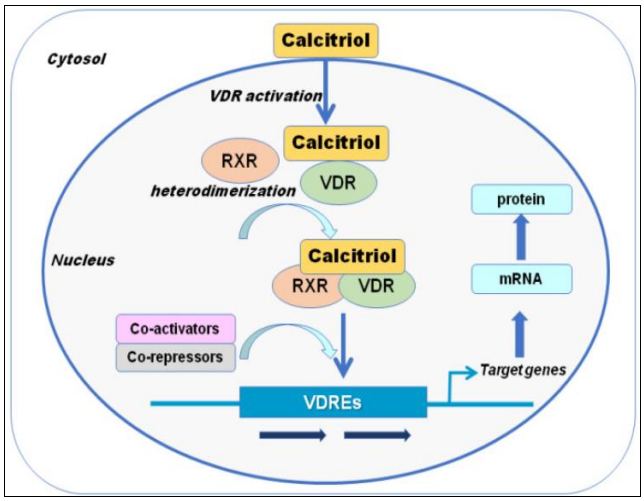

Fig 2

Once vitamin D (2 and 3) enters the bloodstream, it forms a weak association with the vitamin D binding protein is responsible for transporting vitamin D and storing it in fat cells. It then goes through a process of metabolization into 25(OH)D, mainly in the liver. This metabolic process is facilitated by various hydroxylases such as cytochrome P450 (CYP)2R1 and CYP27A1, although it can also occur in other body tissues in an autocrine/paracrine manner. High doses of vitamin D may cause individuals to experience a reduced rate of conversion to 25(OH)D [21].

Magnesium plays a crucial role in the synthesis and release of parathyroid hormone (PTH), which is suppressed in states of magnesium depletion. In addition, inadequate dietary magnesium intake has the potential to affect the response of PTH to 25-hydroxyvitamin D. [22]. Therefore, the shortage of both magnesium and vitamin D can exacerbate each other, potentially resulting in a vicious cycle of deteriorating deficiencies. The collective impact of deficiencies in these two compounds could result in significant clinical consequences, including an increased susceptibility to fragility fractures, especially among women [22].

Studies on human kidneys have shown that the distal nephron is the primary location for the expression of 1-alpha-hydroxylase, contrary to findings in experimental models. The level of 1,25(OH)2D in the blood is affected by the presence of 25(OH)D, as well as the functionality of enzymes such as 1-alpha-hydroxylase and 24-alpha-hydroxylase. Various factors, including parathyroid hormone (PTH), calcium, phosphorus, and fibroblast growth factor 23 (FGF23), play a significant role in determining the activity of 1-alpha-hydroxylase [23]. FGF23 possesses the capacity to regulate the activity of 1-alpha-hydroxylase, resulting in the suppression of 1,25(OH)2D synthesis in the kidneys. Concurrently, it facilitates the generation of 24-alpha-hydroxylase and 24,25(OH)2D. The active form 1,25(OH)2D triggers FGF23, which in turn lowers the reabsorption of phosphate in the kidneys, countering the increased absorption in the gastrointestinal tract caused by 1,25(OH)2D. Both 1,25(OH)2D and its precursor 25(OH)D are subject to degradation, which is partially catalyzed by 24-hydroxylase. The enzymatic activity of 24-hydroxylase is modulated by 1,25(OH)2D and is suppressed by elevated levels of parathyroid hormone (PTH). 1-alpha-hydroxylase, the enzyme responsible for the synthesis of 1,25(OH)2D, is not only present in the kidneys but also found in various other tissues such as the gastrointestinal tract, vascular tissue, breast, skin, osteoblasts, and osteoclasts [24].

Additional non-osseous or mineral functions

Vitamin D possesses a wide range of functions beyond its roles in regulating calcium and phosphate levels and maintaining bone health. This is due to the widespread presence of vitamin D receptors in various tissues, such as the skin, muscles, pancreas, immune system, brain, fat cells, breast tissue, blood vessels, and even in certain cancer cells and the placenta [19]. Many observational studies in epidemiology have demonstrated strong links between inadequate levels of 25(OH)D and heightened health risks among individuals, both in the short term and in the long run, aligning with the diverse roles of vitamin D. Given that the majority of individuals enrolled in these trials did not exhibit a deficiency in vitamin D, additional supplementation is unlikely to yield any advantageous outcomes. Conversely, those participants who did present with a deficiency in vitamin D at the onset of the trial would likely require higher doses to reach optimal levels associated with health benefits [25]. The results of an extensive examination of 25 randomized controlled trials reveal the effect of vitamin D supplementation in lowering the incidence of upper respiratory tract infections. The study showed that people with lower levels of 25(OH)D at the beginning, particularly under 10 ng/mL, saw a greater reduction in risk when taking regular doses of supplementation either daily or weekly. Nonetheless, this decrease in risk was not evident in those who received higher amounts of vitamin D, as these quantities have been associated with possible negative impacts on bone health [26]. Numerous studies have been undertaken to investigate the relationship between vitamin D levels and muscle strength, as well as athletic performance, in athletes. However, a recent analysis of current research indicates that the results are inconclusive and fail to definitively establish a connection between serum 25(OH)D levels and performance in sports [27]. In like manner, studies on older adults indicate possible advantages of vitamin D supplementation for muscle function, yet research results on athletes are inconsistent. The differences in the results may be due to the high occurrence of vitamin D deficiency among athletes, with the efficacy of supplementation differing based on the severity of the deficiency. These aspects, particularly in regards to respiratory infections, will be delved into in greater detail in the following sections. [27].

The role of vitamin D in skin health: A comprehensive review of its synthesis and impact on skin function

There are two distinct forms of Vitamin D: Vitamin D3 is essential for animals and is primarily synthesized in the skin, whereas Vitamin D2 is distinguished from D3 by the presence of a methyl group in C24 and a double bond in C22-C23, and is predominantly obtained from plants. The synthesis of Vitamin D3 in the skin involves the conversion of 7-dehydrocholesterol (7DHC), which is an intermediate in cholesterol production. Exposure to sunlight containing ultraviolet B (UVB) radiation in the 290-315 nm wavelength range triggers an electrocyclic rearrangement in the ring at the C9-C10 position, resulting in the formation of pre-vitamin D (PreD3). Following the formation of PreD3, a thermal isomerization process occurs, leading to the production of vitamin D3 (VitD3) by transferring a hydrogen atom from C19 to C9 [28].

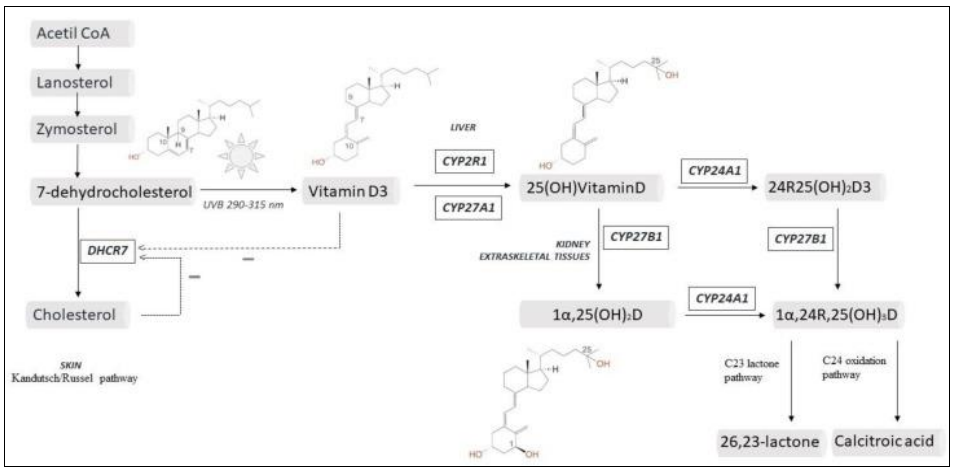

Fig 3

Important stages in the metabolic process of vitamin D

The reaction in question has the ability to be reversed, and both PreD3 and VitD3 can be found together. Viewing this situation from an evolutionary perspective, one can determine that the production of VitD3 relies heavily on UVB exposure, suggesting that the hormone originated over 1.2 billion years ago when algae first started synthesizing cholesterol. It is likely that this mechanism evolved as a means of scavenging to provide protection against UVB radiation by absorbing and dissipating it through the rearrangement of double bonds [29]. A deficiency in vitamin D has only been examined in a small sample of individuals diagnosed with Smith-Lemli-Opitz syndrome. Research conducted by Rossi *et al*. in 2005 revealed that there was no notable difference in the levels of vitamin D in 15 patients with SLOS when contrasted with a similar group of healthy individuals of the same age, However, this discovery could be linked to the photosensitivity experienced by individuals with SLOS, resulting in decreased sunlight exposure.Conversely, Movassaghi and colleagues examined 53 pediatric SLOS patients and observed notably elevated levels of 25 hydroxyvitamin D (25OHD), which serves as an indicator of vitamin D levels without any indications of vitamin D overdose (normal serum calcium levels) [30]. It has been observed that both vitamin D and cholesterol have the ability to lower the expression of DHCR7 at the level of gene transcription. The suppression of AMP-activated protein kinase and protein kinase A resulted in a notable decrease in DHCR7 activity, ultimately boosting vitamin D synthesis while concurrently lowering cholesterol production [31].

Metabolic Processes of Vitamin D in Small-Minded Animals

Two primary forms of vitamin D exist, namely cholecalciferol and ergocalciferol, also known as vitamin D2. Vitamin D2 is derived from ergosterol present in fungi and plants, which undergoes a conversion process upon exposure to UVB ultraviolet rays with specific wavelengths. In contrast, cholecalciferol is synthesized in the skin of different mammalian species upon exposure to sunlight. [32]. Within the deeper levels of the epidermis, particularly in the spinous and basal layers, lies 7-dihydrocholesterol, the precursor of cholecalciferol, housed within the phospholipid bilayer of cell membranes. This particular molecule of 7-dihydrocholesterol absorbs a UVB photon, which triggers the photolytic cleavage of a bond within the pentanoperhydrophenanthrene cycle, ultimately leading to the creation of previtamin D3 with two rings broken. This particular form of D3 is heat-stable and undergoes isomerization induced by heat, transforming into the more stable vitamin D3 with a distinct three-dimensional conformation. Dogs and cats depend solely on the nutrients they consume for their sustenance. The uptake of cholecalciferol and ergocalciferol happens after ingestion, a mechanism that relies on digestive enzymes, bile acids, and chylomicrons [33]. When there are increased levels of circulating calcidiol, cholecalciferol that is absorbed may be stored in adipose tissue and, to a lesser degree, in muscle tissue, rather than being transported to the liver for hydroxylation [33]. Dogs are capable of converting ergocalciferol to calcidiol along with cholecalciferol, whereas cats exhibit a more efficient utilization of cholecalciferol. This disparity in vitamin D processing between the two species may be attributed to their respective dietary habits during the course of evolution. Dogs, being more omnivorous in nature, have historically consumed ergocalciferol in their natural habitat, thus developing the capacity to convert it into calcidiol in the liver. Conversely, cats, classified as strict carnivores, did not naturally consume ergocalciferol, which may explain their diminished ability to utilize this substance for hepatic calcidiol synthesis [34].

Paracellular calcium transport

In addition to transcellular calcium transport, calcium can also be taken up via the paracellular pathway, which occurs between epithelial cells. The extent to which this nonsaturable aspect of calcium absorption depends on vitamin D has been a topic of discussion and is not as clearly understood as vitamin D-driven transcellular calcium transport. Previous research conducted on cultured chick intestine and live rat studies have indicated that 1,25(OH)2D3, also known as active vitamin D, increases paracellular permeability [35]. New studies have shown that specific proteins related to the paracellular pathway, such as claudin-2 and claudin-12 (which are integral parts of tight junctions), cadherin-17 (a protein crucial for cell adhesion), and aquaporin 8 (a channel found within tight junctions), can be impacted by 1,25(OH)2D3 in the intestinal system. This indicates that vitamin D may regulate the absorption of calcium through both the paracellular and transcellular pathways [36]. (Figure 4). Further investigation is necessary to clarify the roles of these cell-to-cell adhesion molecules in intestinal function and to comprehend the significance of their control by 1,25(OH)2D3 in the uptake of calcium in the gastrointestinal tract. The absorption of calcium in the intestines.

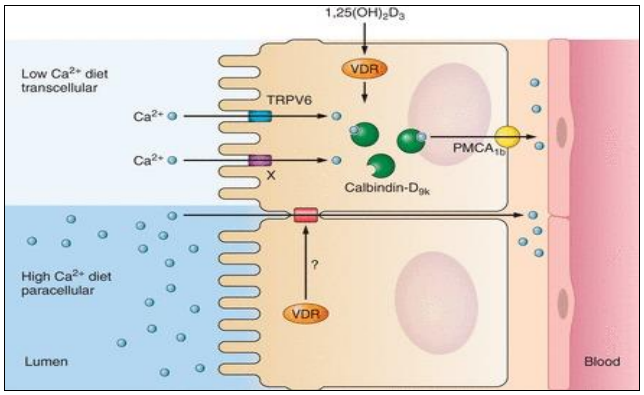

Fig 4

Kidney

The vast majority of calcium initially filtered by the glomerulus is subject to reabsorption in both the proximal and distal tubules, resulting in only a minimal amount (1% to 2%) being eliminated through urine. Roughly 65% of the filtered calcium undergoes passive reabsorption in the proximal tubules, regardless of 1,25(OH)2D3. The reabsorption of calcium in the distal tubules is influenced by the actions of 1,25(OH)2D3 and PTH. The passive reabsorption of calcium in the proximal tubule is facilitated by a sodium gradient, while active transcellular mechanisms similar to those involved in intestinal calcium absorption play a role in calcium reabsorption in the distal tubule. The process involves the entry of calcium through TRPV5, the movement of calcium within the cytoplasm facilitated by binding to calbindin-D9k and calbindin-D28k, and the removal of calcium through the sodium/calcium exchanger (NCX1) and plasma membrane calcium pump 1b. Disruption of Trpv5 leads to increased calcium levels in urine; however, these mice are able to maintain normal blood calcium levels by increasing intestinal calcium absorption due to elevated serum 1,25(OH)2D3 levels. These findings suggest that calcium uptake via TRPV5 plays a crucial role in renal calcium reabsorption. The absence of calbindin-D28k does not significantly impact urinary calcium excretion, as its functions are largely assumed by calbindin-D9k [37]. The lack of Calbindin-D28k in Trpv5 null mice did not exacerbate the Trpv5 null phenotype. The activity of renal calcium reabsorption is modulated by PTH and 1,25(OH)2D3, both of which facilitate calcium reabsorption. Specifically, mice deficient in Cyp27b1 exhibit reduced levels of TRPV5, calbindin-D9k, calbindin-D28k, and NCX1 mRNAs; however, this reduced expression was restored with the introduction of 1,25(OH)2D3 [38]. Based on these discoveries, mice lacking αKlotho and Fgf23 show increased levels of calcium excretion [39].

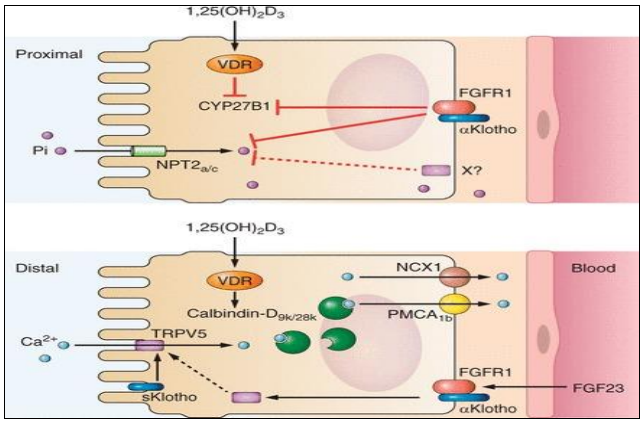

Fig 5

Figure 5 depicts the intricate processes involved in the functions of the Vitamin D receptor in the kidneys, which encompass a diverse array of regulatory pathways. Within the cells of the proximal tubules, the activity of CYP27B1 is inhibited by 1,25(OH)2D3 and FGF23.

Regulation of the synthesis of 1,25-dihydroxy vitamin D3 and absorption of phosphate

The enzyme CYP27B1, responsible for this synthesis, is regulated by PTH, FGF23, and 1,25(OH)2D3, with PTH upregulating its activity while FGF23 and 1,25(OH)2D3 downregulate it. Typically, around 80% of filtered phosphate from urine is reabsorbed in the proximal tubule under normal dietary conditions. Sodium-phosphate cotransporters NPT2a and NPT2c are crucial for transporting phosphate across the epithelium of the proximal tubule, utilizing energy from sodium transport to facilitate phosphate uptake. The regulation of phosphate reabsorption in the proximal tubules is influenced by a range of factors including FGF23, PTH, and 1,25(OH)2D3. PTH and FGF23 impact the excretion of phosphate in the kidneys by reducing the presence of sodium-phosphate cotransporters at the apical membrane through distinct mechanisms. The relationship between FGF23 and the expression of NPT2a and NPT2c is not entirely understood, particularly given that αKlotho, a key component in FGF23 signaling, is predominantly found in the distal tubules, whereas the effects of FGF23 on phosphate absorption are primarily observed in the proximal tubules [40]. The limited presence of FGFR1-αKlotho complexes in the proximal tubules could be adequate for signaling functions. Conversely, recent research indicates that a paracrine factor is discharged from the distal tubules, impacting neighboring proximal tubules. In addition to PTH and FGF23, 1,25(OH)2D3 might have

the ability to control phosphate equilibrium by boosting FGF23 production in osteocytes and αKlotho production in the distal tubule, thereby facilitating renal phosphate elimination. I'm sorry, but it seems like you have not provided any text to be paraphrased [41].

Conclusions

Vitamin D, an essential component for bone health, remains deficient worldwide among individuals of all ages, genders, ethnicities, and socioeconomic statuses, presenting a significant public health challenge. Despite being a curable ailment, nutritional rickets continues to impact a considerable number of infants and children on a global scale, emphasizing the need for a comprehensive global initiative to eliminate this preventable condition. This inconsistency results in discrepancies in the guidelines provided by scientific bodies and global organizations, as they are based on diverse research outcomes. Additionally, there is a dearth of data on the ideal 25(OH)D levels in specific demographics such as infants, children, pregnant and lactating women, and certain ethnic groups. Furthermore, there is a lack of focus on individuals at higher risk of deficiency, such as bariatric surgery patients and athletes. Moreover, there is a lack of proper evaluation and treatment for vitamin D deficiency in vulnerable populations such as older adults, obese individuals, and those with conditions like diabetes, chronic kidney disease, or malabsorption issues. On the other hand, a concerning trend is observed in the general population where individuals are self-administering vitamin D supplements for prolonged periods without adequate monitoring, even when they are not at a high risk of deficiency, potentially increasing the likelihood of adverse effects. Furthermore, there are different compounds available to address vitamin D deficiency, each with distinct pharmacokinetic properties and potency levels in raising 25(OH)D serum concentrations, underscoring the importance of individualized selection of compounds and dosages. Lastly, while observational studies have linked low 25(OH)D levels to various health complications, randomized controlled trials and meta-analyses have often failed to show significant benefits of vitamin D supplementation, except for a decrease in mortality rates. One of the key factors to consider when interpreting these findings is the fact that the majority of participants in the studies did not exhibit a deficiency in vitamin D.

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