DEFICIENCY OF VITAMIN D AND CALCIUM: A HIDDEN EPIDEMIC AFFECTING WOMENS MUSCULOSKELETAL AND REPRODUCTIVE HEALTH

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ABSTRACT

Vitamin D and calcium deficiencies represent a widespread yet underrecognized public health concern, particularly among women across different life stages. These micronutrients play a crucial role in maintaining musculoskeletal integrity and regulating reproductive health. Inadequate levels of vitamin D and calcium contribute significantly to decreased bone mineral density, osteoporosis, muscle weakness, and an increased risk of fractures, especially in postmenopausal women. Beyond skeletal effects, emerging evidence highlights their involvement in reproductive functions, including menstrual regularity, fertility and the pathophysiology of disorders such as polycystic ovary syndrome and preeclampsia. Lifestyle factors, limited sun exposure, dietary insufficiency, hormonal changes, and socio-cultural practices further exacerbate the prevalence of these deficiencies among women. Despite their high burden, vitamin D and calcium deficiencies often remain undiagnosed until clinical complications arise. This article reviews the epidemiology, physiological roles, clinical implications, and risk factors associated with vitamin D and calcium deficiency in women, emphasizing their combined impact on musculoskeletal and reproductive health. Early screening, nutritional interventions, supplementation strategies, and public health awareness are essential to mitigate this hidden epidemic and improve women's overall health outcomes.

Key words: Vitamin D deficiency, Calcium deficiency, Women's health, Musculoskeletal disorder, Reproductive health, Hormonal imbalance, Public health

INTRODUCTION OF VITAMIN D

Vitamin D is a conditionally essential fat-soluble vitamin found in foods such as fish, fish oil, egg yolks, animal fats,some mushroom varieties, and fortified foods such as cheese, margarine ,milk ,infant formula and ready-to-eat cereals[1]Some lichens produce vitamin D3 and may be useful for those who do not want to use animal-derived products, such as vegans and vegetarians [1,2].There are more than fifty metabolitesforms of vitamin D [3].Dietary vitamin isD in the intestines through a complex series of mechanisms, which is not fully understood[4]. Most studies investigating vitamin D absorption utilized murine models or vitamin d in supplement form and only a few have examined human absorption of vitamin d from food[5].Absorption of vitamin Dmostly occurs by passive diffusion but similar to cholesterol absorption.Both are formed into micelles pass, through the brush border, are absorbed into the enterocytes, and are transferred

through the cytosol in intracellular transport-binding proteins, specifically the niemann-pick c1-like carrier, scavenger receptor class B type I, cluster determinant 36, and ATP-binding cassette transporter A1 [5,6]. Niemann pick C1 is the gastrointestinal phytosterol and the cholesterol transporter is a primary modulator for overall body cholesterol homeostasis [6,7].Afterwards the packing into chylomicrons and through lymphatic transport to the liver .Food containing vitamin D oleate can be partially broken up the pancreas lipase protein or brush border enzymes.Some foods minimize the uptake on vitamin D3 in particular long chain fatty acids ,and this is considered to be generated by a change in the micellar charge that affects membrane transporters re-esterification in the enterocyte may occur as well. Some vitamin D could be embedded in phospholipid bilayers or attached to whey proteins that transport vitamin D to the enterocyte certain meals especially those with lengthy chain lipids lower vitamin D3 intake this is thought to be because of a shift in micellar charge with impacts transporters found in membranes[5].

INTRODUCTION OF CALCIUM

Calcium (Ca) is an essential macro-mineral involved in bone and teeth matrices strength and hardness muscle movement including (cardiovascular movement), neurological messaging, and the release of hormones [8]. Major food sources include milk yogurt,cheese,canned fish, dark green leafy vegetables, fortified milk substitutes ,sports drinks ,tofu and ready-to-eat cereals[9].The major regulation of Ca homeostasis in humans is by parathyroid hormone (PTH),Vitamin D, serum Ca, serum phosphorous(PO4),bone-derived fibroblast growth factor 23(FGF23), and calcitonin [10,11,12,13].Normal adult serum calcium concentrations range from 8.5 to 10.5 mg/DL or 2.12 to 2.62 mmol/L and may be reduced in older adults.

Because vitamin d and calcium have an interdependent relationship, a variety of factors may hinder or interfere with the bodys ability to absorb or utilize vitamin D and/or calcium, Which may result in low or excessive levels of each.Additionally vitamin d has been linked to a number of female health and reproductive conditions such as polycystic ovaries, ovarian cysts, and premenstrual syndrome (PMS)and it seems to play a role in fertility[14,15,16,17,18,19].According to laboratory data vitamin d receptors are expressed in reproductive organs including the ovary and the ovary is a target organ for 1,25-dihydroxyvitamin D3, the active metabolite of vitamin D3,the idea that vitamin D delays ovarian aging issupported by recent studies showing astrong correlation between reserve and plasma levels of 25-hydroxyvitamin D 25(OH)D9 amounts[21].

We postulated that there might be a negative correlation between early stages of menopause vitamin D as well as calcium consumption among NHS2 participants the current studys goal was to investigate the relationship between the possibility of early menopause in the prospective nurses medical study and vitamin D and calcium intakes through supplemented, milk, dairy-free ,dietary sources.Additionally we postulated that early menopause would be adversely affected by calcium as well as vitamin d consumed through medication dietary intake and milk products.

Given that observational studies are anticipated to exhibit significant variability a clinical epidemiology and evidence-based medicine specialist is in charge of a study to determine the prevalence of vitamin d deficiency both locally and globally the study data was transformed using the freeman-tukey double arcsine transformation [29].And estimates to stabilize variances

were produced using random-effects meta-analysis previous systematic reviews and meta-analyses have examined the current prevalence of vitamin d deficiency in Europe,africa, and asia[22-28]as well as the mean value of serum 25(OH)D in the global population from 1990 to 2011.

HEALTH IMPLICATION OF VITAMIN D AND CALCIUM

It is essential to evaluate potential reasons of vitamin D deficiency, and this should involve regular evaluation of the person's exposure to sunlight and dietary sources of vitamin D. Because comorbid conditions including hypertension, type 2 diabetes, and abdominal obesity .Deteriorate with age, the effects of vitamin D insufficiency are more noticeable in older persons.[30] This also entails inquiring about specific aspects of sun exposure, such as the time of day, the amount of time spent wearing protective clothes or sunscreen, and whether or not vitamin D blood levels, have been assessed.

When it comes to sun exposure one must consider the optimal time of day,season,latitude,weather,and skin tone .In order to achieve the required quantities of vitamin d according to fitzpatricks skin typing system melanin acts as a barrier to stop UVB radiation from reaching skin 7-dehydrocholesterol[31,32].Skin types are fair-vi always tan[33].When receiving the minimal erythemal dose medication after two to three sun exposures in a week a person with dark skin may need 30 to 60 minutes of sunlight whereas a person with fair skin may need 5 to 15 minutes.One medication requires exposing the limbs/extremities, back and abdomen, if possible which would cause a mild stinging feeling of sunburn.

Vitamin D toxicity is exceedingly uncommon and either occurs by accident or when people purposefully choose to take very high doses that result in serum vitamin D levels of hypercalcemia >200 ng/mL to 500 nmol/L over several months[34,35,36,37].Because the body may convert excess previtaminD hormone to other isoforms that have non-calcemic photoproducts and are easily eliminated sun exposure is known to not result in vitamin d intoxication[34]. If toxicity does arise, treatment entails staying hydrated and cutting off all vitamin D sources, which is enough to correct hypercalcemia and typically has no negative effects.

VITAMIN D AND BONE

MECHANISM -Vitamin d exerts indirect as well as direct effect on the bone [38]. vitamin D is a key component of mineral balance, by promoting gut calcium and phosphorus absorption which are needed for complete mineralization of bone. Vitamin D additionally performs direct actions on bone.The direct actions of vitamin d on bone are more complex to demonstrate, and studies on vitamin d receptor or Cyp27B1 knockout animal models treated with a rescue high-calcium high-phosphorus and high-lactose diet have shown that even though severe bone abnormalities such as rickets(i.e., defective mineralization of the growth plate and adjacent metaphysis in the growing skeleton) and osteomalacia (i.e., the accumulation of unmineralized osteoid at sites other than the growing metaphysis) are prevented[39,40].Changes in osteoblast number, mineral apposition level, bone volume remain[41]

VITAMIN D, MUSCLE STRENGTH, MUSCLE MASS, MUSCLE POWER AND RISK OF FALLS

MECHANISM- Vitamin Ddeficiency is being associated with musculoskeletal dysfunction, decreased muscle growth, as well as strength and an elevated level in intramuscular inflexible tissue[42,43]

since quads strength is a crucial predictor of falls [44]and vitamin D scarity has also been linked to an improve risk of falls [45,46].An improvement in lower limb muscle strength could be a promising mechanism between which vitamin d augmentation could diminish the risk of drop whether vitamin D augmentation confers protection from lessen has received a lot of attention but meta-analyses on this topic have produced conflicting results. Early quantitative review initiate that vitamin D augmentation was valuable in lowering the chances of drops and two asses initiate that vitamin D augmentation. In combination with calcium but not vitamin D augmentation alone decrease the chance of falls [46,48]. Although later quantitative review initiate that vitamin D augmentation had neutral results on drops[47]and that using excessive dose of vitamin D augmentation raised the risk of falls[49,50].

VITAMIN D AND HYPERTENSION

MECHANISM-Preclinical demonstration indicated that a lack of vitamin d may predispose to hypertension through upregulation of the renin-angiotensin-aldosterone system (RAAS) along with elevated vessel resistance and vascular constriction[51,52].On the opposite side,vitamin d receptor activation has been shown to inhibit intrarenal mRNA levels and protein expression of key components of the RAAS[51].

Evidence shows that vitamin D intake helps for minimizing blood pressure among patients with elevated pressure and vitamin D deficiency[53].Once again, the modality of vitamin D consumption impacts the outcome with regular [54-56] or weekly[57] administrations of vitamin D improving hypertension outcomes whereas large bolus vitamin D dosing (e.g., 100000 IUVD every 2 months) failed to reduce blood pressure in vitamin D deficient subjects[58].Large doses of vitamin D might also have detrimental vascular effects since they can result in vascular calcification[59].Conversely, vitamin D consumption in vitamin D deficient individuals has null effects on lowering blood pressure[60].Antihypertensive medications might also have impact on whether vitamin d consumption will affect blood pressure.Forexample,Bernini et al did not observed any effect of acute or chronic vitamin D supplementation on RAAS in patients with essential hypertension on RAAS inhibitor treatment[54];However, they also showed that chronic vitamin D receptor activation in drug-free essential hypertensives suppresses RAAScomponents [61].This evidence further underlines that the blood pressure effects of vitamin D in humans are dependent on the activity of RAAS (Renin-Angiotensin-Aldosterone System).

CARDIOVASCULAR EVENTS

MECHANISM –Vascular cells smooth muscle of the vascular system as well as cardiac myocytes everything express the vitamin D receptor[62].Vitamin D protects functions of how vascular cells by blocking the growth of vascular smooth muscle cells[63],it also

decrease oxidative strain inflammation as well as thrombogenesis [64].It has also been proposed that it can modify lipid metabolism by raising the amount of lipase an enzyme in fat tissue [65]along with decreasing the amount of lipid absorption [66].As discussed earlier, it can also reduce RAAS, activity thereby decreasing blood pressure.

TUBERCULOSIS

MECHANISM -It is believed that vitamin D was utilized pre-antibiotic era to promote the recovery of patients with infectious disease such as tuberculosis (TB) when the ancient Greeks had first introduced "heliotherapy"(i.e., sunlight exposure to treat TB[70].Moreover in preclinical studies it has been shown that 1,25(OH)2D induces antimycobacterial activity in vitro in monocytes and macrophages[67,68].However, recent controlled studies and systemic reviews have produced either minimal or null effects in a variety of TB-associated outcomes. A systematic review reported that serum vitamin d quantities have no relationship with the rate of infection caused by latent tuberculosis [69].

COVID 19

Considering the previous implications of vitamin D in acute infection, of the respiratory tract immediately following the outbreak of the covid -19 pandemic the research group started investigating whether vitamin D supplementation might have an impact in prohibiting infection with severe acute respiratory syndrome coronavirus (SARS-COV2), or on the extent of covid -19. This was particularly significant at the onset of the pandemic when the medical community had almost no treatments in the fight against covid-19.

MECHANISM-There are a number of ways that vitamin D can help to protect against covid-19. Initially, by controlling the immune system natural reaction, vitamin D induces the production of the antimicrobial peptides Cathelicidin or ll-37 and defensin blocking the viral entry into cells[71].Because of the actions of vitamin D on the adaptive immune system and specifically the shift away from a proinflammatory state, it diminishes the risk of a cytokine storm, that is particularly dangerous in fatal cases of covid-19 [72].

TYPE 2 DIABETES

MECHANISM -Preclinical research has demonstrated that vitamin D may enhance the secretion of insulin cell growth and differentiation[73,74],insulin receptor expression and diabetes-mediated blood glucose transfer[75].

DIABETIC NEUROPATHY AND DIABETIC FOOT ULCER (DFU)

MECHANISM - The functions of vitamin D may involved in the operation of the body autonomic nervous system is still not been extensively studied[77].Research have shown that vitamin D may be concerned with pain perception[78]and that it can induce nerve-growth factor synthesis in human cell lines [79]Lack of vitamin D also reported to impair the maturation and propagation of both keratinocytes and skin fibroblasts and to delay Diabetic foot ulcer(DFU) healing [80,81] vitamin D has been shown to induce production of antimicrobial peptides in keratinocyte cells from DFU [82].Early clinical experiment have shown that topical application

of vitamin D promoteshealing injuries in a dose-dependent manner[83] and activates the expression of angiogenic molecules in keratinocytes and the promotes the movement of endothelial and keratinocyte cells in a diabetic foot ulcer model[84].

According to studies Vitamin D deficiency is linked to diabetic foot infections diabetic foot ulcers and severe diabetic neuropathy [85,87].Severe Vitamin D deficiencyi.e 25(OH)D<10 ng/ml is linked to an elevated risk of diabetic foot ulceration (or 3.2; 95 CI 2.4-4.3 [88] and /or 3.6; 95% CI 2.9-4.4;< p 00001)[89].According to two recent meta-analyses involving a total of 1115 and 1644 T2D patients in a short RCT 60 patients with grade 3 dfu based on the 'wagner-meggit' criteria were randomly assigned to receive either a placebo for 12 weeks or 50,000 IU of vitamin D every two weeks the length width depth and erythema rate of ulcers have all been demonstrated to decrease with vitamin D administration [90] for the duration of 48 weeks of rehab an ulterior RCT compared excessive vitamin D administration 170 µg/day approximately(i.e.,6800 IU via low-dose 20 µg/day or 800 IU) those who at present took high-dose intake had a greater rate of ulcer healing (70% versus 35%= p= 001), in the high versus low intake group according to the intention-to-treat analysis [91].

CANCER

MECHANISM –1,25(OH)2D analogs have strong antiproliferative and pro-differentiating effects on cancer cells in vitro according to early research [92] Additionally vitamin d reduces angiogenesis metastatic tendency and tumor invasiveness [93 ,94]

Higher concentrations of vitamin D are protective against a number of cancers including women with breast cancer [95],metastatic colorectal cancer [96], prostate cancer [97] and hematological malignancies [98].According to research from meta-analyses and systematic reviews on dietary vitamin D content and morbid outcomes within cancer survivors however these encouraging results which depends on qualitative studies can be skewed by those who participated in higher levels of 25(OH)D having generally better health andor leading healthier lifestyle (e.g.,exercising with more sun exposure).

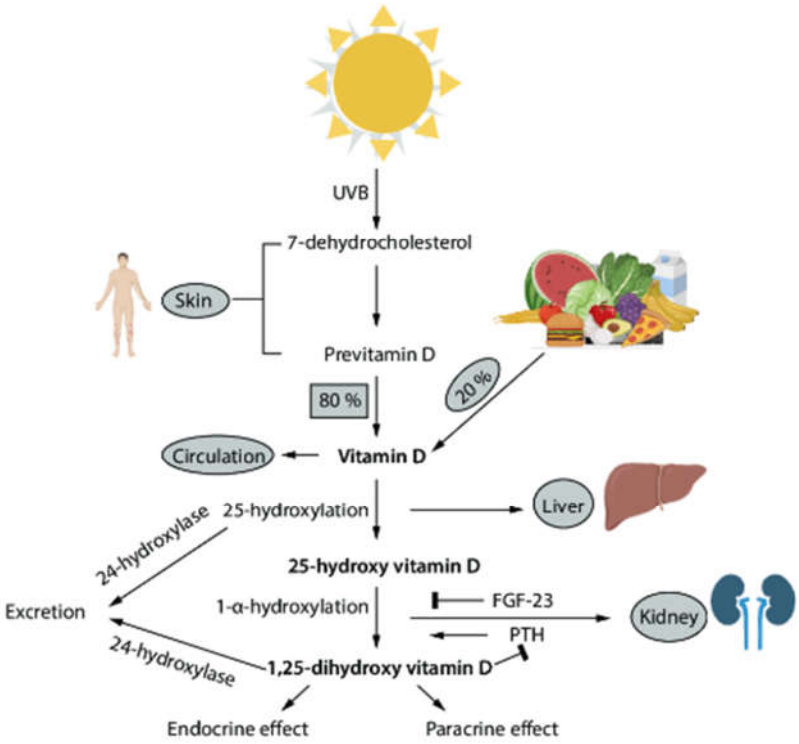
INFLAMMATORY BOWEL DISEASES (IBD)

MECHANISM - IL-10 knockout mice is an animal model used for the study of IBD these animals spontaneously develop enterocolitis within 5-8 weeks of birth due to an uncontrolled immune response to resident intestinal flora [99,100].People who have an IL-10 gene polymorphism also have an increased risk of developing colitis[101].In the animal model it has been shown that Vitamin D deficiency exacerbates the symptoms of IBD and increases morbidity and mortality in the affected mice whereas supplementation with [102].People with IBD are at risk for Vitamin D deficiency because they frequently have small-bowel resection and are treated with cholestyramine to reduce postresectional diarrhea induced by malabsorption of bile acids. Both of the circumstance promotes bile acid reduction which is required for vitamin D absorption[103].Vitamin D administration has been suggested to reduce swelling in those suffering from IBD by decreasing penetration in the GI tract and raising collagen levels a peptide that helps to minimize inflammation as well as promotes healing [104,105].

VITAMIN D METABOLISM SYNTHESIS AND ACTIVATION

METABOLISM

Further synthesis is required regarding the effectiveness of the D3 vitamin produced in the epidermis. The first phase, the 25-hydroxylation process, is primarily connected with the liver, although other tissues also show comparable enzyme functions. As will be discussed below, there are numerous 25-hydroxylases. 25OHD is the most common form of the vitamin D in bloodstreams. The most powerful metabolic product of vitamin D, 1,25(OH)2D, bears responsibility for most of its pharmacological effects, but it appears that the CYP27B1 enzyme also needs to hydroxylate the nutrient metabolites at the 1α position for them to achieve optimal biologic activity. The enzymatic agent 25-hydroxylase is present in various tissues, but the renal system is the primary target of 1α hydroxylation. Vitamin D and its metabolites 25ohd and 125oh2d can also be hydroxylated in the 24 position.This may serve to activate the metabolite or analog as 1,25(OH)2D and 1,2(OH)2D have similar biologic potency. and 1,24,25(OH)3D has activity approximately 1/10 that of 1,25(OH)2D.However,24-hydroxylation of metabolites with an existing 25(OH) group leads to further catabolism.[105] The micellar charge that affects membrane transporters (5 the micellar charge that affects membrane transporters).



ROLE

Calcium signaling in the process of bone remodeling

In the instance of bones regrowth, calcium channel transmission is crucial for the breakdown of calcium, and bone marrow proliferation & bone production is seriously affected by unbalanced Ca2 state. While mitochondria are necessary for flawless buildup of bones, excessive levels of calcium within cells can interfere with the internal DNA membrane's capability to operate, which may delay the creation of bone. Excessive Ca2+ loading in skeletal cells could restrict cell division by triggering dying in your mitochondria and the ER. [109,110]. Osteoblasts may undergo mortality due to comparable elevated calcium levels in the cells.[111]Bone marrow derived embryonic connective tissue give increase to osteogenic cell as well as modulate bone-resorbing cells role by releasing ligand of nuclear factor-b ligand RANKL and osteoprotegerin(OPG), thereby maintaining. Skeletal homeostasis these cells are middle to osteo restoration as they contribute directly to new ossification together with indirectly control bone resorption li et al. Demonstrated that disturbances in intracellular calcium signaling in bone tissue from osteoporotic patients and mouse ,models impair osteoblast differentiation and reduce bone formation.[112]

The outermost protective layer in the cell provides ca permeable openings that is vital for extracellular supply of Ca to pass through and for the healthy operation of bones calcium trafficking networks are intriguing targets since a decrease in the amount of Ca generated by these networks may affect the osteoclast process and development.

Calcium Ca2+ is pumped from the Endoplasmic reticulum(ER) by its Ryanodine receptors(RyRs) and IP3Rs is stimulated Ca2+ holds are released,whenIP3 is produced as a result in PLC stimulating when binds to IP3Rs on the ERmembrane.According to gene knockout analysis IP3R2 is essential for Ca oscillation throughout the osteoclastogenesis process and its depletion causes an aberrant impairment in osteoblast development, while peripheral membrane-resident RyR2 enzymes can influence osteoclast enzymes upon cellular Ca RyRs channels for Ca may aid to the liberation of within-cell calcium reserves [115].

Bone production restructuring while destruction in the presence of physical stress are mediated by osteocytes that are tissues that sense stress from motion [116].Osteocytes found inside the superficial cell matrix may be activated by some kinds of structural influences such as fluids shear stresses matrix strains such as compressive tensile and torsional pressures [117].The osteocytes are encapsulated by a cellular structure at the interface of the hard bone matrix and cell walls in the bone microclimate from spatial dislocation.Small force stimulation cause fluid shearing of the extracellular fluid flow which triggers integrins and mechanically stimulus-sensitive ion channels on the osteocyte membranes.

ACTIVATION

It is assumed that vitamin D3 which is only be triggered by 25- and also 1α-hydroxylations has been contested.Estabrook in addition associates initially identified an intriguing alternative mechanism to obtain vitamin D3 and D2 formation in certain tissues in 2003[118] and Slominski and Tuckey and associates[119,120] further investigated.It the steroidogenic enzyme Cyp11A1

initiates this alternative synthesis process and it results in the formation of non-classical vitamin d metabolites like 20 in addition 22-hydroxylated vitamin D derivatives.The side chains initial cyp11a1-mediated 20- and 22-hydroxylations are followed by additional metabolism via 1- 24- 25- or 26-hydroxylations catalyzed by the regular vitamin D enzymes. The by product in these routes are reported to be physiologically useful some of them inhibit growth of the cell but they lacking calcemic action making them interesting candidates for anti-cancer treatment[119].

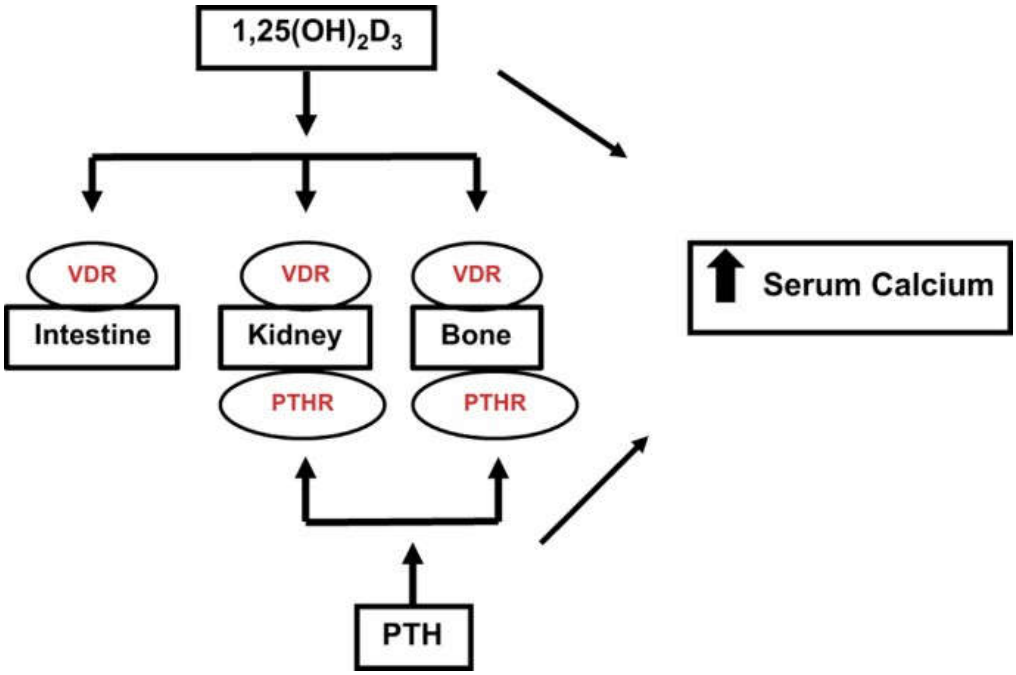
VITAMIN D, METABOLISM AND MAINTENANCE OF CALCIUM HOMEOSTATIS

Vitamin D is either absorbed by way of consumed food into fortifying dairy products together with omega 3 fatty acids or it is generated in the skin by UV light from 7-dehydrocholesterol[121,122].The livers 25-hydroxylation of vitamin D yields 25-hydroxyvitamin D compound 25(OH)D3 which serves as the most prevalent form of naturally occurring vitamin d in circulating system in addition the most reliable indicator of vitamin d status the active form of vitamin D 1,25(OH)2D3 requires a series of hydroxylations the first at carbon 25th carbon c-25 and the second at carbon 1 carbon C-1. Currently Cyp2R1 is thought to be the primary enzyme that converts vitamin d to 25(OH)D3[123,124].The role of Cyp2R1 in the hydroxylation of vitamin D at C-25[125] has been supported by investigations with Cyp2R1 null mice that show much lower amounts of 25(OH)D3 in these mice .However the synthesis of low levels of 25(OH)D3 in these mice indicates that additional 25-hydroxylases that have not yet been discovered are also involved in the conversion of vitamin D to 25(OH)D3.Following its synthesis in the liver 25(OH)D3 is carried to the kidney by Diastolic blood pressure (DBP) where megalin a trans membrane protein that functions as a surface receptor for DBP internalizes it. the 25(OH)D31α hydroxylase (Cyp27B1)hydroxylates 25(OH)D3[126,127].In the proximal renal tubule forming 1,25(OH)2d3 and this enzyme is necessary for the metabolic activities of daily vitamin d compound in humans beings the genetic changes that lead to nonfunctional or deleted substances Cyp27b1 result in vitamin D dependency the low calcium levels hyperparathyroidism in addition to reduced bone mineralization associated with rickets syndrome type 1 highlight the importance of substances cyp27b1 for the preservation of calcium homeostasis[128].25-hydroxyvitamin D3 24hydroxylase Cyp24A1 is the enzyme that catabolizes 1,25(OH)2D[129,130] research using Cyp24A1 null mice has shown that Cyp24A1 plays a role in the catabolism of 1,25(OH)2D3.About 50 of homozygous variation survive the surviving Cyp24A1 null mice cannot eliminate 1,25(OH)2D3 given exogenously [131] further evidence for the role of Cyp24A1 in 1,25(OH)2D3 catabolism comes from reports that halt the change in Cyp24A1 have a causative effect in a few people with idiopathic infantile hypercalcemia[132] hypocalcemia-induced raised parathyrin PTH inhibits Cyp24A1 and causes the kidney to produce 1,25(OH)2D3[132].Raised parathyrin PTH resulting from hypocalcemia induces 1,25(OH)2D3 process in the kidney and inhibits Cyp24A1. 1,25(OH)2D3 in turn acts to suppress PTH production at the parathyroid gland and to negatively regulate Cyp27B1 thus regulating its own production[133,134]. 1,25(OH)2D3 can also do so by inducing Cyp24A1 thus completing an auto-regulatory feedback loop and maintaining a stringent control mechanism[129,130,134].FGF23 a phosphaturic factor that assist renal phosphate excretion also control vitamin D metabolism.

Klotho is a co-receptor for FGF23.Along with FGF23 and klotho suppress Cyp27B1 and induce Cyp24A1 resulting in a reduction in 1,25(OH)2D3 levels[135].

The gene activity of 1,25(OH)2D3 are intervened through the steroid hormone receptor 1,25(OH)2D3-occupied heterodimerizes along with 9-cis retinoic acid receptor and also accompanied co-regulatory proteins communicate with vitamin d feedback component moreover around the gene of interest and intervenes their transcription[136,137].

The major purpose of 1,25-dihydroxyvitamin d within calcium balance means the rise in intestinal calcium uptake the ligand transcription factors is present throughout the pair of little and large intestine and vitamin D depending on calcium absorption occurs in proximal as well as distal gut via regions proof from vitamin D receptor deficient mice shows that rachitis and soft bone tissue can be avoided when animals are provided with a calcium- and lactose-rich diet demonstrating that 1,25-dihydroxyvitamin D and its receptor are essential for proper osteo crystallization via their control of intestinal calcium consumption. Rachitis and bone softening are forbid when calcitriol receptor null mice are fed a diet high in calcium and lactose specify that 1,25(OH)2D3 and Vitamin D receptor have a critical role in ossification by regulating intestinal calcium absorption[138,139] 1,25(OH)2D3 has been described to regulate every step of the intestinal active calcium transport procedure it persuade the declaration of the apical membrane calcium channel TRPV6 the calcium-binding protein calbindin-D9k (it has been proposed that calbindin ease in part translocation of calcium through the intestinal absorptive cells and buffers calcium holding back lethal quantity of calcium from assemble in the cell),and the plasma membrane Ca ATPase,PMCA1b.Thereby 1,25(OH)2D3 apply its limitation in the intestine on calcium approach calmodulin and delamination of calcium[140]



The active constituents in a daily vitamin D supplement and the ligand that triggers the vitamin D receptor respond to low serum calcium quantities are enhanced by intestinal calcium consumption.If this is crucial for the normal calcium protect 1,25(OH)2D3 in addition PTH, act via their receptors to mobilize calcium from osseous tissue as well as improve the reintake of calcium by nephron cells.

Although Calbindin-D9k and TRPV6 are transcriptionally regulated by 1,25(OH)2D3 mice lacking either calbindin-D9k or TRPV6 still exhibit vitamin D stimulated duodenal calcium absorption comparable to that of wild-type animals.This examination suggest that alternative calcium channels or calcium-binding proteins can compensate for their absence and sustain efficient calcium transport[141].However greater bone turnover and damaged ossification have been noticed in TRPV6 null mice that are continued on a low-calcium diet[142]. Additionally, overexpression of TRPV6 in the mouse intestine effects in excess calcium in urine high blood calcium and muscle tissue crystallization suggesting a important part for TRPV6 in intestinal calcium absorption[143].Moreover investigation in calbindin-D9k/TRPV6 double-knockout mice show that the absence of both genes outcome in markedly reduced bioavailability below low-calcium dietary state indicating that calbindin-D9k as well as TRPV6 may function cooperatively in specific components of calcium transcytosis[141].

When luminal calcium uptake is inadequate to maintain usual serum calcium levels 1,25-dihydroxyvitamin D 1,25(OH) D works together with parathyrin PTH to increase renal calcium consumption and promote calcium mobilization from bone in the distal nephron calcium handling involves mechanisms similar to those in the intestine specifically 1,25(OH)D stimulates calcium transcytosis by upregulating the epithelial calcium channel trpv5 which shares approximately (75 Percentage sequence homology with TRPV6)and mediates apical calcium entry additionally 1,25(OH)D induces the expression of calcium-binding proteins including calbindin-D9k and calbindin-D28k both proteins are demonstrated in the mouse kidney whereas only vitamin d- dependent calcium- binding protein d28k is present in rat and human kidneys[144,145].However the situation remain debatable investigations in the enzyme Cyp27b1 lacking laboratory mice have shown that the activity of the Na and ca 2+ transmitter is diminished, showing the regulation of the naca2 transmitter along with the cal binding protein and TRPV5 protein with 1,25(OH)2d3[146]projection of calcium at the distal convoluted tubule is caused by PMCA lb and the Na and Ca2+transmitter studies on TRPV5 lacking laboratory mice revealed .The essential role of TRPV5 in kidney calcium reabsorption these mice suffering from severe hypercalciuria and notable alterations in bone composition[141].Additionally both PTH and 1,25(OH)2d3 promoted osteoclastogenesis[137].In bone which causes breakdown of osteoclastic bone which releases calcium from bone to restore calcium equilibrium.

CAUSE AND SYMPTOMS

Moreover poor food consumption persons by kidney renal and skin illnesses also suffered vitamin d insufficiency.There are numerous reasons why this state is so general in India.

- Raised indoor lifestyle which prevents adequate exposure to sunlight this is primarily seen in urban populations due to modernization.

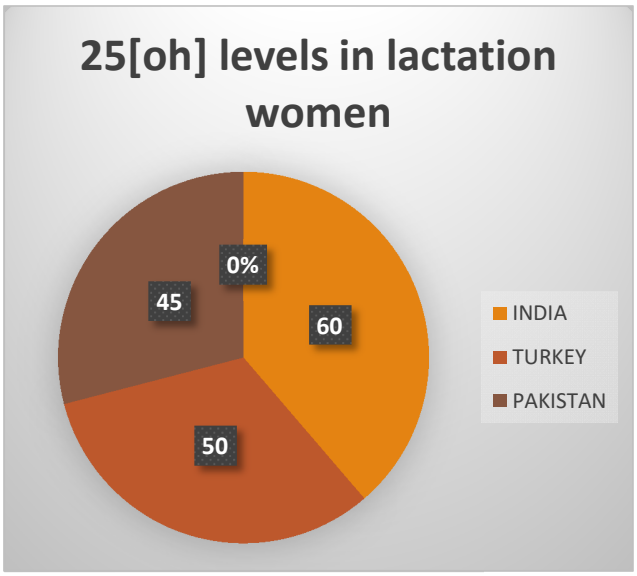
- Pollution can hinder the skins ability to process of vitamin D through UV rays[149] .
- Changing food administer can result i.e., low nourishing calcium as well as vitamin D absorption.
- Phytates additionally Phosphates these are found in diets high in fiber can diminish the vitamin D stores as well as calcium requirements[150]
- Cultural customs like the burqa and purdah system
- Raised skin pigmentation and sunscreen use [151]
- Unplanned as well as Sporadic pregnancies in women with nutrition.

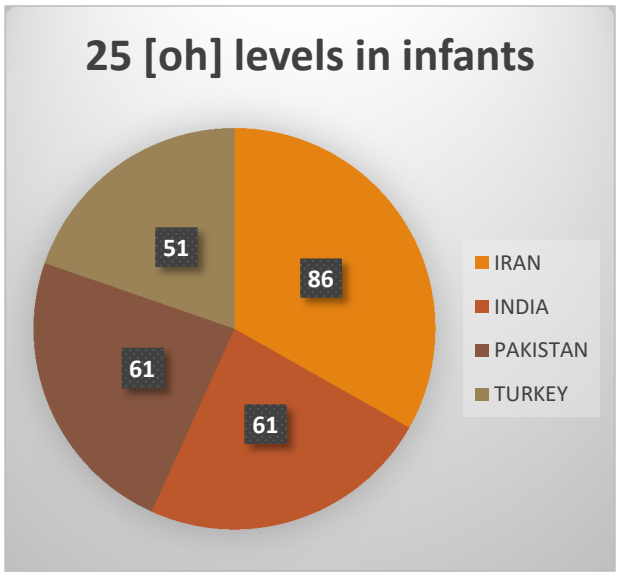
EPIDEMIOLOGY AND GLOBAL PREVALENCE

Vitamin D status has been assessed in numerous studies worldwide. However data from africa and latinamerica are currently scarce.It should be noted that studies are not always directly comparable since there are several different assays and inter- laboratory variation is still considerable for the purposes of this review the threshold has been set at a serum level of 50nmol//l 25(OH)D and vitamin D deficiency is described as a 25(OH)D level of less than 25nmol/l unless otherwise stated as these are the most commonly used definitions. In 2010 the institute for medical science created a conceptual model illustrating the association between vitamin d statusassessed by serum 25-hydroxyvitamin Dlevelsand overall bone health outcomes this model was based on findings from two large systematic reviews that analyzed the link between the calcium absorbs vitamin d and parathyrin quantities the institute concluded that a blood serum amounts of 50 nmol/l would be adequate for 97.5% of individuals,while 40 nmol/l would meet the skeletal health requirements of approximately half the population, while 50nmol/l would be sufficient for 97.5% of the population.They concluded that people are at risk of deficiency when serum 25(OH)D is <30 nmol/l that some people are potentially at risk of inadequacy when serum 25(OH)D is 30-50 nmol/l and that over 50nmol/l is sufficient for almost all of the population[152] although several recent review papers have highlighted the global extent

of vitamin D deficiency there are significant data gaps especially for LMICs[153].[154-156]representative population-level 25(OH)D data are not available for most countries and the surveys that do exist often present an incomplete picture of vitamin d status and its determinants (i.e., lacking complementary data related to dietary intake,UVB exposure).

Furthermore as noted earlier serum 25(OH)D can be measured using multiple assay methods each differing in accuracy and precision consequently substantial variation in results may occur both across assay types and between laboratories.The absence of standardized laboratory technique makes it challenging to cluster population-level data or to compare the discovery across research over time in addition differences in data reporting practices and the use of varying deficiency thresholds proportions below 30 nmol/l versus below 50 nmol/l further hinder direct comparisons between studies. Evidence from a recent global review illustrates that a lack of vitamin d has been highly prevalent across entire population worldwide regardless of geographic latitude or a countries level of human development in some regions deficiency persists.Additionally in the presence of various food enhancement initiatives intended aim to encourage sufficient sunlight consumption but a lots of the data on vitamins status and shortage of incidence comes from investigations that are either over ten years old or based on small non-representative samples rather than from large population-based surveys. Still seems to be consistent evidence showing that the cases of inadequate level of vitamin d is highest in asia - pacific region,the middle east and africa as well as among immigrants from these regions living in the nations at higher latitudes[158].It should be noted that utilization of calcium tends to be very low within these zones increasing the risk of child premature development of bone and other bone problem due to vitamin d shortages [158,159,160].Numerous brief investigation within asia have shown that the majority of young infants have 25(OH)D below 30 nmol/l such as 51% in turkey 86% iniran and 61% in pakistan[153].





CONCLUSION

Vitamin D and calcium deficiency represents a widespread yet often overlooked public health challenge that significantly affects women's musculoskeletal and reproductive health. Inadequate levels of these micronutrients weaken bone mineral density, impair muscle function, and increase the risk of osteoporosis and fractures, particularly in postmenopausal women. Emerging evidence also links these deficiencies to reproductive disorders, adverse pregnancy outcomes, and hormonal imbalances. Contributing factors such as poor dietary intake, limited sun exposure, and physiological changes across the female lifespan further exacerbate the problem. Routine screening, improved nutritional awareness, and appropriate supplementation are essential preventive measures. Integrating vitamin D and calcium assessment into women's healthcare programs can help reduce disease burden, improve overall health outcomes, and address this hidden epidemic effectively.

REFERENCE

1. National Institutes of Health. Dietary Supplement Label Database. Search DSLD. 2020. (Accessed on 23 June 2023).

2. United States Department of Agriculture. Food Data Central. Food Search. (accessed on 22 July 2024).

3. Makris, K.; Sempos, C.; Cavalier, E. The measurement of vitamin D metabolites: Part I-metabolism of vitamin D and the measurement of 25-hydroxyvitamin D. Hormones 2020, 19, 81–96.

4. Silva, M.C.; Furlanetto, T.W. Intestinal absorption of vitamin D: A systematic review. Nutr Rev. 2018, 76, 60–76.

5. Reboul, E. Intestinal absorption of vitamin D: From the meal to the enterocyte. *Food Funct.* 2015, *6*, 356–362.

6. Davis, H.R., Jr.; Zhu, L.-J.; Hoos, L.M.; Tetzloff, G.; Maguire, M.; Liu, J.; Yao, X.; Iyer, S.P.N.; Lam, M.-H.; Lund, E.G.; et al. Niemann-Pick C1 Like 1 (NPC1L1) is the intestinal phytosterol and cholesterol transporter and a key modulator of whole-body cholesterol homeostasis. *J. Biol. Chem.* 2004, *279*, 33586–33592.

7. Cai, L.; Eckhardt, E.R.M.; Shi, W.; Zhao, Z.; Nasser, M.; de Villiers, W.J.S.; van der Westhuyzen, D.R. Scavenger receptor class B type I reduces cholesterol absorption in cultured enterocyte CaCo-2 cells. *J. Lipid Res.* 2004, *45*, 253–262.

8. US Department of Health and Human Services. NIH Office of Dietary Supplements. Calcium-Health Professional. Updated 6 October 2022 (accessed on 23 July 2023).

9. United States Department of Agriculture. Food Data Central. Component search. Calcium. (accessed on 22 July 2023).

10.Essig, G.F. Parathyroid physiology. Medscape. Updated Sept 16, 2022. (accessed on 12 October 2022).

11.Quinn, S.J.; Thomsen, A.R.B.; Pang, J.L.; Kantham, L.; Bräuner-Osborne, H.; Pollak, M.; Goltzman, D.; Brown, E.M. Interactions between calcium and phosphorus in the regulation of the production of fibroblast growth factor 23 in vivo. *Am. J. Physiol. Metab.* 2013, *304*, E310–E320.

12.Mace, M.L.; Olgaard, K.; Lewin, E. New aspects of the kidney in the regulation of fibroblast growth factor 23 (FGF23) and mineral homeostasis. *Int. J. Mol. Sci.* 2020, *21*, 8810.

13.Martin, A.; Valentin, D.; Quarles, L.D. Regulation, and function of the FGF23/Klotho endocrine pathways. *Physiol. Rev.* 2012, *92*, 131–155.

14.Yildizhan R, Kurdoglu M, Adali E, Kolusari A, Yildizhan B, Sahin HG, Kamaci MSerum 25-hydroxyvitamin D concentrations in obese and non-obese women with polycystic ovary syndrome Arch GynecolObstet, 280 (2009), pp. 559-563.

15.Wehr E, Pilz S, Schweighofer N, Giuliani A, Kopera D, Pieber TR, Obermayer-Pietsch BAssociation of hypovitaminosis D with metabolic disturbances in polycystic ovary syndromeEur J Endocrinol, 161 (2009), pp. 575-582.

16.Li HW, Brereton RE, Anderson RA, Wallace AM, Ho CKVitamin D deficiency is common and associated with metabolic risk factors in patients with polycystic ovary syndromeMetabolism, 60 (2011), pp. 1475-1481.

17.Harris HR, Chavarro JE, Malspeis S, Willett WC, Missmer SADairy-food, calcium, magnesium, and vitamin D intake and endometriosis: a prospective cohort studyAm J Epidemiol, 177 (2013), pp. 420-430.

18.Rojansky N, Brzezinski A, Schenker JGSeasonality in human reproduction: an update Hum Reprod, 7 (1992), pp. 735-745.

19.Dokoh S, Donaldson CA, Marion SL, Pike JW, Haussler MRThe ovary: a target organ for 1,25-dihydroxyvitamin D3Endocrinology, 112 (1983), pp. 200-206.

20.Halloran BP, DeLuca HFEffect of vitamin D deficiency on fertility and reproductive capacity in the female ratJ Nutr, 110 (1980), pp. 1573-1580.

21.Jukic AM, Steiner AZ, Baird DDAssociation between serum 25-hydroxyvitamin D and ovarian reserve in premenopausal womenMenopause, 22 (2015), pp. 312-316.

22.Hilger J, Friedel A, Herr R, Rausch T, Roos F, Wahl DA, et al. A systematic review of vitamin D status in populations worldwide. Br J Nutr. (2014) 111:23–45. 10.1017/S0007114513001840.

23.Manios Y, Moschonis G, Lambrinou CP, Tsoutsoulopoulou K, Binou P, Karachaliou A, et al. A systematic review of vitamin D status in southern European countries. Eur J Nutr. (2018) 57:2001–36. 10.1007/s00394-017-1564-2

24.Mogire RM, Mutua A, Kimita W, Kamau A, Bejon P, Pettifor JM, et al. Prevalence of vitamin D deficiency in Africa: a systematic review and meta-analysis. Lancet Glob Health. (2020) 8:e134–e42. 10.1016/S2214-109X(19)30457-7.

25.Jiang Z, Pu R, Li N, Chen C, Li J, Dai W, et al. High prevalence of vitamin D deficiency in Asia: a systematic review and meta-analysis. Crit Rev Food Sci Nutr. (2021) 1–10. 10.1080/10408398.2021.1990850.

26.Cashman KD, Dowling KG, Škrabáková Z, Gonzalez-Gross M, Valtueña J, De Henauw S, et al. Vitamin D deficiency in Europe: pandemic? Am J Clin Nutr. (2016) 103:1033–44. 10.3945/ajcn.115.120873

27.van Schoor N, Lips P. Global overview of vitamin D status. Endocrinol Metab Clin North Am. (2017) 46:845–70. 10.1016/j.ecl.2017.07.002

28.van Schoor NM, Lips P. Worldwide vitamin D status. Best Pract Res Clin Endocrinol Metab. (2011) 25:671–80. 10.1016/j.beem.2011.06.007

29.Barendregt JJ DS, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. J Epidemiol Community Health. (2013) 67:974–8. 10.1136/jech-2013-203104

30.Matyjaszek-Matuszek, B. · Lenart-Lipinska, M. · Wozniakowska, E.Clinical implications of vitamin D deficiencyPrzMenopauzalny. 2015; 14:75-81

31.O'Sullivan, F. · Laird, E. · Kelly, D. ...Ambient UVB dose and sun nnjoyment are important predictors of vitamin D status in an older populationJ Nutr. 2017; 147:858-868

32. Sakamoto, R. · Thorpe, D. · Knutsen, R. ...Ethnic variations in serum 25(OH)D levels and bone ultrasound attenuation measurements in blacks and whitesJ Racial Ethn Health Disparities. 2018; 5:439-448

33.Webb, A.R. · Kazantzidis, A. · Kift, R.C. ...Colour counts: sunlight and skin type as drivers of vitamin D deficiency at UK latitudesNutrients. 2018; 10:E457

34.Holick, M.F.Sunlight, ultraviolet radiation, vitamin D and skin cancer: how much sunlight do we need?Adv Exp Med Biol. 2014; 810:1-16

35.Grant, W. · Bhattoa, H. · Pludowski, P.Determinants of vitamin D deficiency from Sun exposure: a global perspectiveFeldman (Editor)Vitamin D: Volume 2: Health, Disease and Therapeutics

36.Holick, M.F.The vitamin D deficiency pandemic: approaches for diagnosis, treatment and preventionrevEndocrMetabDisord. 2017; 18:153-165

37.Pludowski, P. · Holick, M.F. · Grant, W.B. ...Vitamin D supplementation guidelinesJ Steroid Biochem Mol Biol. 2018; 175:125- 135

38.van Driel M, van Leeuwen JPTM. Vitamin D and bone: a story of endocrine and auto/paracrine action in osteoblasts. Nutrients. Switzerland. 2023;15:480.

39.Amling M, Priemel M, Holzmann T, Chapin K, Rueger JM, Baron R, et al. Rescue of the skeletal phenotype of vitamin D receptor-ablated mice in the setting of normal mineral ion homeostasis: formal histomorphometric and biomechanical analyses. Endocrinology. United States. 1999;140:4982–4987. doi: 10.1210/endo.140.11.7110.

40.Dardenne O, Prud'homme J, Hacking SA, Glorieux FH, St-Arnaud R. Correction of the abnormal mineral ion homeostasis with a high-calcium, high-phosphorus, high-lactose diet rescues the PDDR phenotype of mice deficient for the 25-hydroxyvitamin D-1alpha-hydroxylase (CYP27B1). Bone. United States;2003;32 :332–40.

41.Panda DK, Miao D, Bolivar I, Li J, Huo R, Hendy GN, et al. Inactivation of the 25-hydroxyvitamin D 1alpha-hydroxylase and vitamin D receptor demonstrates independent and interdependent effects of calcium and vitamin D on skeletal and mineral homeostasis. J Biol Chem. United States. 2004;279:16754–16766.

42.Kalyani RR, Corriere M, Ferrucci L. Age-related and disease-related muscle loss: the effect of diabetes, obesity, and other diseases. Lancet Diabetes Endocrinol. 2014;2:819–829.

43.Bignotti B, Cadoni A, Martinoli C, Tagliafico A. Imaging of skeletal muscle in vitamin D deficiency. World J Radiol. 2014;6:119–124.

44. Scott D, Stuart AL, Kay D, Ebeling PR, Nicholson G, Sanders KM. Investigating the predictive ability of gait speed and quadriceps strength for incident falls in community-dwelling older women at high risk of fracture. Arch GerontolGeriatr. Netherlands. 2014;58:308–313.

45.Murad MH, Elamin KB, Abu Elnour NO, Elamin MB, Alkatib AA, Fatourechi MM, et al. Clinical review: the effect of vitamin D on falls: a systematic review and meta-analysis. J Clin Endocrinol Metab. United States. 2011;96:2997–3006.

46.Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, et al. Effect of vitamin D on falls: a meta-analysis. JAMA. United States. 2004;291:1999–2006.

47.Kärkkäinen MK, Tuppurainen M, Salovaara K, Sandini L, Rikkonen T, Sirola J, et al. Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65–71 years? A 3-year randomized population-based trial (OSTPRE-FPS) MaturitasIrel.2010;65:359–365.

48.Guo J-L, Tsai Y-Y, Liao J-Y, Tu H-M, Huang C-M. Interventions to reduce the number of falls among older adults with/without cognitive impairment: an exploratory meta-analysis. Int J Geriatr Psychiatry. England. 2014;29:661–669.

49.Glendenning P, Zhu K, Inderjeeth C, Howat P, Lewis JR, Prince RL. Effects of three-monthly oral 150,000 IU cholecalciferol supplementation on falls, mobility, and muscle strength in older postmenopausal women: a randomized controlled trial. J Bone Miner Res Off J Am Soc Bone Miner Res. United States. 2012;27:170–176.

50.Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. United States. 2010;303:1815–1822.

51.Yuan W, Pan W, Kong J, Zheng W, Szeto FL, Wong KE, et al. 1,25-Dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. J Biol Chem. United States. 2007;282:29821–29830.

52.Chen S, Sun Y, Agrawal DK. Vitamin D deficiency and essential hypertension. J Am Soc Hypertens. 2015;9:885–901.

53.hen S, Gemelga G, Yeghiazarians Y. Is vitamin D supplementation an effective treatment for hypertension? CurrHypertens Rep. United States. 2022.

54.Bernini G, Carrara D, Bacca A, Carli V, Virdis A, Rugani I, et al. Effect of acute and chronic vitamin D administration on systemic renin angiotensin system in essential hypertensives and controls. J Endocrinol Investig Italy. 2013;36:216–220. doi: 10.1007/BF03347275.

55.Forman JP, Scott JB, Ng K, Drake BF, Suarez EG, Hayden DL, et al. Effect of vitamin D supplementation on blood pressure in blacks. Hypertens (Dallas, Tex 1979) 2013;61:779–785.

56.Bricio-Barrios JAR, Palacios-Fonseca AJMS, Del Toro-Equihua M, Sanchez-Ramirez CA. Effect of calcitriol supplementation on blood pressure in older adults. J NutrGerontolGeriatr. United States. 2016;35:243–52.

57.Sheikh V, Mozaianimonfared A, Gharakhani M, Poorolajal J, Ph D. Effect of vitamin D supplementation versus placebo on essential hypertension in patients with vitamin D deficiency: a double-blind randomized clinical trial. J Clin Hypertens (Greenwich) 2020;22:1867–1873.

58.Witham MD, Ireland S, Houston JG, Gandy SJ, Waugh S, Macdonald TM, et al. Vitamin D therapy to reduce blood pressure and left ventricular hypertrophy in resistant hypertension: randomized, controlled trial. Hypertens (Dallas, Tex 1979). United States. 2014;63:706–712.

59.Wang J, Zhou JJ, Robertson GR, Lee VW. Vitamin D in vascular calcification: a double-edged sword? Nutrients. 2018;10:652.

60.Jorde R, Sneve M, Torjesen P, Figenschau Y. No improvement in cardiovascular risk factors in overweight and obese subjects after supplementation with vitamin D3 for 1 year. J Intern Med. England. 2010;267:462–472.

61.Carrara D, Bernini M, Bacca A, Rugani I, Duranti E, Virdis A, et al. Cholecalciferol administration blunts the systemic renin-angiotensin system in essential hypertensives with hypovitaminosis D. J Renin Angiotensin Aldosterone Syst. England. 2014;15:82–87.

62.Challoumas D, Stavrou A, Pericleous A, Dimitrakakis G. Effects of combined vitamin D–calcium supplements on the cardiovascular system: should we be cautious? Atherosclerosis Ireland. 2015;238:388–398. doi: 10.1016/j.atherosclerosis.2014.12.050.

63.Davies MR, Hruska KA. Pathophysiological mechanisms of vascular calcification in end-stage renal disease. Kidney Int. United States. 2001;60:472–479.

64.Carvalho LSF, Sposito AC. Vitamin D for the prevention of cardiovascular disease: are we ready for that? Atherosclerosis Ireland. 2015;241:729–740. doi: 10.1016/j.atherosclerosis.2015.06.034.

65.Wang J-H, Keisala T, Solakivi T, Minasyan A, Kalueff AV, Tuohimaa P. Serum cholesterol and expression of ApoAI, LXRbeta and SREBP2 in vitamin D receptor knock-out mice. J Steroid Biochem Mol Biol. England. 2009;113:222–226.

66.Christensen R, Lorenzen JK, Svith CR, Bartels EM, Melanson EL, Saris WH, et al. Effect of calcium from dairy and dietary supplements on faecal fat excretion: a meta-analysis of randomized controlled trials. Obes Rev Off J Int Assoc Study Obes. England. 2009;10:475–486.

67.Rook GA, Steele J, Fraher L, Barker S, Karmali R, O'Riordan J, et al. Vitamin D3, gamma interferon, and control of proliferation of Mycobacterium tuberculosis by human monocytes. Immunology. 1986;57:159–163.

68.Crowle AJ, Ross EJ, May MH. Inhibition by 1,25(OH)2-vitamin D3 of the multiplication of virulent tubercle bacilli in cultured human macrophages. Infect Immun. 1987;55:2945–2950.

69.Cao Y, Wang X, Liu P, Su Y, Yu H, Du J. Vitamin D and the risk of latent tuberculosis infection: a systematic review and meta-analysis. BMC Pulm Med. 2022;22:39.

70.Martineau AR, Honecker FU, Wilkinson RJ, Griffiths CJ. Vitamin D in the treatment of pulmonary tuberculosis. J Steroid Biochem Mol Biol. England. 2007;103:793–798.

71.Bilezikian JP, Bikle D, Hewison M, Lazaretti-Castro M, Formenti AM, Gupta A, et al. Mechanisms in endocrinology: vitamin D and COVID-19. Eur J Endocrinol. England. 2020;183:R133–R147.

72.Charoenngam N, Shirvani A, Holick MF. Vitamin D and its potential benefit for the COVID-19 pandemic. EndocrPract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol. 2021;27:484–493.

73.Takiishi T, Gysemans C, Bouillon R, Mathieu C. Vitamin D and diabetes. Endocrinol Metab Clin N Am. United States. 2010;39:419–446.

74.Cade C, Norman AW. Vitamin D3 improves impaired glucose tolerance and insulin secretion in the vitamin D-deficient rat in vivo. Endocrinology. United States. 1986;119:84–90.

75.Szymczak-Pajor I, Drzewoski J, Śliwińska A. The molecular mechanisms by which vitamin D prevents insulin resistance and associated disorders. Int J Mol Sci. Switzerland. 2020;21:6644.

76.Maestro B, Campión J, Dávila N, Calle C. Stimulation by 1,25-dihydroxyvitamin D3 of insulin receptor expression and insulin responsiveness for glucose transport in U-937 human promonocytic cells. Endocr J Jpn. 2000;47:383–391.

77.Faye PA, Poumeaud F, Miressi F, Lia AS, Demiot C, Magy L, et al. Focus on 1,25-dihydroxyvitamin D3 in the peripheral nervous system. Front Neurosci. Switzerland; 2019;13:348.

78.Tague SE, Smith PG. Vitamin D receptor and enzyme expression in dorsal root ganglia of adult female rats: modulation by ovarian hormones. J Chem Neuroanat. Netherlands. 2011;41:1–12.

79.Shehab D, Al-Jarallah K, Abdella N, Mojiminiyi OA, Al MH. Prospective evaluation of the effect of short-term oral vitamin d supplementation on peripheral neuropathy in type 2 diabetes mellitus. Med PrincPract Int J Kuwait Univ Heal Sci Cent. Switzerland. 2015;24:250–256.

80.Costa PLF, França MM, Katayama ML, Carneiro ET, Martin RM, Folgueira MAK, et al. Transcriptomic response to 1,25-dihydroxyvitamin D in human fibroblasts with or without a functional vitamin D receptor (VDR): novel target genes and insights into VDR basal transcriptional activity. Cells. 2019;8:318.

81.Dobak J, Grzybowski J, Liu FT, Landon B, Dobke M. 1,25-Dihydroxyvitamin D3 increases collagen production in dermal fibroblasts. J Dermatol Sci. Netherlands. 1994;8:18–24.

82.Gonzalez-Curiel I, Trujillo V, Montoya-Rosales A, Rincon K, Rivas-Calderon B, deHaro-Acosta J, et al. 1,25-dihydroxyvitamin D3 induces LL-37 and HBD-2

production in keratinocytes from diabetic foot ulcers promoting wound healing: an in vitro model. PLoS ONE. 2014;9:e111355.

83.Tian XQ, Chen TC, Holick MF. 1,25-dihydroxyvitamin D3: a novel agent for enhancing wound healing. J Cell Biochem. United States. 1995;59:53–56.

84.Trujillo V, Marín-Luevano P, González-Curiel I, Rodríguez-Carlos A, Ramírez-Reyes M, Layseca-Espinosa E, et al. Calcitriol promotes proangiogenic molecules in keratinocytes in a diabetic foot ulcer model. J Steroid Biochem Mol Biol. England. 2017;174:303–311.

85.Alam U, Petropoulos IN, Ponirakis G, Ferdousi M, Asghar O, Jeziorska M, et al. Vitamin D deficiency is associated with painful diabetic neuropathy. Diabetes Metab Res Rev. England. 2021;37:e3361.

86.Zubair M, Malik A, Meerza D, Ahmad J. 25-Hydroxyvitamin D [25(OH)D] levels and diabetic foot ulcer: is there any relationship? Diabetes MetabSyndr. Netherlands. 2013;7:148–153.

87.Tiwari S, Pratyush DD, Gupta SK, Singh SK. Vitamin D deficiency is associated with inflammatory cytokine concentrations in patients with diabetic foot infection. Br J Nutr. England. 2014;112:1938–1943.

88.Dai J, Jiang C, Chen H, Chai Y. Vitamin D and diabetic foot ulcer: a systematic review and meta-analysis. Nutr Diabetes. 2019;9:8.

89.Yammine K, Hayek F, Assi C. Is there an association between vitamin D and diabetic foot disease? A meta-analysis. Wound Repair Regener Off Publ Wound Heal Soc Eur Tissue Repair Soc. United States. 2020;28:90–6.

90.Razzaghi R, Pourbagheri H, Momen-Heravi M, Bahmani F, Shadi J, Soleimani Z, et al. The effects of vitamin D supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial. J Diabetes Complic. United States. 2017;31:766–772.

91.Halschou-Jensen PM, Sauer J, Bouchelouche P, Fabrin J, Brorson S, Ohrt-Nissen S. Improved healing of diabetic foot ulcers after high-dose vitamin D: a randomized double-blinded clinical trial. Int J Low Extrem Wounds. United States. 2021;15347346211020268.

92.Abe E, Miyaura C, Sakagami H, Takeda M, Konno K, Yamazaki T, et al. Differentiation of mouse myeloid leukemia cells induced by 1 alpha,25-dihydroxyvitamin D3. Proc Natl Acad Sci USA. 1981;78:4990–4994.

93.Deeb KK, Trump DL, Johnson CS. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. Nat Rev Cancer. England. 2007;7:684–700.

94.Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin D in reducing cancer risk and progression. Nat Rev Cancer. England. 2014;14:342–357.

95.Estébanez N, Gómez-Acebo I, Palazuelos C, Llorca J, Dierssen-Sotos T. Vitamin D exposure and risk of breast cancer: a meta-analysis. Sci Rep. 2018;8:9039.

96.Maalmi H, Walter V, Jansen L, Boakye D, Schöttker B, Hoffmeister M, et al. Association between blood 25-hydroxyvitamin D levels and survival in colorectal cancer patients: an updated systematic review and meta-analysis. Nutrients. 2018;10:896.

97.Song Z-Y, Yao Q, Zhuo Z, Ma Z, Chen G. Circulating vitamin D level and mortality in prostate cancer patients: a dose-response meta-analysis. Endocr Connect. 2018;7:R294–303.

98.Wang W, Li G, He X, Gao J, Wang R, Wang Y, et al. Serum 25-hydroxyvitamin D levels and prognosis in hematological malignancies: a systematic review and meta-analysis. Cell PhysiolBiochem Int J Exp Cell PhysiolBiochemPharmacol Germ. 2015;35:1999–2005.

99.Li S, Jin Y, Fu W, Cox AD, Lee D, Reddivari L. Intermittent antibiotic treatment accelerated the development of colitis in IL-10 knockout mice. Biomed Pharmacother France. 2022;146:112486.

100.Kühn R, Löhler J, Rennick D, Rajewsky K, Müller W. Interleukin-10-deficient mice develop chronic enterocolitis. Cell. United States. 1993;75:263–274.

101.Liu M, Yuan W, Park S. Association between IL-10 rs3024505 and susceptibility to inflammatory bowel disease: a systematic review and meta-analysis. Cytokine. England. 2022;149:155721.

102.Cantorna MT, Munsick C, Bemiss C, Mahon BD. 1,25-Dihydroxycholecalciferol prevents and ameliorates symptoms of experimental murine inflammatory bowel disease. J Nutr. United States. 2000;130:2648–2652.

103.Lim W-C, Hanauer SB, Li YC. Mechanisms of disease: vitamin D and inflammatory bowel disease. Nat Clin Pract Gastroenterol Hepatol. England. 2005;2:308–315.

104.Raftery T, Martineau AR, Greiller CL, Ghosh S, McNamara D, Bennett K, et al. Effects of vitamin D supplementation on intestinal permeability, cathelicidin and disease markers in Crohn's disease: results from a randomised double-blind placebo-controlled study. United Eur Gastroenterol J. 2015;3:294–302.

105.Zhao H, Zhang H, Wu H, Li H, Liu L, Guo J, et al. Protective role of 1,25(OH)2 vitamin D3 in the mucosal injury and epithelial barrier disruption in DSS-induced acute colitis in mice. BMC Gastroenterol. 2012;12:57.

106.Daniel D. Bikle, MD, PhD.Vitamin D: Production, Metabolism, and Mechanism of Action June 15, 2025.
107. Zayzafoon M. Calcium/calmodulin signaling controls osteoblast growth and differentiation. J Cell Biochem. (2006) 97:56–70.
108. Cheng Z, Liu Y, Ma M, Sun S, Ma Z, Wang Y, et al. Lansoprazole-induced osteoporosis via the IP3R- and SOCE-mediated calcium signaling pathways. Mol Med. (2022) 28:21.
109. Nie Z, Deng S, Zhang L, Chen S, Lu Q, Peng H. Crocin protects against dexamethasone−induced osteoblast apoptosis by inhibiting the ROS/Ca2+−mediated mitochondrial pathway. Mol Med Rep. (2019) 20:401–8.
110 Cai WJ, Chen Y, Shi LX, Cheng HR, Banda I, Ji YH, et al. AKT-GSK3β Signaling pathway regulates mitochondrial dysfunction-associated OPA1 cleavage contributing to osteoblast apoptosis: preventative effects of hydroxytyrosol. Oxid Med Cell Longev. (2019) 2019:4101738.
111. Liu W, Xu C, Ran D, Wang Y, Zhao H, Gu J, et al. CaMKII mediates cadmium induced apoptosis in rat primary osteoblasts through MAPK activation and endoplasmic reticulum stress. Toxicology. (2018) 406–407:70–80.
112. Li J, Liu C, Li Y, Zheng Q, Xu Y, Liu B, et al. TMCO1-mediated Ca(2+) leak underlies osteoblast functions via CaMKII signaling. Nat Commun. (2019) 10:1589.
113.Kuroda Y, Hisatsune C, Nakamura T, Matsuo K, Mikoshiba K. Osteoblasts induce Ca2+ oscillation-independent NFATc1 activation during osteoclastogenesis. Proc Natl Acad Sci U.S.A. (2008) 105:8643–8.

114.Zhang D, Lin L, Yang B, Meng Z, Zhang B. Knockdown of Tcirg1 inhibits large-osteoclast generation by down-regulating NFATc1 and IP3R2 expression. PLoS One. (2020) 15:e0237354.

115. Robinson LJ, Blair HC, Barnett JB, Zaidi M, Huang CL. Regulation of bone turnover by calcium-regulated calcium channels. Ann N Y Acad Sci. (2010) 1192:351–7.
116.Choi JUA, Kijas AW, Lauko J, Rowan AE. The mechanosensory role of osteocytes and implications for bone health and disease states. Front Cell Dev Biol. (2021) 9:770143.
117. Wittkowske C, Reilly GC, Lacroix D, Perrault CM. In vitro bone cell models: impact of fluid shear stress on bone formation. Front BioengBiotechnol. (2016) 4:87.

118.O. Guryev, R.A. Carvalho, S. Usanov, A. Gilep, R.W. Estabrook A pathway for the metabolism of vitamin D_3: unique hydroxylated metabolites formed during catalysis with cytochrome P450scc (CYP11A1) Proc. Natl. Acad. Sci. U. S. A., 100 (2003), pp. 14754-14759

119.A.T. Slominski, T.K. Kim, J.V. Hobrath, A.S.W. Oak, E.K.Y. Tang, E.W. Tieu, W. Li, R.C. Tuckey, A.M. JettenEndogenously produced nonclassical vitamin D hydroxy-metabolites act as "biased" agonists on VDR and inverse agonists on RORα and RORγJ. Steroid Biochem. Mol. Biol., 173 (2017), pp. 42-56.

120.A. Slominski, I. Semak, J. Zjawiony, J. Wortsman, W. Li, A. Szczesniewski, R. C. TuckeyThe cytochrome P450scc system opens an alternate pathway of vitamin D_3 metabolismFEBS J., 272 (2005), pp. 4080-4090

121.Plum LA, DeLuca HF. Vitamin D, disease and therapeutic opportunities. Nat Rev Drug Discov 2010; 9: 941–955.

122.Bikle DD, Adams J, Christakos S. Vitamin D: production, metabolism and clinical requirements//Rosen C. Primer on Metabolic Bone Diseases. Hoboken: John Wiley and Sons, 2013: 235–245.

123.Zhu J, DeLuca HF. Vitamin D 25-hydroxylase - four decades of searching, are we there yet? Arch BiochemBiophys 2012; 523: 30–36

124.Cheng JB, Motola DL, Mangelsdorf DJ et al. De-orphanization of cytochrome P450 2R1: a microsomal vitamin D 25-hydroxylase. J Biol Chem 2003; 278: 38084–38093.

125.Zhu JG, Ochalek JT, Kaufmann M et al. CYP2R1 is a major, but not exclusive, contributor to 25-hydroxyvitamin D production in vivo. Proc Natl Acad Sci USA 2013; 110: 15650–15655.

126.Chun RF, Peercy BE, Orwoll ES et al. Vitamin D and DBP: the free hormone hypothesis revisited. J Steroid Biochem Mol Biol 2014; 144: 132–137.

127.Nykjaer A, Dragun D, Walther D et al. An endocytic pathway essential for renal uptake and activation of the steroid 25-(OH) vitamin D3. Cell 1999; 96: 507–515.

128.Kitanaka S, Takeyama K, Murayama A et al. Inactivating mutations in the 25-hydroxyvitamin D3 1alpha-hydroxylase gene in patients with pseudovitamin D-deficiency rickets. N Engl J Med 1998; 338: 653–661.

129.Jones G, Prosser DE, Kaufmann M. 25-Hydroxyvitamin D-24-hydroxylase (CYP24A1): its important role in the degradation of vitamin D. Arch BiochemBiophys 2012; 523: 9–18.

130.Veldurthy V, Wei R, Campbell M et al. 25-Hydroxyvitamin D(3) 24-hydroxylase: a key regulator of 1,25(OH)(2)D(3) catabolism and calcium homeostasis. VitamHorm 2016; 100: 137–150.

131.St-Arnaud R, Arabian A, Travers R et al. Deficient mineralization of intramembranous bone in vitamin D-24-hydroxylase-ablated mice is due to elevated

1,25-dihydroxyvitamin D and not to the absence of 24,25-dihydroxyvitamin D. Endocrinology 2000; 141: 2658–2666.

132.Schlingmann KP, Kaufmann M, Weber S et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. N Engl J Med 2011; 365: 410–421.

133.Henry HL. Regulation of vitamin D metabolism. Best Pract Res Clin Endocrinol Metab 2011; 25: 531–541.

134.Brenza HL, DeLuca HF. Regulation of 25-hydroxyvitamin D3 1alpha-hydroxylase gene expression by parathyroid hormone and 1,25-dihydroxyvitamin D3. Arch BiochemBiophys 2000; 381: 143–152.

135.Hu MC, Shiizaki K, Kuro-o M et al. Fibroblast growth factor 23 and Klotho: physiology and pathophysiology of an endocrine network of mineral metabolism. Annu Rev Physiol 2013; 75: 503–533.

136.Pike JW, Meyer MB. Fundamentals of vitamin D hormone-regulated gene expression. J Steroid Biochem Mol Biol 2014; 144: 5–11.

137.Christakos S, Dhawan P, Verstuyf A et al. Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. Physiol Rev 2016; 96: 365–408.

138.Amling M, Priemel M, Holzmann T et al. Rescue of the skeletal phenotype of vitamin D receptor-ablated mice in the setting of normal mineral ion homeostasis: formal histomorphometric and biomechanical analyses. Endocrinology 1999; 140: 4982–4987.

139.Li YC, Amling M, Pirro AE et al. Normalization of mineral ion homeostasis by dietary means prevents hyperparathyroidism, rickets, and osteomalacia, but not alopecia in vitamin D receptor-ablated mice. Endocrinology 1998; 139: 4391–4396.

140.Christakos S. Recent advances in our understanding of 1,25-dihydroxyvitamin D(3) regulation of intestinal calcium absorption. Arch BiochemBiophys 2012; 523: 73–76.

141.Benn BS, Ajibade D, Porta A et al. Active intestinal calcium transport in the absence of transient receptor potential vanilloid type 6 and calbindin-D9k. Endocrinology 2008; 149: 3196–3205.

142.Lieben L, Benn BS, Ajibade D et al. Trpv6 mediates intestinal calcium absorption during calcium restriction and contributes to bone homeostasis. Bone 2010; 47: 301–308.

143.Cui M, Li Q, Johnson R et al. Villin promoter-mediated transgenic expression of transient receptor potential cation channel, subfamily V, member 6 (TRPV6) increases intestinal calcium absorption in wild-type and vitamin D receptor knockout mice. J Bone Miner Res 2012; 27: 2097–2107.

144.de Groot T, Bindels RJ, HoenderopJG. TRPV5: an ingeniously controlled calcium channel. Kidney Int 2008; 74: 1241–1246.

145.Ajibade D, Benn BS, Christakos S. Mechanism of action of 1.25 dihydroxyvitamin D3 in intestinal calcium absorption and renal calcium transport//Holick MF. Vitamin D: Physiology, Molecular, Biological and Clinical Applications. Totowa: Humana Press, 2010: 175–187.

146.Hoenderop JG, Dardenne O, Van Abel M et al. Modulation of renal Ca2+ transport protein genes by dietary Ca2+ and 1,25-dihydroxyvitamin D3 in 25-hydroxyvitamin D3-1alpha-hydroxylase knockout mice. FASEB J 2002; 16: 1398–1406.

147.Hoenderop JG, van Leeuwen JP, van der Eerden BC et al. Renal Ca2+ wasting, hyperabsorption, and reduced bone thickness in mice lacking TRPV5. J Clin Invest 2003; 112: 1906–1914.

148.Aparna p1,Muthathal s1,Baridalyne Nongkynrih1,Sanjeev Kumar Gupta1 Vitamin D deficiency in India,July 12,2018,IP:177.220.65.35

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149. Babu US, Calvo MS. Modern India and the Vitamin D dilemma: Evidence for the need of a national food fortification program. Mol Nutr Food Res 2010;54:1134-47.

150. Harinarayan CV, Ramalakshmi T, Prasad UV, Sudhakar D, Srinivasarao PV, Sarma KV, et al. High prevalence of low dietary calcium, high phytate consumption, and Vitamin D deficiency in healthy South Indians. Am J Clin Nut 2007;85:1062-7

151. Ajmani SN, Paul M, Chauhan P, Ajmani AK, Yadav N. Prevalence of Vitamin D deficiency in burka-clad pregnant women in a 450-bedded maternity hospital of Delhi. J ObstetGynaecol India 2016;66:67-71. 152. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Dietary Reference Intakes for Calcium and Vitamin D, 2011.

153.Palacios, C. & L. Gonzalez. 2014. Is vitamin D deficiency a major global public health problem? J. Steroid Biochem. Mol. Biol. 144: 138–145.

154.Hilger, J., A. Friedel, R. Herr, et al. 2014. A systematic review of vitamin D status in populations worldwide. Br. J. Nutr. 111: 23–45.

155.Saraf, R., S.M.B. Morton, C.A. Camargo, et al. 2015. Global summary of maternal and newborn vitamin D status—a systematic review. Matern. Child Nutr. 25: 1–22.

156.Cashman, K.D., T. Sheehy & C.M. O'Neill. 2018. Is vitamin D deficiency a public health concern for low middle income countries?: a systematic literature review. Eur. J. Nutr.

157.Munns, C.F., P.J. Simm, C.P. Rodda, et al. 2012. Incidence of vitamin D deficiency rickets among Australian children: an Australian Paediatric Surveillance Unit study. Med. J. Aust. 196: 466–468.

158.Aggarwal, V., A. Seth, R.K. Marwaha, et al. 2013. Management of nutritional rickets in Indian children: a randomized controlled trial. J. Trop. Pediatr. 59: 127–133.

159.Thacher, T.D., P.R. Fischer, J.M. Pettifor, et al. 1999. A comparison of calcium, vitamin D, or both for nutritional rickets in Nigerian children. N. Engl. J. Med. 341: 563–568.

160.Fischer, P.R., A. Rahman, J.P. Cimma, et al. 1999. Nutritional rickets without vitamin D deficiency in Bangladesh. J. Trop. Pediatr. 45: 291–293.