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Vitamin D Deficiency and Geroscience: Systemic Mechanisms Underlying Multi-Organ Aging of the Skin, Liver, Brain, and Kidney

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Abstract:
Vitamin D functions as a steroidal prohormone essential for calcium-phosphate balance and systemic cellular regulation. Increasing evidence reveals its integral role in the homeostasis of multiple organ systems, particularly the skin, kidneys, brain and liver as described here. Deficiency of vitamin D is now recognized as a multifaceted disorder arising from both intrinsic and extrinsic etiopathogenic factors. Cutaneous insufficiency in 7-dehydrocholesterol conversion due to aging, limited ultraviolet B exposure, or melanin pigmentation leads to reduced synthesis of cholecalciferol, causes of various dermatological diseases. A decline in collagen production as aging proceeds with few metabolism are discussed here. Hepatic dysfunction impairs 25-hydroxylation, while chronic renal disease compromises 1α-hydroxylase-mediated activation to calcitriol. The aging of organs are interdependent on each other as liver and brain discussed here. Furthermore, diminished vitamin D receptor (VDR) signaling and altered neurosteroid activity in the central nervous system are implicated in neuroinflammation, oxidative stress, and cognitive decline. The cumulative impact of these mechanisms contributes to metabolic derangements, immune dysregulation, and accelerated multi-organ aging. This review reveals the understanding of cross-talk between these organ systems and the underlying molecular pathways of vitamin D metabolism provides a foundation for novel therapeutic targets and precision-based interventions in chronic disease and geroscience.

Keywords: Calcitriol, Neurosteroid, Geroscience, Vitamin D receptor.

Introduction

Vitamin D is a key micronutrient known to prevent both intrinsic and extrinsic skin aging, as supported by chronological and epidemiological studies. The interaction between vitamin D status and the aging process has emerged as an important focus in geriatric medicine. Maintaining adequate vitamin D levels is essential for promoting healthy aging, whereas deficiency has been associated with an accelerated decline in physiological and cognitive functions.

Vitamin D is a fat-soluble secosteroid hormone with multiple functions across organ systems (Table 1) [1]. Several physiological changes associated with aging—such as reduced cutaneous synthesis, dietary insufficiency, and impaired metabolism—contribute to the high prevalence of vitamin D deficiency in older adults. The biological role of vitamin D extends beyond calcium and bone homeostasis. It regulates key cellular mechanisms, including oxidative stress responses, DNA repair, mitochondrial function, and

inflammatory pathways. Dysregulation of these processes contributes to the pathogenesis of age-related disorders such as osteoporosis, sarcopenia, cardiovascular disease, and cognitive decline. [2]

Aging is characterized by both genotypic and phenotypic alterations in gene expression. Phenotypic manifestations, such as skin thinning and loss of elasticity, reflect the underlying molecular changes occurring in cells and tissues. These cumulative alterations affect nearly all organs and cellular systems throughout the lifespan. This review discusses the pleiotropic role of vitamin D in the aging process and highlights evidence from current literature supporting its role in maintaining cellular homeostasis and delaying age-associated degeneration.

Organ System	Functions of Vitamin D	Clinical conditions
Skeletal System	Promotes calcium and phosphate absorption; maintains mineral homeostasis; supports bone formation and remodelling	Rickets (children); osteomalacia, and osteoporosis (adults)
Muscular System	Improves muscle strength, contraction, and coordination	Increased risk of falls in elderly; Muscle weakness, Myopathy
Immune System	Modulates innate and adaptive immunity; enhances antimicrobial peptides; regulates T and B cells	Increased susceptibility to infections; Autoimmune diseases (e.g., Multiple Sclerosis, Type 1 Diabetes, Rheumatoid Arthritis)
Nervous System	Supports neurodevelopment; aids neurotransmitter synthesis; provides neuroprotection	Depression, Cognitive decline, Alzheimer's disease, Schizophrenia
Cardiovascular System	Regulates blood pressure via renin–angiotensin system; improves endothelial function; reduces inflammation	Deficiency linked to hypertension and atherosclerosis; coronary artery disease
Endocrine / Metabolic	Influences insulin secretion and sensitivity; regulates parathyroid hormone (PTH)	Type 2 Diabetes Mellitus, Secondary Hyperparathyroidism
Cancer / Cell Regulation	Promotes cell differentiation; inhibits cell proliferation and angiogenesis; promotes apoptosis	Protective role in colon, breast, and prostate cancers thus deficiency may result in these cancers
Skin	Regulates keratinocyte growth and differentiation; aids wound healing; maintains barrier function	Topical analogs (calcipotriol) used in psoriasis treatment, delayed wound healing, increased risk of infections
Renal System	Converts 25(OH)D to active $1,25(OH)_2D$ form; regulates calcium reabsorption	Chronic Kidney Disease-related mineral bone disorder
Hepatic System	Site of Vitamin D 25-hydroxylation; involved in metabolic activation	Liver disease can impair Vitamin D activation
Respiratory System	Enhances immune defense in airway epithelium	Increased risk of respiratory infections, Asthma exacerbation

Reproductive System	Supports placental development and fetal skeletal growth, influences fertility	Pre-eclampsia, Infertility, Low birth weight, Neonatal rickets
Anti-inflammatory / Antioxidant	Suppresses pro-inflammatory cytokines; boosts anti-inflammatory pathways; reduces oxidative stress	Chronic inflammatory diseases, Accelerated aging, tissue damage

Table 1: Vitamin D's roles in the multi-organ system and its clinical conditions.

1. Role of Vitamin D in Ageing – Skin:

From birth until death, the active form of vitamin D plays a variety of roles in the aging of the skin. Depending on the expression of various proteins and the requirements of various cell types, the amount of vitamin D in blood, its availability through essential bodily fluids, and its receptor interaction result in downstream processes that can be both genomic and non-genomic.

The vitamin D receptor (VDR) is covered later in this session, it is broadly distributed throughout the human body. Reduced immune function results from a decrease in vitamin D levels or deficiencies. As a result, pathogenesis takes place and several bacteria can enter. Here, we go over a few reviews of the literature to support the ideas and data about vitamin D's effects on both healthy and aging skin.

1.1 A feature of Ageing - Progressive skin Atrophy:

As we all know, aging affects vitamin D production and metabolism. As we age, the skin's dermis and epidermis undergo structural, molecular, and cellular changes. Cellular changes brought on by aging include the dermo-epidermal junction flattening, a decrease in melanocyte formation, and a decline in skin immune cells such as Langerhans cells. [3, 4]

Skin aging is caused by both internal (genetics and the natural aging process) and external (sun exposure, smoking, alcohol, environmental contaminants, and stress) elements, figure 1. [5, 6] Cellular senescence linked to oxidative stress and programmed aging are the mechanisms underlying intrinsic factors. The imbalance between reactive oxygen species (ROS) and the ability of reactive products, such as superoxide anion species (O_2^-), hydroxyl radical ($^{\bullet}OH$), singlet oxygen ($^1O_2$), etc., to neutralize them is known as oxidative stress. High ROS levels are linked to mitochondrial damage, which results in the leakage of inner electrons, decreased growth factors, diminished defense against antioxidants, and diminished hormonal effects. While external factors of aging include thicker epidermis, deep wrinkles, laxity, dullness, roughness, mottled discolouration like livedo reticularis, blotchy, marbled skin, etc., and laxity, intrinsic elements of aging include fine wrinkles and thinning of the epidermis. [7,8, 9]

Through a variety of mechanisms involving numerous proteins, including TGF-beta, IL-4, IL-10, and others, vitamin D plays a part in preventing photoaging. It contributes to defense against oxidative stress, DNA damage, skin inflammation, and other organ damage. [10]

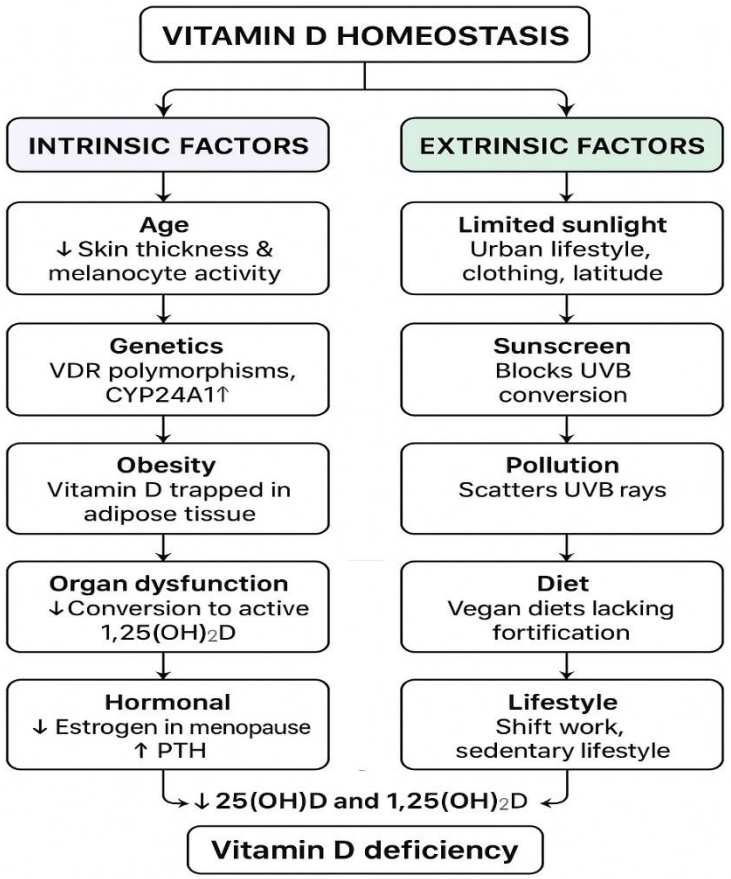

Figure 1: The systemic effects of aging on the liver, skin, kidneys, and brain are depicted in a schematic flow chart, emphasizing organ-specific structural and functional changes impacted by vitamin D insufficiency.

The precursor molecule (7-dehydrocholesterol) required to produce vitamin D from sunshine is less prevalent in the thinner skin of older people. Numerous studies have been conducted to support the claim that a 70-year-old may only create 25% of the vitamin D that a 20-year-old does with the same amount of sun exposure. Previous research has shown that vitamin D levels fall by more than 50% between the ages of 20 and 80 [11]. Compared to younger skin, isolated older skin generates 40% less vitamin D. [12, 13] Jenna R. Chalcraft et al. (Figure 2) [14] have demonstrated that older persons, particularly those who are weak, institutionalized, or have mobility challenges, frequently spend less time outside, which results in less sun exposure and a lower serum vitamin D level. As people age, their appetite frequently declines, and they may not eat enough foods that are fortified with vitamin D. [15]

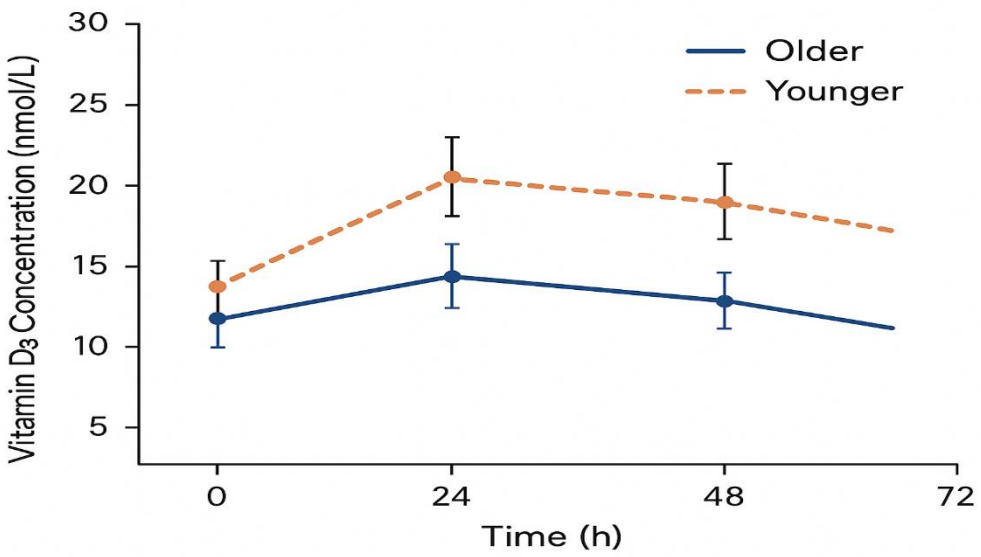

Figure 2: The relationship between blood vitamin D3 levels and sun exposure in older individuals (solid lines) and young adults (dotted lines) [5].

1.2 A feature of Ageing - dermatologic pathophysiology - etiology of skin diseases:

According to recent studies, vitamin D insufficiency causes psoriasis, rosacea, seborrhoeic dermatitis, atopic dermatitis, congenital ichthyosis, vitiligo, alopecia areata, atopic eczema, and hidradenitis suppurativa, among other cutaneous illnesses. As a result, vitamin D supplements are administered to treat a variety of skin conditions as people age. Skin conditions have been treated using vitamin D derivatives such as calcitriol, tacalcitol, calcipotriol, maxacalcitol, and hexafluoro-1, 25 (OH)2D.

Vitamin D analogs are used to treat a number of dermatological conditions, including epidermolytic acanthoma, clear cell acanthoma, circumscribed plantar hypokeratosis, dystrophic epidermolysis bulllosa (DEB), Sorafenib-associated hand-foot syndrome, linear atrophoderma of moulin, and warts that are treated with topical calcipotriol. Similarly, other dermatoses like axillary granular parakeratosis with osmidrosis, bullous congenital ichthyosiform erythroderma (BCIE) treated with topical maxacalcitol, recessive dystrophic epidermolysis bullosa (RDEB) treated with vitamin D3 supplementation, etc. [16] According to these findings, vitamin D is crucial for maintaining healthy skin throughout life.

1.3 Vitamin D: Collagen Production:

Vitamin D receptor (VDR) in collagen-producing cells, particularly fibroblast cells, which are present in the skin, tendons, ligaments, and bones of the body. It has been demonstrated that vitamin D metabolites, such as 1, 25- (OH)2D3-Calcitriol (an active metabolite) and 24, 25- (OH)2D3-Calcitriol secondary metabolite (an inactive metabolite), have an impact on collagen synthesis and the proliferation of growth zone and resting zone cartilage cells in vitro (Table 2). [17] Collagen plays a crucial role in aging, particularly skin elasticity, which falls under phenotypic expression and is controlled by our body's vitamin D levels. The dermal fibroblast cell produces more collagen type I and type III when stimulated with 1,25-(OH)2D3, which is independent of proliferation. [18]

A mechanism of study using 1, 25 (OH)2 vitamin D3 that promotes human osteoblast cell differentiation to create collagen in bone. The human osteoblastic cell line MG-63 was used in the investigation, either with or without vitamin D3 and/or L-ascorbic acid 2-phosphate. Both vitamin D3 and L-ascorbic acid 2 phosphate enhanced type I collagen synthesis and alkaline phosphatase (ALP) activity, which are

indicators of early stage osteoblast development. Additionally, vitamin D3 raised the mRNA levels of Runx2 and osterix, transcription factors essential for osteoblast development, as well as differentiation markers such osteocalcin, bone, kidney, and liver type ALP, as well as COL1A1 (the gene encoding the alpha1 chain of type I collagen). These findings come from human bone marrow-derived mesenchymal stem cells (hBMSC) and normal human osteoblasts. [19] As a result, this experimental investigation has demonstrated the importance of vitamin D for young, healthy bone.

Another mechanism through TGF-β and other interleukins, vitamin D has an anti-inflammatory effect. The zinc-containing endopeptidases known as matrix metalloproteinases are secreted by fibroblasts and keratinocytes and work by breaking down extracellular matrix (ECM). Gelatin I and IV are broken down by several matrix metalloproteinases, including MMP 1, 8, 13, and 18; type IV collagen is broken down by MMP 9. The endopeptidase (MMP), which decreases with age, is inhibited by the tissue inhibitor metalloproteinase-1 (TIMP-1). [20] Applying vitamin D metabolites - 25 (OH)D, 1, 25 (OH)2D, can counteract the effects of IL-1 beta, which inhibits TIMP-1 and TIMB-2. [21] Calcitriol contributes to the inflammatory response brought on by UV damage by lowering the levels of cytokines including TNF, IL-1, IL-2 alpha, and interferon-gamma while raising IL-4 and IL-10, which have anti-inflammatory properties. [22] Wiseman demonstrated the anti-oxidant properties of vitamin D in liposomal lipid peroxidation more than 20 years ago. This is because its structure is identical to that of ergosterol and cholesterol. Via its cytosolic and nuclear receptors, vitamin D controls a number of genes that are essential to the antioxidant system, including glutathione peroxidase and superoxide dismutase. ROS indicators are reduced by vitamin D supplementation. [23]

Mechanism	Effect on Collagen	Outcome
Direct (VDR Activation)	Stimulates fibroblasts to produce more Type I collagen.	Increased collagen synthesis.
TGF-β Pathway	Enhances pro-collagen signalling pathways.	Increased collagen synthesis.
Anti-Inflammatory	Reduces cytokines that inhibit collagen production.	Creates a better environment for synthesis.
Reduces MMPs	Lowers levels of enzymes that break down collagen.	Preserves existing collagen structure.
Antioxidant	Protects collagen and fibroblasts from oxidative damage.	Prevents collagen degradation.

Table 2: The stimulation of different mechanism over collagen and its effects.

2. Ageing-Vitamin D – Renal mechanism:

As is well known, the kidneys are in charge of converting vitamin D into its active form, calcitriol. Even when intake is sufficient, age-related declines in kidney function might lower this conversion, resulting in a functional shortage. The kidneys create calcitriol, the active form of vitamin D that helps the body absorb calcium, from 25-hydroxyvitamin D3 (Calcidiol). The kidney's proximal convoluted tubule contains the enzyme 1 alpha hydroxylase, which is synthesized and closely regulated by parathyroid hormone (PTH), 1, 25 (OH)2D (self regulation/feedback regulation), and fibroblast growth factor 23 (FGF23). Other places, including the epithelial cells of the skin, lungs, prostate, endocrine glands, macrophages, breast, gut, dendritic cells, and T and B lymphocytes, also produce calcitriol to a lower degree. 1, 25(OH)2D and

FGF23 suppress CYP27B1, which produces the essential enzyme 1 alpha hydroxylase, whereas PTH increases its synthesis. Another important kidney enzyme called 24 hydroxylase maintains the level of active vitamin D by converting the active vitamin D (calcitriol) into the inactive form of calcitroic acid, which is a component of bile and is subsequently eliminated in the stool. Another vitamin D activation pathway has been discovered in keratinocytes, where CYP11A1 plays a crucial role in starting the local steroidogenesis that forms 20-hydroxyl vitamin D, which has some action similar to 1,25 (OH)2D. [24]
In the cytosol, calcidiol binds to the vitamin D receptor (VDR) and forms a complex with the retinoic acid receptor (RXR). [25] It then translocates to the nucleus, where it acts as a transcription factor by binding to vitamin D response elements in target genes such TRPV6, claudins, and calbindins. [26] These result in the creation of particular proteins that are essential for the absorption of calcium. According to the aforementioned process, as people age, their serum vitamin D levels decrease, which lowers their absorption of calcium. This effect is more pronounced in women than in men, particularly in postmenopausal women.

2.1 Vitamin D Receptor- A secondary bile acid and PTH:

It has been demonstrated that lithocholic acid (LCA), a secondary bile acid that acts as an agonist of VDR, enhances paracellular calcium/phosphate absorption with the aid of several proteins, particularly claudin. [27] As is already known, PTH affects calcium absorption independently of intestinal absorption by inducing the renal proximal tubule to synthesize vitamin D3. As people age, their intestines absorb less calcium, [28, 29] and the CYP24A1 gene produces more of the enzyme 25-hydroxyvitamin D3-24-hydroxylase, which breaks down and lowers the concentration of calcitriol. [30, 31] As a result, calcitriol-dependent proteins like TRPV6 and calbindin D9k will no longer be down-regulated, [32] and this must be taken into account in addition to the postmenopausal women's lower calcium absorption, [33] which is another factor besides estrogen decline.
The PTH hormone rises with age, which causes improper calcium absorption and vitamin D inadequacy despite dietary consumption. These diseases are common in older persons as a result of aging. Classical-25 (OH)D3 and non-classical-24,25(OH)2D3 and 25(OH)D3/24,25(OH)2D3—vitamin D metabolite ratio—are among the vitamin D metabolites (Table 3). PTH and vitamin D metabolites were found to be correlated in this cohort study, which was conducted between young and elderly people. PTH levels are elevated in older people even when their kidneys are functioning normally, and they may be resistant to the effects of vitamin D. In younger people, PTH levels are elevated only when their vitamin D levels are low. Compared to other vitamin D metabolites, the VMR can be regarded as a biomarker for vitamin D status.[34] Age-related increases in PTH levels and decreases in VDR, CYPB1, and CYP24A1 expression in the thyroid gland were seen in a study involving thyroidectomy for 70 individuals ranging in age from 10 to 70 years [35]. Therefore, frailty, osteoporosis, and sarcopenia are caused by increased PTH in older age. [36] According to another study in rodents, renal CYP24A1 increases with age, as previously mentioned. This suggests that the aging kidney's decreased ability to convert 25(OH)D3 to 1,25(OH)2D3 and the increased catabolism of 1,25(OH)2D3 by CYP24A1 further contributes to age-related bone loss and a decrease in calcium absorption.[37]

2.2 Vitamin D: Fibroblast growth factor 23:

Fibroblast growth factor 23 (FGF23) works in conjunction with the Klotho transmembrane protein to inhibit the essential kidney enzyme that produces the active form of vitamin D, hence lowering the synthesis of vitamin D. The human Klotho gene (KL), an aging suppressor gene, generates only the Klotho protein, which is essential for calcium and phosphate metabolism and protects against aging, particularly

vascular aging and chronic kidney disease. This protein is produced in the kidney's distal convoluted tubules (DCT) and the brain's choroid plexus cells, where it functions as a hormone. Its concentration decreases with age. [38, 39] It is essential for both neuroprotection and cognitive function in the brain.[40]
As a result, vitamin D levels are down here, and taking supplements of 1, 25 (OH)D (calcitriol-vitamin D) raises klotho protein and slows down aging and CKD problems. The true research gap is that while exogenous vitamin D supplementation increases Klotho protein through its binding site VDRE in the Klotho gene, endogenous FGF 23 has a negative connection with both vitamin D and Klotho protein. In this case, vitamin D concentration is important. Therefore, it is necessary to identify the unique relationship between endogenous and exogenous vitamin D in the regulation of klotho in aging. [41, 42, 43]

Vitamin D Metabolite	Common names and Functions
25-Hydroxyvitamin D (Site of Formation- Liver)	Calcidiol, 25(OH)D, Calcifediol, 25-Hydroxycholecalciferol Major circulating storage form; used to assess vitamin D status
1,25-Dihydroxyvitamin D (Site of Formation- Kidney)	**Calcitriol**, **1,25(OH)$_2$D**, **1,25-Dihydroxycholecalciferol** Active hormonal form; regulates calcium and phosphate balance
24,25-Dihydroxyvitamin D (Site of Formation- Kidney)	**24,25(OH)$_2$D**, **24,25-Dihydroxycholecalciferol** Involved in feedback regulation and bone metabolism

Table 3: Metabolites of vitamin D and their common names and purposes. Although the principal synthesis site is indicated, many metabolites can also be synthesized at other locations with lower concentrations

3. Ageing- vitamin D- Brain:

The blood-brain barrier can be crossed by both the hormonally active form of vitamin D, 1,25(OH)2D3, and its main circulatory form, 25(OH)D3. [44] Since there is evidence of its receptor in the cerebral structures, the micronutrient vitamin D exerts cognitive activities on those structures. [45] Vitamin D interacts with neurons and glial cells in different parts of the brain and exhibits pleomorphic effects by stimulating cellular processes and down-regulating gene expressions through vitamin D response elements, such as neurotropin expression-nerve growth factor, neurotropin 3, and glial-derived neurotropic factors, and further development of neural cells. [46]
As a result, as people age, their vitamin D levels decrease, which causes cognitive loss as well as mental and neurological disorders. As previously stated, vitamin D is essential for neurotropism, neuroprotection, neurotransmission, neuroplasticity, and cellular proliferation and differentiation. [47] Vitamin D has been linked to dementia or cognitive impairment as people age, according to research by Andy P. Dickens et al. According to a cohort research, 60% of older Italian adults had low vitamin D levels (less than 25 nmol/liter) compared to older adults with levels greater than 75 nmol/liter. [48] As this paper will demonstrate, there is a correlation between the aging of the liver and the aging of the brain.

3.1 Vitamin D- Brain- Disorders

As previously stated, vitamin D plays a critical role in both adult brain health and brain development through a number of important pathways. Neurons are shielded from harm by vitamin D's anti-inflammatory and antioxidant properties. This article explains a few brain disorders that are brought on by a variety of reasons, with vitamin D deficiency being one of the main contributing factors.

3.2 Vitamin D – Alzheimer disease:

Low serum vitamin D levels are associated with an increased risk of dementia and Alzheimer's disease, according to meta-analyses of the literature. [49] As people age, low vitamin D levels are more common in elderly persons. One of the primary causes is the widespread presence of both calcitriol and the enzyme 1 alpha hydroxylase, which transforms calcidiol into calcitriol. [50] Vitamin D has been shown to have numerous important roles, including clearing glial (amyloid plaques) and so reducing the cytotoxic and apoptotic effects of cortical neurons. [51]

The concentration of vitamin D has an inverse relationship with the incidence of ischemic stroke. [52] In addition to stroke, there is evidence in the Caucasian community that older adults with vitamin D levels below 50 nmol/liter have larger pressured lateral cerebral ventricles than adults in the same population with vitamin D levels above 50 nmol/liter who do not exhibit any clinical hydrocephalus. [53]

As a result, it has been established that vitamin D levels are crucial for a healthy brain since brain cell capacity decreases with age. Interleukin 34 (IL 34) is an immune-functioning protein whose gene expression is dependent on 1-alpha 25 (OH)2D3-active vitamin D, which binds to its receptor (VDR) and is subsequently downregulated. This cytokine, IL 34, contributes to the survival and upkeep of Langerhans cells and microglial cells by sending out neuroprotective signals. Consequently, vitamin D deprivation causes brain pathophysiology that results in AD. [54] Demyelination of neurons, including Helicobacter pyroli, is caused by vitamin D deficiency in certain clinical circumstances. [55] Here, the vitamin D receptor in oligodendrocytes contributes to the remyelination process, and there is experimental evidence that the administration of caprizole results in demyelination that can be reversed by vitamin D supplementation. [56, 57]

3.3 Vitamin D – Parkinson's disease:

Another neurodegenerative ailment that affects older folks is Parkinson's disease, which can range in severity from mild to severe. Here, there is insufficient dopamine for the brain's normal functions, which causes synuclein to build up. It is further distinguished by a deficit in the substantia nigra's pars compacta portion. [58] Chronic vitamin D insufficiency, which results in dopaminergic neuron death in the substantia nigra region, is one of the causes of Parkinson's disease. [59]

Exogenous vitamin D improves Parkinson's disease by stimulating matrix metalloproteinases, nerve growth factor, and the L-type voltage channel. [60] Since vitamin D3 plays a number of essential roles in immune function, neuroinflammation, cytokine release, nuclear and mitochondrial gene regulation, the manufacture of several proteins, including neurotransmitters, and the maintenance of brain plasticity. In addition to its genomic effects, vitamin D also controls non-genomic effects. A lack of vitamin D can result in mental illnesses like depression and schizophrenia because it plays a part in the gut flora and the production of the well-known hormone serotonin. [61]

4. Vitamin D – Ageing- Liver:

The secondary organ that is essential to the production of the active form of vitamin D is the liver, which contains hepatocytes. Here, the first step in vitamin D activation is catalyzed by the primary enzyme 25-hydroxylase, which forms 25-hydroxy vitamin D3 (25(OH)D3/calcifediol/calcidiol) from the substrate cholecalciferol, which was produced by the skin and travels via circulation binding with the vitamin D binding protein (DBP). Therefore, the liver is crucial for the production of calcidiol, which serves as a quantifiable biomarker for the body's level of vitamin D. [1] With a half-life of two to three weeks, at least 88% of calcidiol has been proven to be bounded with DBP. In contrast, the kidney's secondary phase in

producing calcitriol, the fully active form of vitamin D, has a four- eight hours half-life.[62] Because the VDR in the liver binds to vitamin D, it is essential for keeping the liver healthy. Because vitamin D has anti-fibrotic, proliferative, and inflammatory actions on the liver, the VDR can lessen chronic liver disorders when expressed in large quantities. [63]

The pleiotropic effects of several genes, which produce various genotypic and phenotypic traits, determine weight gain and decrease as aging progresses. One example is the relationship between obesity and aging, which affects vitamin D metabolism through the vitamin D receptor and results in a lower amount of 25(OH)D, particularly in adipose tissue and plasma. According to experiment data from various literature studies, aging caused vitamin D deficiency. This could be caused by a variety of factors, including decreased absorption of vitamin D, decreased synthesis of vitamin D, decreased protein that regulates vitamin D, increased protein (enzyme) that breaks down vitamin D, an enzyme that changes the active form of vitamin D into a less active or unusable form, etc. [64, 65]

4.1 Vitamin D: Mitochondrial protein:

Non-alcoholic fatty liver disease (NAFLD), now known as metabolic dysfunction-associated steatotic liver disease (MASLD), is caused by a deterioration in the liver's ability to metabolize vitamin D, which reduces the amount of active vitamin D. As people age, the enzymes CYP2R1 and CYP27a1, which control the synthesis of vitamin D (calcidiol), decrease. Additionally, important mitochondrial proteins like Mic60, which are essential for liver cell activity, may become less abundant as we age. The structure and operation of mitochondria depend on the mitochondrial contact site and cristae organizing system (MICOS) complex, which includes Mic60 (mitofilin). Vitamin D favorably regulates this Mic60 protein. Vitamin D levels in the blood are crucial for preserving mitochondrial activity. Because vitamin D binds to its receptor, the Mic60 gene is up-regulated, increasing its expression. Serum vitamin D levels decline with age, which is thought to be insufficient for the general metabolism of several cell types to maintain homeostasis. Triacylglycerides (TG) build up in the liver cells as a result of decreased Mic60 expression. Thus, there is proof that vitamin D therapy saved older people from age-related MASLD. [66] Another study by Feng Zhu et al. from China revealed that the progression of aging-related NAFLD/MASLD was reduced when VDR was knocked down in hepatocytes. [67]

4.2 Vitamin D- liver ageing: lipoprotein:

The aging liver's metabolism of cholesterol and lipoproteins is another major factor. Maintaining sufficient amounts of vitamin D seems to be a possible way to assist control lipoprotein levels and promote liver function as people age, particularly in preventing age-related fatty liver disease. Supplementing with vitamin D can help control lipid profiles, especially in those who are deficient, according to meta-analyses of randomized controlled trials (RCTs). Supplementation has been shown to raise HDL cholesterol and dramatically lower TG and TC levels. There has been less consistency in the impact on LDL cholesterol across all investigations. [68] The decreased expression of the LDL receptor causes the clearance of chylomicron remnants and an increase in fat accumulation. This is caused by age-related changes in elevated plasma triglyceride and cholesterol levels as well as impaired lipoprotein metabolism as a result of altered lipoprotein structure composition. For instance, adults have higher phospholipid concentrations than children, and adults have lower triacylglycerol concentrations. Bile can decrease by up to 37% in older people, depending on the size of the liver. Aged liver was also shown to have elevated VLDL, which is positively linked with aged liver phospholipids. Vascular thickening and ultimately atherosclerosis are the results of these disorders. [69, 70] As people age, the process by which HDL in various forms undergoes reverse cholesterol transport decreases.

A study conducted on rodents demonstrated that the high quantity of cholesterol 24-hydroxylase (CYP46A1) released reduced cholesterol by converting it to 24S-hydroxycholesterol, which is the form that can be expelled from the brain. The level of cholesterol in the liver has now grown. Therefore, if liver illness persists, it also causes brain aging. The brain and liver, which are both significant organs, are connected in terms of cholesterol homeostasis. [71] One of the metabolites of cholesterol, 27-hydroxycholesterol (oxysterol), is released at various locations, including the intestine, brain, vascular endothelium, blood, liver (primary site), macrophages, and more. [72] This metabolite can pass across the blood-brain barrier, and large concentrations can cause neurological problems. It preserves the equilibrium of cholesterol in the brain. Aging causes an increase in all of these. As people age, their levels of 27-hydroxycholesterol rise, which contributes to cellular alterations, affects cholesterol metabolism, modulates estrogen receptors, and accelerates cellular senescence. [73]

Since oxysterol is transformed into bile and eliminated for many purposes, it is utilized to remove cholesterol from several areas, including the endothelium. 27-hydroxy cholesterol speeds up cellular senescence, which affects fibroblast function and causes aging and age-related illnesses. [74] As the liver ages, its mitochondria deteriorate. This is caused by a decrease in mitochondrial biogenesis, mitophagy, ATP synthase activity, ROS buildup that damages nearby macromolecules, and impairment of most of the primary functions of mitochondria. [73] Because the liver produces the majority of essential macromolecules and circulates them through bodily fluids, the liver plays a crucial role in aging.

The cholesterol metabolite 27-hydroxycholesterol (27HC) can be reduced by vitamin D, most likely by inhibition of the enzyme CYP27A1. Studies have shown that vitamin D administration reduces 27HC concentrations in patients with breast cancer. Vitamin D appears to play a role in controlling the levels of 27HC, which can have both positive and negative effects. A vitamin D shortage may cause an increase in 27HC. [75] Likewise further research must be undergone to confirm that vitamin D and its metabolites have any regulation towards cholesterol 24-hydroxylase (CYP46A1).

4.3 Vitamin D liver etiopathogenesis:

For the immune system to function properly and maintain healthy organs, vitamin D levels are essential. VDR is present in the immune cells of the liver, including T lymphocytes, dendritic cells, macrophages (i.e., Kupffer cells), natural killer cells (NK), natural killer T cells (NKT), B cells, and hepatic stellate cells. [76] Kupffer cells, the fixed macrophage cell of the liver, have the highest concentration of VDR. In order to combat liver pathology, VDR binds with calcitriol, the active form of vitamin D, and activates both the innate and acquired immune systems. According to research on autoimmune disorders such rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, and type 1 diabetes, vitamin D administration corrected these aberrant situations. [77] It is evident from this meta-analysis that vitamin D promotes T cell differentiation, cytokine production, and immune system enhancement. [78] As a result, using vitamin D therapeutically lengthens the life of the corresponding organs. It is necessary to verify whether individuals receiving vitamin D orally, intravenously, or intradermally have any additional effects on non-targeted organ systems. Therefore, vitamin D is involved in the pathophysiology of autoimmune illnesses as well as the aging of specific organs.

Another study on the hepatitis virus found that calcitriol directly binds to the Hepatitis B virus's central promoter, reducing both the replication process and the synthesis of viral protein. HBV burden and vitamin D levels are adversely correlated (figure 2), particularly in CHB patients. [79] Vitamin D insufficiency is more common in cirrhotic patients than in non-cirrhotic patients, both in Hepatitis B and Hepatitis D viruses, which increases morbidity and mortality. [80]

According to research by Asako Murayama et al., the antiviral activity of one of the vitamin D metabolites, 25-hydroxyvitamin D3 (25(OH)D3), decreased another class of hepatitis virus C infection. Nine of the 14 vitamin D derivatives that were used in their mechanistic research were discovered to have anti-viral HCV effects. The most effective of the two derivatives is 25 (OH)D3; the other form, 1 alpha 25(OH)D3, has no antiviral properties. The specialized transport protein expression, apolipoprotein (particularly A1 and C3), which is involved in the HCV infectious cycle, was inhibited by the 25 (OH)D3 and other substances utilized in the experiment. [81]

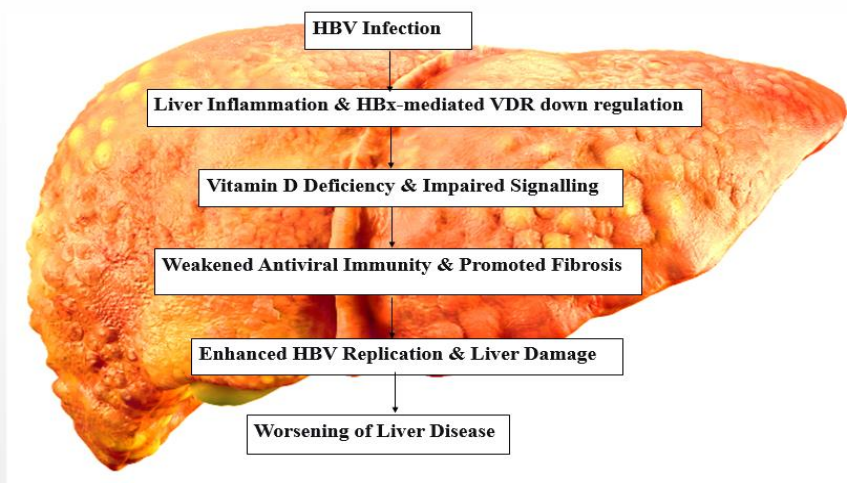

Figure 3: The picture illustrates the vicious loop that exists between the Hepatitis B virus and vitamin D.

A higher risk of non-alcoholic fatty liver disease (NAFLD) is also linked to low vitamin D levels. Evidence suggests that vitamin D deficiency is more common in NAFLD, particularly during the winter. Shiying LIU et al. studied 9782 people, both male and female, and found that mild to severe NAFLD conditions predominated in all categories without NAFLD. Regardless of gender, age, race, BMI, or diabetes, severe NAFLD patients had the highest and most prevalent rate of vitamin D insufficiency. [82]

In addition to cirrhosis and liver fibrosis, vitamin D levels are also linked to oxidative stress, glycemic index, inflammatory mediators, and liver enzyme levels. Vitamin D supplements can help treat NAFLD and other related conditions. [83] Together, these demonstrate once more how crucial an adequate amount of vitamin D is for a healthy liver and extending the life of liver cells, which delays aging. To manage or slow down the aging process from the inside out, the underlying reason must be precisely determined.

5. Review-Vitamin D: Vitamin D Receptor:

The nuclear receptor superfamily, which includes the vitamin D receptor (VDR), is essential to biological systems. In a ligand-dependent manner, the VDR increases the expression of many genes related to calcium homeostasis, cell division and proliferation, and immune system response. Numerous organs and non-organ systems include vitamin D receptors. The brain, immune system, lung, liver, pancreas, gut, bone, arteries, kidney, heart, skin, muscle, and parathyroid gland were all shown to contain VDR (figure 3).

Intestinal enterocytes, renal distal tubules (tubular epithelial cells), lung (bronchial epithelial cells), skin (epithelial cells), bone (osteoblasts and chondrocytes), immune system (T lymphocytes), parathyroid glands, pituitary gland (where it is co-localized with the pituitary hormones), spermatozoa, prostate gland, pancreatic beta cells, and mature muscle, including the liver. [84] Numerous brain areas, including the

cerebellum, thalamus, hypothalamus, posterior ganglia, hippocampus, olfactory system, and temporal and orbital regions of the brain, have been found to have vitamin D receptors [85].

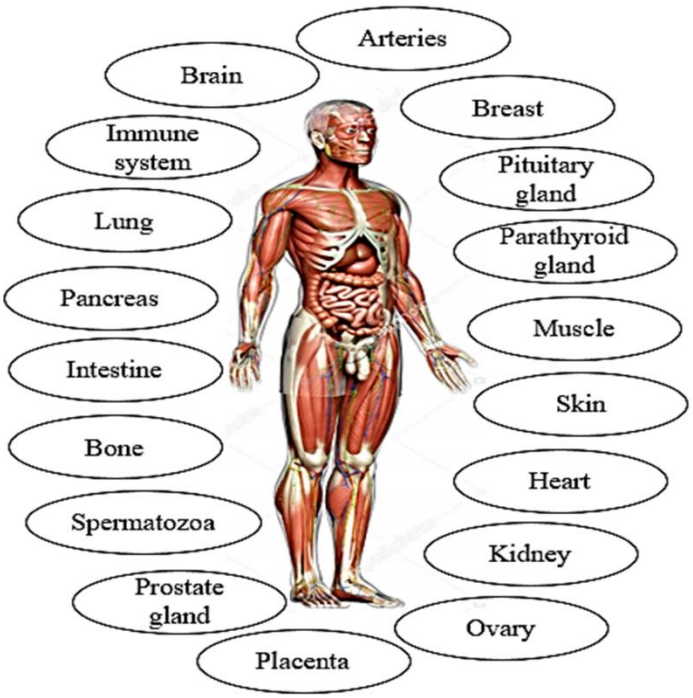

Figure 4: The expression of Vitamin D receptor in various tissues of the body.

The VDR in various cells is intended to either fully or partially correct the illness circumstances or to lessen them. The medications that are structural analogs of vitamin D metabolites are listed in table 4. It is evident from table 1a that vitamin D metabolites are essential for preserving the health of several organs. It is necessary to verify whether the aging process of specific organs is slowed down by employing these synthetic analogs of vitamin D metabolites, as well as how long it is sustained [86]. Since just vitamin D affects aging, the literature evaluation indicates that several critical macromolecules, minerals, and gasses are also important for healthy aging.

Therapeutic drugs	**Clinical conditions**
Vitamin D3 (calciferol) [87]	Vitamin D deficiency conditions such as Rickets, osteomalacia, osteoporosis, hypoparathyroidism.
Vitamin D2 (ergocalciferol) [87]	Vitamin D deficiency conditions such as Rickets, familial hypophosphatemia, secondary hypoparathyroidism, chronic kidney disease.
Calcidiol (25 (OH)D3) [87]	Rickets, chronic hypocalcemia, osteodystrophy
Calcitriol (1,25 (OH)2D3) [87]	Renal osteodystrophy, osteoporosis and psoriasis

Alphacalcidol (1α-hydroxyvitamin D)[88]	**Osteoporosis, Kidney disease, hypoparathyroidism.**
Calcipotriene (calcipotriol- 22-ene-26,27-dehydro-1 alpha, 25 (OH)2D3) [89,90]	A topical analog used to treat psoriasis.
Tacalcitol (1 alpha, 24 (R) (OH)2D3) [90]	Psoriasis
Maxacalcitol (22oxa-1 alpha, 25 (OH)2D3) [90, 91]	Secondary hyperparathyroidism in patients with CKD and psoriasis; declines the risk of hypercalcemia, unlike other vitamin D analogs
Doxercalciferol (1α-hydroxyvitamin D2) [92]	Secondary hyperparathyroidism in kidney disease. Reduces the risk of hypercalcemia and hyperphosphatemia
Paricalcitol (19-nor-1,25 dihydroxyvitamin D) [93, 94, 95,96]	Secondary hyperparathyroidism in kidney disease.Reduces the risk of hypercalcemia and hyperphosphatemia Anti-cancer activity – myeloid leukemia, myeloma, colon cancer cells Act as a Radiosensitizer, prostate cancer, breast cancer, pancreatic cancer
Eldecalcitol (2 beta- (3-hydrxypropoxy)- 1 alpha, 25 (OH)2D3)[97]	Osteoporosis (Japan only)
Falecalcitriol (26,27 F6-1 alpha, 25 (OH)2D3)[97]	Secondary hyperparathyroidism (Japan only)
Oxacalcitriol (22-oxa-1,25$(OH)_2D_3$)[97]	secondary hyperparathyroidism and psoriasis (in Japan)
Inecalcitol[99, 100]	Prostate cancer, Breast cancer, chronic myeloid leukaemia
Seocalcitol [100]	Under study in cancer conditions Such as breast, hepatocellular, pancreas.

Table 4: The structural analogue of Vitamin D metabolites used under medication purpose.

6. Conclusion:

A widespread component that speeds up aging-related changes in the liver, skin, kidneys, and brain is vitamin D insufficiency. Metabolic, immunological, and neurocognitive homeostasis are disrupted by its multifactorial etiopathogenesis, which includes diminished cutaneous synthesis, poor hepatic 25-hydroxylation, renal 1α-hydroxylation abnormalities, and altered vitamin D receptor signaling. Tissue atrophy, organ-specific senescence, and functional decline are all influenced by these disturbances.

The significance of preserving adequate vitamin D levels as a potential method to minimize multi-organ aging, retain physiological function, and lessen vulnerability to chronic age-associated illnesses is highlighted by evidence from mechanistic and clinical research. The aforementioned literature analysis makes it abundantly evident that an organ's ability to function and malfunction is always contingent on another organ's ability to function concurrently with the aging process.

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