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A Review on Vitamin D

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Abstract: -

Vitamin D is a fat-soluble vitamin that plays a crucial role in maintaining bone health and regulating the immune system. It is obtained from exposure to sunlight and dietary sources, such as fatty fish, egg yolks, and fortified foods. Recent studies have suggested that vitamin D may also play a role in preventing a variety of chronic diseases, including certain cancers, cardiovascular diseases, and autoimmune disorders.

This review article will provide an overview of the current understanding of the physiological functions of vitamin D, the sources of vitamin D, and the effects of vitamin D deficiency. It will also summarize the evidence for the potential health benefits of vitamin D supplementation, as well as the controversies and limitations of the current research.

The article will cover the latest research on vitamin D and its role in bone health, immune function, and chronic disease prevention. It will examine the evidence for the optimal levels of vitamin D intake and the safety and efficacy of vitamin D supplementation.

Finally, the article will discuss the implications of the current research for clinical practice and public health recommendations, and identify areas where further research is needed to better understand the role of vitamin D in health and disease. Overall, this review article aims to provide a comprehensive and up-to-date overview of the current knowledge on vitamin D, its sources, functions, and potential health benefits, and to stimulate further research in this important area of nutrition and health.

Keywords: - Metabolism, Supplementation, Immunity, Sunlight, Deficiency

Introduction: -

Investigation of the effects of vitamin D and its metabolites and analogs has exploded in the past 10 yr, leading to substantial revisions in the understanding of both the mode of action of vitamin D and the extent of its role in the functioning of a still growing number of body tissues, systems, and organs. Vitamin D functions in the body through both an endocrine mechanism (regulation of calcium absorption) and an autocrine mechanism (facilitation of gene expression). The former acts through circulating calcitriol, whereas the latter, which accounts for more than 80% of the metabolic utilization of the vitamin each day, produces, uses, and degrades calcitriol exclusively intracellularly. In patients with end-stage kidney disease, the endocrine mechanism is effectively disabled; however, the autocrine mechanism can function normally so long as the patient has adequate serum levels of 25(OH) D, on which its function is dependent. For this reason, calcitriol and its analogs do not constitute adequate replacement in managing the vitamin D needs of such patients. [13]

Currently, there is no standard definition of optimal vitamin D status. The circulating 25(OH) D level needed to suppress maximally the serum parathyroid hormone (PTH) concentration has been proposed and used by several investigators. Recently, data have emerged that allow several other endpoints to be considered. This editorial will consider these possibilities and convey the current thinking of the authors on the question: What is the optimal level of serum 25(OH) D for the skeleton? It will also consider the amount of vitamin D3 needed to reach the optimal serum level of 25(OH) D. [12]

Vitamin D sources: -

Vitamin D may come from three potential sources: nutritional sources, UVB-dependent endogenous production and supplements. In humans, vitamin D is mainly synthesized in the skin after exposure to UVB whereas only a minor part is derived from dietary sources. Very few natural, non-fortified products such as fatty fish (salmon, mackerel, sardines, cod liver oil) or some types of mushrooms (Shiitake), especially if sundried, contain relevant amounts of one of the two major forms, cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2). Some countries like the United States and Canada fortify staple products such as dairy products with vitamin D. Thus, the individual vitamin D dietary intake is highly dependent on nutritional habits, and the country's fortification strategy. However, a review with a global perspective

found that 6 to 47% of vitamin D intake may come from dietary supplements. Consequently, without supplementation, vitamin D status strongly depends on endogenous vitamin D production which is also influenced by genetic determinants, latitude, season, skin pigmentation, and lifestyles such as the use of sunscreen and clothing[26] Vit D 2 is plant-derived, produced exogenously by irradiation of ergosterol, and enters the circulation through diet.16 Vit D 3, like vit D 2, is available from foods (eg, Vit D 3 is found in cod liver oil) and vit supplements, and can enter the circulation through gastrointestinal (GI) absorption. Studies have shown that dietary supplementation with vit D 2 is effective in preventing vit D deficiency, although others have found that vit D 3 is more efficacious than vit D 2 in increasing serum 25-OH vit D levels, possibly because of a greater affinity for the serum vit D binding protein.[28] Whether this difference is biologically significant is unknown, as Rapuri et al, 16 in 2004, found no significant difference in serum 25-OH vit D levels between elderly women who self-reported taking a daily vit D 2 -versus D 3 -containing supplement. In addition, the vit D 2-supplemented but not the vit D 3 -supplemented group had wintertime total serum 25-OH vit D levels significantly greater than the unsupplemented group. Importantly, these studies used dietary vit D 3, obviating the need for sun exposure to obtain this vit D precursor metabolite. [17]

Table 1. Vitamin D3 and D2 sources and content

Source		Typical Vitamin D content
Natural source	Salmon, fresh, wild (3.5 oz)	600-1000 IU of vitamin D3
	Salmon, fresh, farmed (3.5 oz)	100-250 IU of vitamin D3 or D2
	Salmon, canned (3.5 oz)	300-600 IU of vitamin D3
	Sardines, canned (3.5 oz)	300 IU of vitamin D3
	Mackerel, canned (3.5 oz)	250 IU of vitamin D3
	Tuna, canned (3.6 oz)	230 IU of vitamin D3
	Cod liver oil (1 tsp)	400-1000 IU of vitamin D3
	Shiitake mushrooms, fresh (3.5 oz)	100 IU of vitamin D2
	Shiitake mushroom, sun-dried (3.5 oz)	1600 IU of vitamin D2
	Egg yolk	20 IU of vitamin D3 or D2
	Exposure to sunlight, UVB (0.5 MED[†])	3000 IU of vitamin D3
Fortified foods	Fortified butter	50 IU/3.5 oz, usually vitamin D3
	Fortified milk	100 IU/8 oz, usually vitamin D3
	Fortified orange juice	100 IU/8 oz, vitamin D3
	Fortified yogurts	100 IU/8 oz, usually vitamin D3
	Infant formulas	100 IU/8 oz, vitamin D3
	Fortified margarine	430 IU/3.5 oz, usually vitamin D3
	Fortified cheeses	100 IU/3 oz, usually vitamin D3
	Fortified breakfast cereals	100 IU/serving, usually vitamin D3

Metabolism and bioactivity of vitamin D: -

Vitamin D is unique because it can be made in the skin from exposure to sunlight. Vitamin D exists in two forms. Vitamin D2 is obtained from the UV irradiation of the yeast sterol ergosterol and is found naturally in sun-exposed mushrooms. UVB light from the sun strikes the skin, and humans synthesize vitamin D3, so it is the most "natural" form. Human beings do not make vitamin D2, and most oil-rich fish such as salmon, mackerel, and herring contain vitamin D3. Vitamin D 3 (cholecalciferol) is taken in the diet (from fortified dairy products and fish oils) or is synthesized in the skin from 7 dehydrocholesterol by ultraviolet irradiation. The vitamin D produced by 7 dehydrocholesterol depends on the intensity of UV irradiation, which varies with season and latitude. 1 Sunscreen and clothing have been reported to prevent the conversion of 7-dehydrocholesterol to vitamin D 3. [11]Vitamin D (D represents D2, or D3, or both) that is ingested is incorporated into chylomicrons, which are absorbed into the lymphatic system and enter the venous blood. Vitamin D that comes from the skin or diet is biologically inert and requires its first hydroxylation in the liver by the vitamin D-25-hydroxylase (25-OHase) to

25(OH)D.[27] However, 25(OH)D requires further hydroxylation in the kidneys by the 25(OH)D-1-OHase (CYP27B1) to form the biologically active form of vitamin D 1,25(OH)2D.[3,11] 1,25(OH)2D stimulates intestinal calcium absorption. Without vitamin D, only 10–15% of dietary calcium and about 60% of phosphorus are absorbed. Vitamin D sufficiency enhances calcium and phosphorus absorption by 30–40% and 80%, respectively Vitamin D is a fat-soluble vitamin Few foods naturally contain vitamin D (oily fish, such as sardines, herring, tuna, mackerel, salmon, and cod liver oil, egg yolks, shiitake mushrooms, liver or organ meats), so dermal synthesis after ultraviolet-B (UVB) radiation remains the major route to obtain vitamin D, accounting for 90% of vitamin D replenishment. Cholecalciferol (vitamin D3) is from animal sources and ergocalciferol (vitamin D2) is from plants. 6 Cholesterol-like precursor (7-dehydrocholesterol) in skin epidermal cells can be converted after UVB radiation (wavelength 290e315 nm) into pre-vitamin D, which also isomerizes to vitamin D3. Both vitamin D3 and D2 are biologically inactive. They need further enzymatic conversion to their active forms. First, it undergoes 25-hydroxylation in the liver to 25(OH)D (calcidiol), the major circulating form of vitamin D, with a half-life of 2e3 weeks. Then it is converted in kidneys through 1-alpha-hydroxylation to its most active form, 1, 25(OH) 2 D (calcitriol), with a half-life of 4e6 h[30]. This process is driven by parathyroid hormone (PTH) and other mediators, including hypophosphatemia and growth hormone. The 1-alpha-hydroxylation also takes place in non-renal sites, such as alveolar macrophages, osteoblasts, lymph nodes, placenta, colon, breasts, and keratinocytes, suggesting a possible autocrine-paracrine role of 1,25(OH)2 D. 7,8 It functions through a vitamin D receptor (VDR) that is universally expressed in nucleated cells. Its most important biological role is promoting enterocyte differentiation and intestinal calcium absorption, facilitating calcium homeostasis. At the time of hypocalcemia, the plasma level of ionized calcium falls and this is detected by parathyroid gland calcium receptors. PTH is secreted by the parathyroid gland, which stimulates 1-alpha-hydroxylation in kidneys to make more 1, 25(OH) 2 D from circulating 25(OH) D. The elevation of 1, 25(OH) 2D increases calcium transport within intestines, bones, and kidneys, and further regulates the osteoblast and osteoclast activity. As plasma calcium rises back to normal, further secretion of PTH decreases. This physiologic loop of vitamin D and calcium homeostasis demonstrates that sufficient circulating 25(OH)D is essential to maintain adequate 1,25(OH) 2 D synthesis and plasma calcium level [1]

Another important fact is that vitamin D is required throughout life. It not only is needed for the formation of bone but also likely plays an important role in several other physiologic systems.

Its use may well prevent several degenerative diseases, and it may also play a role as an anticancer agent.[5]

Keratinocytes are the only cells in the body containing the entire pathway. Most of the circulating 1, 25(OH) 2 D3 is produced by the kidney. However, the expression of CYP27B1 is higher in the keratinocyte than in any other cell including the cells of the proximal renal tubule. Presumably, the 1, 25(OH) 2D 3 produced in the skin is used for autocrine or paracrine purposes. Parathyroid hormone (PTH) exerts a modest stimulation of 1, 25(OH) 2D production by keratinocytes. However, this involves a different mechanism than that resulting in stimulation of 1, 25(OH) 2D 3 production by PTH in the kidney. The keratinocyte does not have a classic PTH receptor coupled to adenylate cyclase.

Furthermore, these effects of PTH are not reproduced by cAMP or its membrane-permeable derivatives, suggesting that the actions of PTH may be operating through a mechanism independent of cAMP the effects of PTH are maximal after 4-h incubation of cells with these agents before adding substrate (25OHD3); that is, the effects are not immediate. In renal cells, PTH exerts a more acute stimulation of 1, 25(OH) 2 D3 production, and cAMP appears to play a second messenger role the mechanism by which PTH stimulates 1, 25(OH) 2 D3 production in the keratinocyte remains unclear. [8]

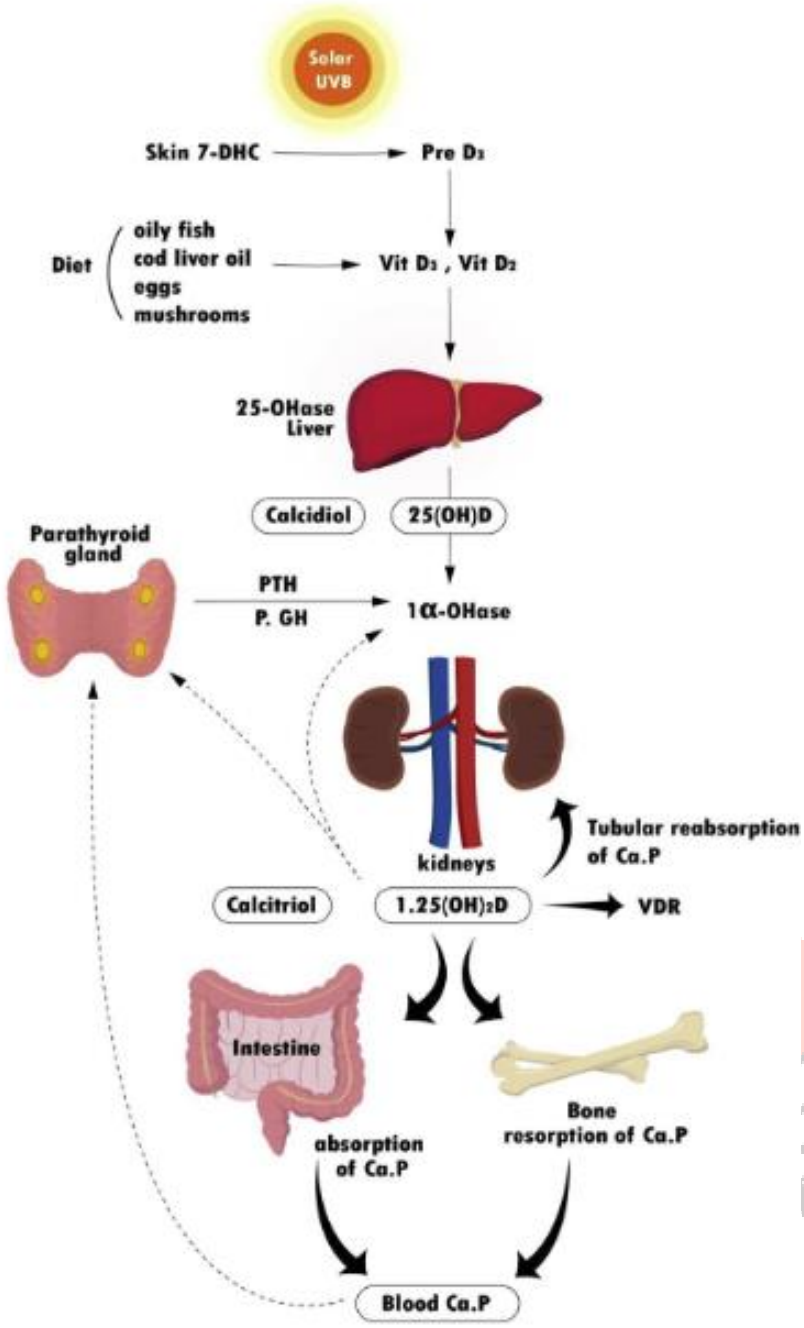

Figure 1 The metabolism and bioactivity of Vitamin D. Flow diagram of vitamin D's metabolism. Solid arrows demonstrate the direct effects of its products and dotted lines indicate the negative feedback of plasma calcium or 1, 25(OH) 2 D (Ca: calcium; 7-DHC: 7-dehydrocholesterol; GH: growth hormone; 1a-OHase: 1-alpha-hydroxylase; 25-OHase: 25-hydroxylase; P: phosphate, PTH: parathyroid hormone; VDR: vitamin D receptor; Vit: vitamin)

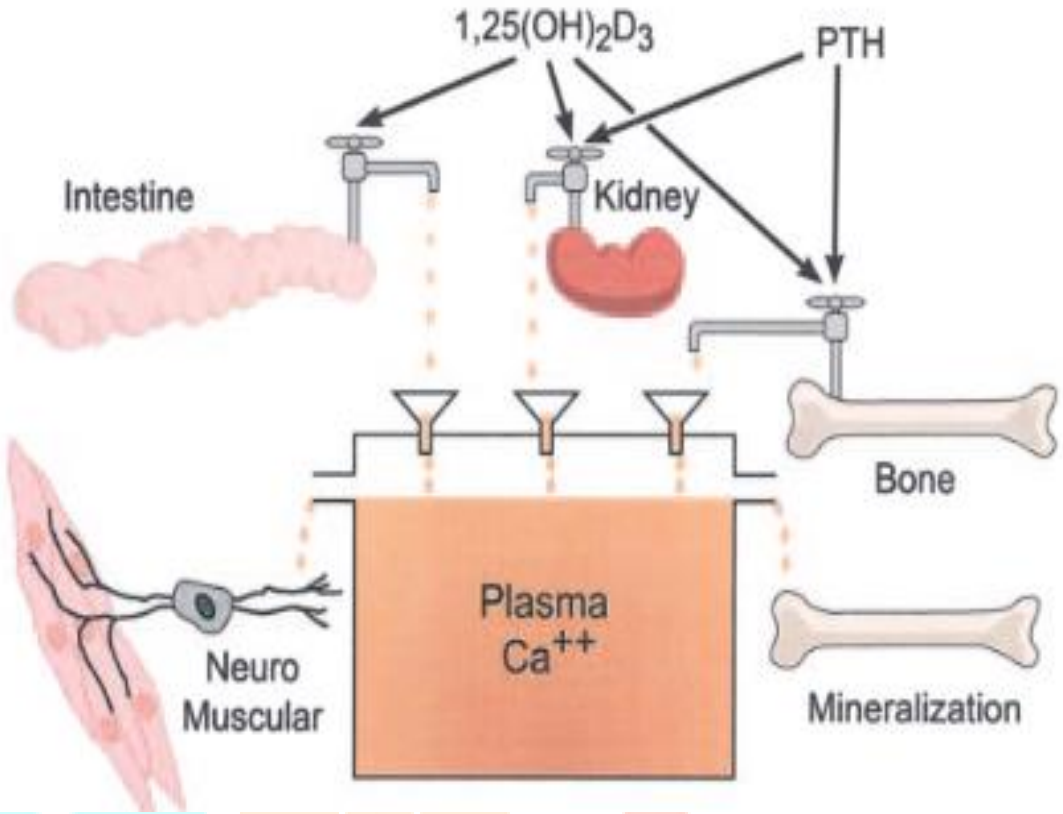

FIGURE 2. Diagrammatic representation of the role of the vitamin D hormone and the parathyroid hormone (PTH) in increasing plasma calcium concentrations to prevent hypocalcemic tetany (neuromuscular) and to provide for mineralization of the skeleton [5]

Vitamin D associations with disease Prevention:-

Rickets

With the re-emergence of widespread vitamin D deficiency and the re-emergence of rickets, the 19th-century plague was inevitable. A recent study found deficiency rates in countries where extreme sun exposure is readily available, but people are covered by or avoid sunlight and lack access to vitamin D-fortified foods. Breastfeeding mothers can, often unwittingly, lead to deficiency symptoms in their children.[36]It is suggested that a supplement level of 400IU/d for infants as practiced in Canada is optimal [18].

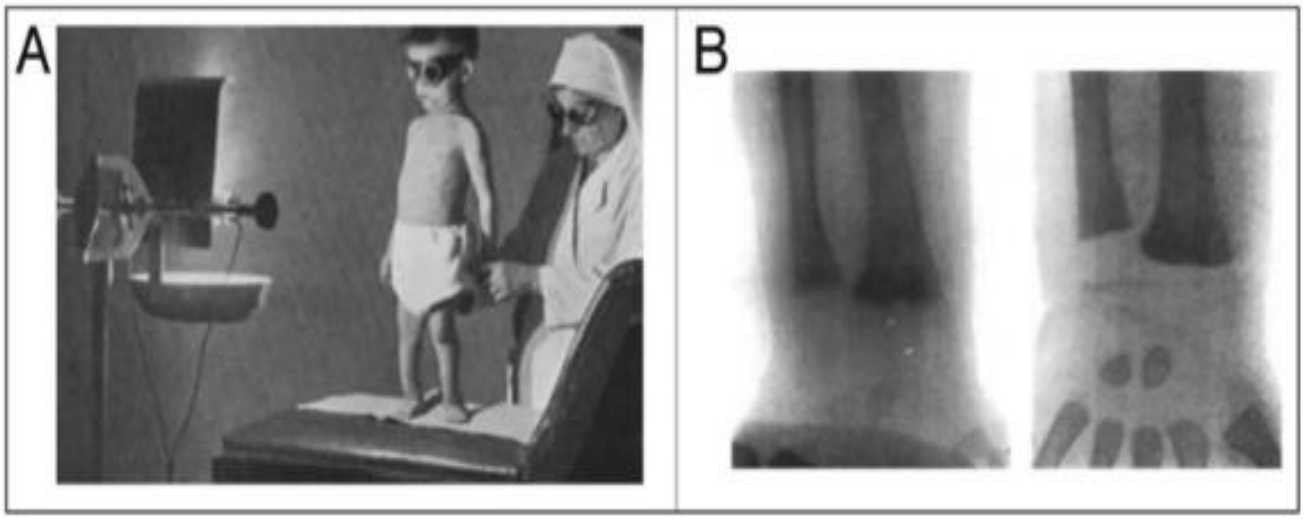

Figure 3. UV radiation therapy for rickets. (A) Photograph from the 1920s of a child with rickets being exposed to artificial UV radiation. (B) Radiographs demonstrating florid rickets of the hand and wrist (left). The same hand and wrist were taken after a course of treatment with 1-h UV radiation 2 times/week for 8 weeks showing mineralization of the carpal bones and epiphyseal plates (right). Holick, copyright 2006. Reproduced with permission. [10]

Cancer

The first study showing that sun exposure can reduce cancer risk was conducted almost seven decades ago [19]. Garland and Garland were the first to suggest that vitamin D deficiency may contribute to a higher risk of dying from colon cancer because vitamin D is made in the skin from the sun's UVB rays. The recent discovery of an increased risk of certain cancers in people with vitamin D deficiency suggests that vitamin D deficiency could be responsible or thousands of premature deaths from colon, breast, ovarian, and prostate cancer each year.[6]

Selected epidemiologic data suggest an inverse correlation between solar UVB exposure and mortality from several cancers, including colon, breast, and prostate, and between sun exposure and the incidence of colon cancer.39,75-82 These studies are observational in nature and, therefore, cannot establish that solar UVB exposure affects cancer incidence or mortality. Moreover, these data generally rely on correlating region-specific mortality with ambient UV radiation. Such studies may be confounded by geographic variations in population genetics or cultural or lifestyle behaviors and do not correlate disease with actual sun exposure at the individual level. In addition, as UV radiation is strongly correlated with latitude, both of these may be confounded by other factors that also vary with geographic location, such as, but not limited to, diet, pollution, or socioeconomic status of the population. Nevertheless, cutaneous vit D photosynthesis is proposed to account for these epidemiologic associations.O bese rational

cross-sectional or case-controlled epidemiologic studies have reported an inverse association between both serum 25-OH vit D levels and vit D intake and several epithelial-derived cancers. In addition, for some cultured human cancer cell lines, 1,25-(OH) 2 vit D has been reported to be antiproliferative, induce apoptosis, promote cell differentiation, inhibit telomerase expression, and suppress tumor-induced angiogenesis. In addition, some 1,25-(OH) 2 vit D analogs have also shown efficacy in vivo in animal models of chemical carcinogenesis.87 Of note, 1,25- (OH) 2 vit D levels generally need to be in the toxic range to show these in vitro and animal model in vivo effects [17]

Vitamin D: Its Role and Uses In Immunology

Until 1980, no one had imagined that vitamin D might play a role in the functioning of the immune system. The function of vitamin D was largely considered to be in the area of calcium, phosphorus, and bone metabolism. It prevents rickets in children, osteomalacia in adults, and hypocalcemic tetany. The major thrust of research until 1980 was to determine how vitamin D functions in these important processes of mineral metabolism regulation. In 1968, the idea appeared that vitamin D itself is biologically inactive and must be metabolically activated before it can function. This led to the isolation and chemical identification of the active forms of vitamin D in 1968 –1971 (3). Continued pursuit of the metabolism of vitamin D resulted in the understanding that vitamin D must first be hydroxylated in the liver to form 25-hydroxyvitamin D3 (25-OH-D3), the major circulating form of the vitamin. This form of vitamin D was subsequently found to be metabolically inactive and must be further converted to a final active form, 1a, 25-dihydroxy vitamin D3 (1,25-(OH)2 D3). This last step occurs predominantly if not exclusively in the proximal convoluted tubule cells of the kidney to produce the metabolically active form of vitamin D, 1,25-(OH)2D3. This major calcium mobilizing hormone then functions directly on the enterocyte of the small intestine to markedly increase the absorption of calcium and phosphorus from the lumen into the plasma compartment. It also plays a major role in the mobilization of calcium from the bone when the parathyroid hormone is present. Together with parathyroid hormone, it markedly improves the renal reabsorption of calcium in the distal tubule. These actions result in the elevation of plasma calcium and phosphorus levels to supersaturating conditions that are necessary to support the mineralization of the skeleton on the one hand and prevent hypocalcemic tetany on the other. The production of the vitamin D hormone is regulated by the need for calcium and phosphorus. Slightly low levels of plasma calcium will stimulate the parathyroid to produce and secrete the parathyroid hormone. This hormone binds to

osteoblasts of bone and the entire length of the nephron of the kidney. In the kidney, the parathyroid hormone stimulates the 1a-hydroxylase enzyme that produces the final vitamin D hormone. If calcium in plasma rises to very high levels, calcitonin is secreted from the c cells of the thyroid gland. This peptide hormone binds to the osteoblasts and osteoclasts to prevent the mobilization of calcium from bone; thus causing a reduction in plasma calcium levels. The exact details of this elegant endocrine system are reported elsewhere [15]

Vitamin D deficiency: Consequences

It is now recognized that vitamin D deficiency is one of the most common diseases in the world. It is estimated that more than 50% of children and adults living in the United States, Canada, Mexico, Europe, Asia, New Zealand, and Australia are vitamin D deficient and get enough calcium from their diet to meet their calcium needs of the body, leading to increased production of parathyroid hormone. 5 As a result, the child will not be able to achieve peak bone density, particularly during periods of rapid growth. Young to middle-aged adults begin to lose an average of 0.5% of their bone mass per year and can lose up to 5%to 10% of their bone mass over a period of 10 to 20 years, increasing the risk of osteoporosis and fractures.[29] After menopause, women begin to rapidly lose 3-5% of their bone mass due to the loss of estrogenic stimulation in the skeleton, and vitamin D deficiency exacerbates this loss and increases the risk of developing osteoporosis. earlier in life, putting him at greater risk for fractures. [20] The main source of vitamin D for children and adults is exposure to natural sunlight. Therefore, the main cause of vitamin D deficiency is insufficient sun exposure. Wearing sunscreen with an SPF of 30 reduces vitamin D synthesis in the skin by more than 95%. Dark-skinned people naturally have sun protection and need at least three to five times more sun exposure to produce the same amount of vitamin D as a white-skinned person. Vitamin D deficiency causes abnormalities in calcium, phosphorus, and bone metabolism. Vitamin D deficiency decreases the absorption of dietary calcium and phosphorus, leading to elevated PTH levels. The path-mediated increase in osteoclast activity creates local foci of bone weakness and causes a general decrease in bone mineral density (BMD), leading to osteopenia and osteoporosis. Improper calcium phosphate product causes defects in skeletalmineralization.In young children, whose skeleton is mineral deficient, this defect causes various skeletal deformities, classically called rickets. Vitamin D deficiency also causes muscle weakness; affected children have difficulty standing and walking, while older adults sway and fall more, increasing their risk of fractures [4]

There is increasing epidemiological evidence linking vitamin D deficiency and autoimmune diseases including multiple sclerosis (MS), rheumatoid arthritis (RA), diabetes mellitus (DM), inflammatory bowel disease, and systemic lupus erythematosus (SLE).Reports of low serum vitamin D predicting the development of autoimmune disease in the future have been published for MS, autoimmune DM, and RA. 21Y23 There also are data linking decreased in-utero exposure to vitamin D and islet cell autoimmunity.24 Lower in-utero exposure assessed by a lower maternal intake of vitamin D during pregnancy in women whose prospective child was at risk of developing autoimmune DM is associated with a statistically increased risk of the child developing pancreatic autoimmunity. Vitamin D also has been shown to facilitate the progression of existing autoimmune diseases. In 1 study, 161 patients with an early undifferentiated connective tissue disease were followed for a mean of more than 2 years. 25 Most patients did not progress and remained undifferentiated. Thirty-five patients (21%) went on to develop a defined rheumatologic diagnosis including RA, SLE, mixed connective tissue disease, and Sjogren disease, whereas 126 did not progress. Baseline characteristics of the 2 groups were similar. Importantly, the mean vitamin D level was significantly lower in the group that progressed to a definitive disease [7]

Vitamin D deficiency causes a mineralization defect in the adult's skeleton resulting in osteomalacia. The associated secondary hyperparathyroidism causes an increase in the mobilization of the matrix and mineral from the skeleton that can increase risk or precipitate osteoporosis. Osteomalacia is not only associated with mineralization defect of the skeleton, but is also associated with isolated or global bone pain, muscle weakness, and muscle pain which are symptoms that often go undiagnosed or misdiagnosed as some type of collagen vascular disease, such as fibromyalgia [21]

Vitamin D deficiency and insufficiency is widespread in the UK; the UK Scientific Advisory Committee on Nutrition recommends supplementation in the general population of 400 IU/day with no need for serum concentration testing [23]

Vitamin D Deficiency in India:-

The prevalence of vitamin D deficiency is reported worldwide, both in sun-poor countries and in countries with sufficient sun exposure. Despite this, it is the most commonly underdiagnosed and undertreated nutritional deficiency worldwide.11,12 However, various studies have found low levels of vitamin D regardless of age, gender and geographic location. Since there are no uniformguidelines for classifying vitamin D levels worldwide, these studies had different

deficiency thresholds. The vast majority of these studiesused serum 25(OH)D levels < 20 ng/mL as vitamin D deficiency.Studies thathave used other cutoffs haveas indicated in the notes. Studies of the Indian community conducted over the past decade using apparently healthy controls have reported prevalence rates ranging from 50% to 94%, with the exception of one study which reported a prevalence of 34.5%, possibly reflecting the low threshold. These studies, which looked at different age groups, reflect the magnitude of the problem. The strong participation was visible throughout the provincecountries [35]

Vitamin D Supplementation

Calcium and vitamin D supplementation did not increase the risk of myocardial infarction, death from coronary artery disease, stroke, coronary artery revascularization, hospitalized angina, congestive heart failure, or transient ischemic stroke. Therefore, women who take these supplements do not haveto worry about adverse cardiovascular consequences while protecting their bone health. [24] The current AI for vitamin D in pregnancy in Canada and the United States remains 5 μg (200 IU)/day,21 despite findings of vitamin D deficiency in pregnancy instudies.[33] A recent Cochrane review of vitamin D supplementation during pregnancy168 identified seven studies, four of which reported clinical outcomes. Due to the small number of studies performed, their small size, problems of adherence, and the poor quality of evidence due to the lack of randomized placebo-controlled trials, there was insufficient evidence to assess the effects of vitamin D supplementation during pregnancy. However, the available data support the need for an upward revision of vitamin D intake recommendations for pregnant women [25].

Vitamin D and Chronic Disease

Some of the chronic diseases in which vitamin D deficiency plays a role, based on epidemiological studies or randomized controlled trials of vitamin D interventions vitamin D deficiency with the risk or severity of the respective disease. Four plus means strong evidence including one or more randomized controlled trials; three plus strong and consistent epidemiological evidence but no evidence from randomized controlled trials; and one and two plus mean less solid but still suggestive evidence. For some items [34]

Osteoporosis

Osteoporosis is the most common metabolic bone disease worldwide. Low vitamin D levels are a recognized risk factor for osteoporosis. Insufficient serum vitamin D reduces active transcellular uptake of calcium.Although combined calcium and vitamin D supplementation is associated with higher bone mineral density and a lower incidence of, the evidence for vitamin D supplementation alone is less conclusive. A recent summary of the evidence showed that vitamin D supplementation of more than 700 IU per day (plus calcium) prevented bone loss compared to placebo [3]. The role of vitamin D in the pathogenesis and progression of osteoporosis includes both its canonical and autocrine functions. Vitamin effect for the canonical function of facilitating calcium absorption, it is difficult, and probably not, to separate the respective roles of calcium and vitamin definitely relevant. It's simply because you can't get enough calcium from a sensible diet unless you have reasonably normal vitamin D levels, and at the same time, regardless of your vitamin D levels, you can't get enough calcium if calcium intake alone is absolutely low. Because they are two nutrients, it is not surprising that most clinical studies showing calcium supplementation to prevent fractures also included vitamin D treatment.All of these studies have shown protection against age-related bone loss and in many cases have shown a reduction in bone fractures. Risk. When thenumber of fractures was reduced, the induced serum 25(OH)D levels exceeded 75-80 nmol/L, and doses that did not reach these serum levels generally did not reduce the number of fractures [13].

Respiratory tract infections

A prospective study of Camargo showed an inverse relationship between cord blood 25(OH)D levels and the risk of developing respiratory tract infections at over 3 months of age and wheezing at 3 months of age. 27 infants born with 25(OH)D < 20 > 30 ng/mL. 28 A recent 2017 meta-analysis of 25 studiesshowed a reduction in the incidence of acute respiratory infections after vitamin D supplementation (OR 0.88, 95% CI 0.81e0.96), which is greater in patients with severe vitamin D deficiency (< 10 ng/mL). [1] At the beginning of the century, children with Ricketswas more likely to develop upper respiratory infections and die. Macrophages have a VDR and when they ingest an infectious agent such as Mycobacterium tuberculosis, Toll-like receptors are activated, resulting in signal transduction to increase expression of VDR and CYP27B1. The 25(OH)D is in turn converted to 1,25(OH)2D, which signals the nucleus to multiplyExpression of cathelicidin, a defensin protein that kills infectious agents such as Mycobacterium tuberculosis.Cord blood 25(OH)D levels have been associated with tolerogenic

immune regulation and reduced respiratory infection in newborns.184 Furthermore, high levels of 25(OH)D during pregnancy have been associated with an almost50% reduction in wheezing in infants compared to low levels of 25(OH)D inthe mother. Neonates with 25(OH)D levels below 10 ng/mL were twice as likely to develop respiratory infections as those with levels at least 30 ng/mL,and reduced 25(OH)D for every 4 ng/mL increase in cord blood the cumulative risk of wheezing up to 5 years of age.184 Serum concentrations of 25(OH)D in 198 healthy adultsshowed that concentrations of 38 ng/mL or higher increased the risk of acute viral respiratory infections and the number of sick days by a factor of 2. 185 Japanese children who received 1200 IU/day vitamin D from December to March had a 42% reduced risk of influenza A compared to those who received placebo Children taking D had a 93% relative reduction in the risk of an asthma attack compared to children not taking it Vitamin D Supplement

Asthma

Maternal vitamin D intake during pregnancy may be associated with a risk of wheezing in the baby later. In a cross-sectional study, 25(OH)D levels were observed between people with asthma and healthy people. Vitamin D concentration was shown to directly correlate with the ratio of forced exploratory volume to forced vital capacity (FEV1/FVC) and predicted FEV1, meaning that lower (OH)D levels were more significantly associated with asthma. A 2016 Cochrane systematic reviewdocumented that vitamin D supplementation was helpful in reducing the risk of an exacerbation requiring systemic glucocorticoids (RR 0.63, 95% CI 0.45-0.88) and risk of at least one exacerbation requiring an emergency department visit or hospitalization or both (OR 0.39, 95% CI 0.19-0.78).[1]

Hypertension and Cardiovascular Disease

the link between vitamin D levels and high blood pressure is particularly strong. Controlled studies and meta-analyses have shown a protective effect of high calcium intake in pregnancy-related hypertension and essential hypertension (40-44), while the risk of new onset hypertension is inversely proportional to previously measured serum 25(OH) levels. . Specifically, in a 4-year prospective study that included both a health worker health check and a nurse health check, Forman et al.reported a relative risk of hypertension of 3.18 for those with 25(OH)D levels of 15 ng/mL compared to those with 30 ng/mL.According to the Framingham Offspring study with a follow-up of 5.4 years, those with 25(OH)D levels of 15 ng/mL were 53% more likely to have a cardiovascular event than those above that level and those with 10 ng/mL/mL were 80% more likely. Finally, Giovanucci et al. [14], analyzing data from the follow-up study by healthcare

professionals, reported an almost 2.5-fold increased risk of myocardial infarction in people with 25(OH)D levels below 15 ng/mL compared to peopleover 30 ng/mL [13]

Diabetes Mellitus

Recent studies in animal models and humans have suggested that vitamin D may also play a role in the homeostasis of glucose metabolism and the development of type 1 and type 2 diabetes mellitus (DM). Epidemiologic data has long suggested a link between exposure to vitamin D early in life and the development of type 1 DM. Vitamin D3 receptors have strong immune-modulating effects. In some populations the development of type 1 DM is associated with polymorphisms in the vitamin D receptor gene. There is also some evidence that increased vitamin D intake by infants may reduce the risk of the development of type 1 DM. Vitamin D has recently been associated with several of the contributing factors known to be linked to the development of type 2 DM, including defects in pancreatic cell function, insulin sensitivity, and systemic inflammation. Several physiologic mechanisms have been proposed, including the effect of vitamin D on insulin secretion, the direct effect of calcium and vitamin D on insulin action, and the role of this hormone in cytokine regulation [3]

Vitamin D deficiency was linked to IGT and type 2 diabetes in humans many years ago. These observations were confirmed in animal models, which demonstrated that pancreatic insulin secretion is inhibited by vitamin D de- ficiency [29]. Several reports have ascribed an active role to vitamin D in the functional regulation of the endocrine pancreas, particularly the beta cells. Not only are receptors for 1,25(OH) 2D 3 found in beta cells [30], but the effector part of the vitamin D pathway is also present in the form of vitamin D-dependent calcium-binding protein, also known as calbindin-D 28k [31]. The expression of calbindin-D 28K has been shown to protect beta cells from cytokine-mediated cell death [32]

FUNCTIONS OF VITAMIN D UNRELATED TO CALCIUM:-

One of the most important findings after discovery of the receptor was that the receptor appeared not only in the target cells of enterocytes, osteoblasts, and distal renal tubule cells but also in parathyroid gland cells, skin keratinocytes, promyelocytes, lymphocytes, colon cells, pituitary gland cells, and ovarian cells. The expression of VDRs in these cells and not in skeletal muscle, heart muscle, and liver suggests that they must serve a function there. Although VDRs have been reported in liver, heart, and skeletal muscle, we and other groups failed to confirm those reports, with the use of specific monoclonal anti- bodies and other methods. This led to the investigation

and discovery of functions of vitamin D not previously appreciated, which takes the vitamin D system beyond bone. An important discovery was made by Suda et al (25), who demonstrated that the vitamin D hormone plays an important role in the terminal differentiation of promyelocytes to monocytes, which are precursors of the giant osteoclasts. Those authors also found that, when the cells differentiated into a functional cell line, growth ceased. This function did not involve calcium and phosphorus and was later shown to be fundamental to vitamin D-induced production of osteoclasts through the RANKL system [5]

Conclusion: -

In conclusion, research on vitamin D has demonstrated its crucial role in various physiological functions, including bone health, immune system regulation, and cardiovascular health. While the optimal vitamin D intake remains a topic of debate, evidence suggests that vitamin D deficiency is prevalent worldwide, especially in high latitudes, and in certain populations such as older adults and individuals with darker skin. Vitamin D supplementation may be necessary for individuals at risk of deficiency, although its benefits for reducing the risk of chronic diseases, including cancer, diabetes, and multiple sclerosis, require further investigation. Future research should aim to determine the optimal vitamin D levels for health outcomes, clarify the mechanisms underlying vitamin D actions, and evaluate the efficacy of vitamin D supplementation in preventing and treating various diseases

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