Hypovitaminosis D: A modifiable Risk Factor for Noncommunicable Diseases

By

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A thesis submitted to the Department of Mathematics and Natural Sciences in partial fulfillment of the requirements for the degree of Master of Science in Biotechnology

Department of Mathematics and Natural Sciences

BRAC University

April 2022

Declaration

It is hereby declared that

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2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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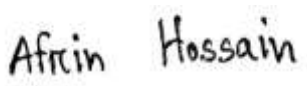

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Approval

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Ethics Statement

This material is an original work, which has not been previously published elsewhere. It is my own research and analysis in a truthful and complete manner. The paper properly credits all the sources used (correct citation).

Abstract

Over the years, a broad spectrum of non-communicable diseases (NCDs), including osteoporosis, asthma, diabetes, cancer, hypertension, cardiovascular diseases, chronic kidney and liver diseases have been linked to poor vitamin D levels. This review presents the circumstances leading to hypovitaminosis D and how such a deficiency can eventually independently induce the development of NCDs. PubMed and EMBASE databases were used to identify all studies that assessed the association between vitamin D and various NCDs up until February 2022, without language restrictions. Available evidence from observational studies suggests a strong link between vitamin D and many NCDs. However, underlying molecular mechanisms of vitamin D mode of action that contribute to the pathophysiology of these non-communicable diseases are often complex and not fully understood. Vitamin D and its biologically active analogs have shown therapeutic potential for treatment or prevention of some NCDs. However, large-scale vitamin D supplementation trials have yet to confirm such a causal relationship. Further studies are required to clearly establish and understand the nature of NCDs association with vitamin D.

This work is dedicated to

My Dear Family

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Finally, I would like to thank my family and for constants support, encouragement, patience and love.

Sincerely,

Afrin Hossain,

Department of Mathematics and Natural Sciences, BRAC University

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List of Acronyms

7-DHC – 7-Dehydrocholesterol

CKD – Chronic kidney disease

COPD – Chronic obstructive pulmonary disease

CVD – Cardiovascular disease

ECF – Extracellular fluid

HDL – High density lipoprotein

IBS – Irritable bowel syndrome

LDL – Low density lipoprotein

MI – Miocardial infarction

MS – Multiple sclerosis

NAFLD – Non-alcoholic fatty liver disease

NCD –Non-communicable disease

NO – Nitric oxide

PTH – Parathyroid hormone

RANK – Receptor Activator of Nuclear Factor Kappa-B

RAS – Renin-angiotensin system

ROS – Reactive oxygen species

RXR – Retinoid X receptor

SPF – Sun protection factor

VDR – Vitamin D receptor

UVB – Ultra-violet B rays

WHO – World Health Organization

Introduction

And

Literature Review

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1. Introduction

For most of history, life expectancy was cut short by famine, injury, and infectious diseases. Economic development and improvement in living conditions conquered these conditions, completely annihilating many major infectious diseases like smallpox. Socioeconomic progress, however, has created an environment that favors the development of non- infectious diseases. The chronic non-infectious diseases are referred to as noncommunicable diseases (NCDs). NCDs are named as such because they cannot be communicated from person to person. These conditions have a long-term health consequence, last for a long period of time and create a need for long-term treatment and care. Every year NCDs account for almost 71% of all worldwide deaths which corresponds to 41 million early deaths (World Health Organization, 2021). Cardiovascular diseases embody most of these deaths, followed by cancers, respiratory diseases, and diabetes. Preventive measures for NCDs focus on reducing the risk factors associated with these diseases. WHO listed 4 modifiable behavioral and metabolic risk factors for NCDs:

Behavioral Risk Factors-

- Tobacco use
- Physical inactivity
- Alcohol abuse
- Unhealthy diets

Metabolic Risk Factors-

- Hypertension
- Hyperglycemia
- Hyperlipidemia
- Obesity

In the last few decades, the listed risk factor awareness propelled change of existing policies and development of new policies that address both behavioral and metabolic risk factors. As the society experiences unparalleled progress and dramatic changes in lifestyle, it is important to identify emerging risk factors contributing to the growing number of NCDs.

Over the years, poor vitamin D level has been recognized as a risk factor for multiple non-communicable diseases. This thesis manuscript will review the circumstances leading to hypovitaminosis D and how such a deficiency can eventually independently induce the development of non-communicable diseases.

2. Methods

PubMed and EMBASE databases were used to identify all studies that assessed the association between vitamin D and various non-communicable diseases up until February 2022, without language restrictions. We included studies that compared vitamin D levels between NCD cases and controls and also those that used vitamin D supplementation to improve NCD status. Reference lists of relevant original papers and review articles were also examined.

3. Vitamin D

Vitamin D was first identified by McCollum *et al* in 1922 as the antirachitic element in cod liver oil. Being the fourth discovered vitamin, it was naturally assigned the fourth alphabet 'D'. Several forms of Vitamin D have been identified after its initial discovery. In 1930s two forms of vitamin D found in food and diet- Ergocalciferol and Cholecalciferol were identified. Structure of biologically active form of Vitamin D- calcifediol and calcitriol were elucidated respectively in the late 1960s and early 1970s (Holick, 1994).

List of several forms of vitamin D (vitamers) and their site of synthesis:

Generic Name	Other Names	Site of synthesis
Ergocalciferol	Vitamin D2	Photochemically synthesized in plants
Cholecalciferol	Vitamin D3	Synthesized in the skin of animals and humans
Calcifediol/ Calcidiol	25(OH)D	Liver
	$25(OH)D_3$	
	25-hydroxycholecalciferol	
	25-hydroxyvitamin D3	
Calcitriol	$1,25(OH)_2D$	Kidney (Primary) Lymphocytes, microglia, keratinocytes, etc
	$1,25(OH)_2D_3$	
	1,25-dihydroxycholecalciferol	
	1,25-dihydroxyvitamin D	
	Vitamin D Receptor Activator	

Table 3.1: Vitamers of vitamin D and their site of synthesis

All forms of vitamin D act in concert to ensure optimal health.

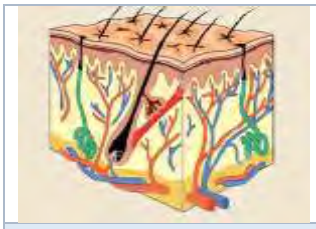		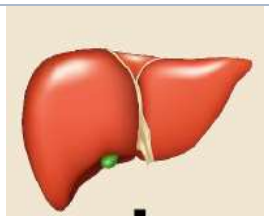	
Cholecalciferol		**Calcifediol**	**Calcitriol**
Cholecalciferol made in the skin is used by skin cells, which cannot rely on vitamin D from the blood	Taken directly into cells for local conversion and use	Form measured in the blood as indicator of vitamin D status	Hormonal vitamin D regulated by PTH for blood calcium control
Decrease DNA damage	Most potent form of endothelial stability	Taken directly into cells and converted to calcitriol for local use	Increases calcium absorption in gut
Decrease Cell death	Anti-inflammatory	Used as signaling molecule in most cells and tissues	Increases bone turnover
Increase DNA repair	Form needed by breastfeeding mothers to transfer to baby through breastmilk		Increases calcium in the blood

Table 3.2: Different forms of vitamin D and their functions

3.1 Biosynthesis of Vitamin D

For most of history sunlight exposure has been enough to cover our requirement of Vitamin D. Now-a-days vitamin D can be obtained through particular diet, fortified food and supplements, yet photosynthesis of Vitamin D under sunlight remains the primary source for most of the population.

7-dehydrocholesterol (7-DHC) is the prime precursor of the active form of vitamin D, calcitriol. Upon exposure to sunlight, high-energy UV photons (290-315nm) penetrate skin epidermis and cause photolysis of provitamin D_3 (7-dehydrocholesterol) to previtamin D_3. Within 2-3 days vitamin D_3 (calciferol or cholecalciferol) is spontaneously formed through a thermally induced isomerization of previtamin D_3 (Holick, 1987).

Cholecalciferol travels to the liver, and there, through the action of a hydroxylase enzyme it is converted to calcidiol. 1α-hydroxylase enzyme in the kidney subsequently converts calcidiol to calcitriol, the biologically active vitamin D. From the kidney calcitriol enters the circulation.

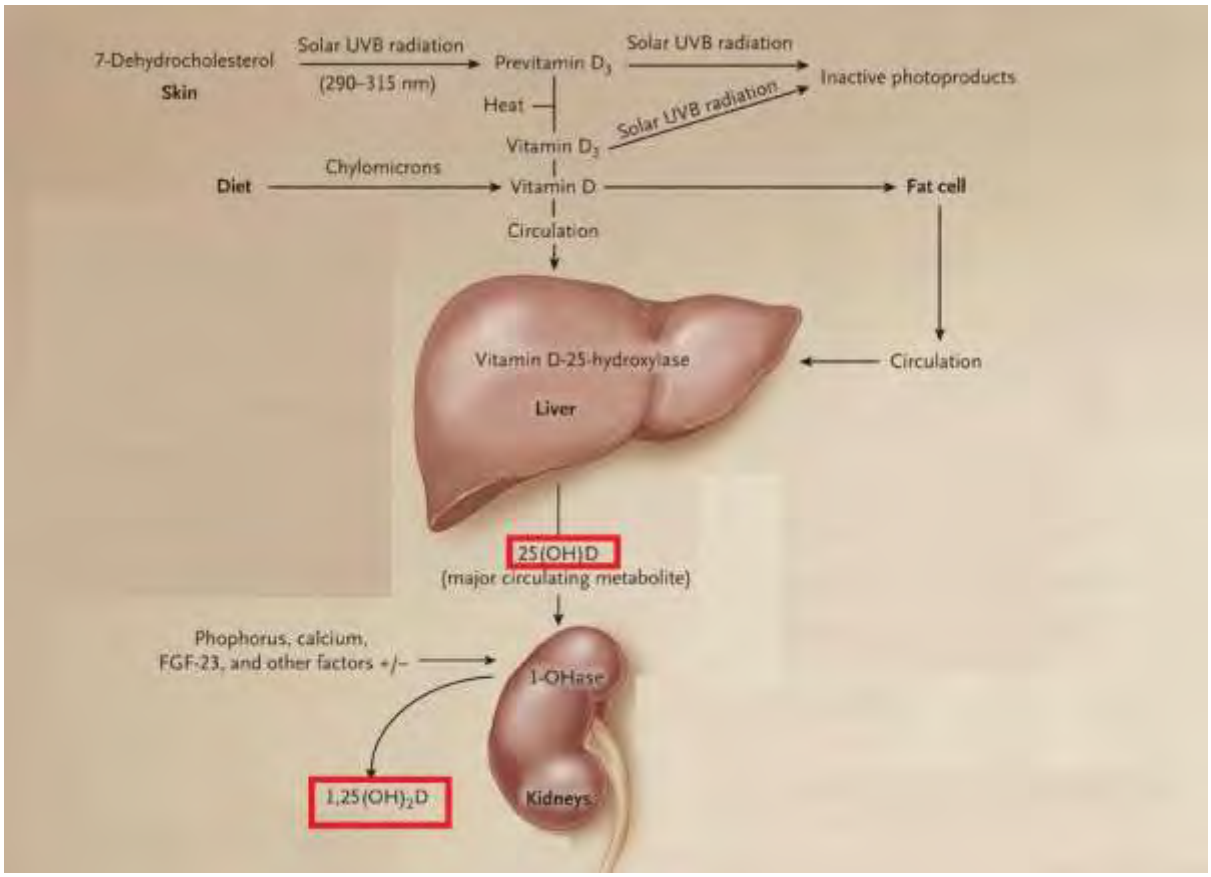

Figure 3.1: Stages of vitamin D biosynthesis (Holick, 2007)

Even if the skin is constantly exposed to sunlight vitamin D is not produced in excess. After initial exposure to UV radiation, provitamin D3 is efficiently converted to previtamin D3. However, previtamin D3 is photosensitive, and sustained exposure to sunlight leads to isomerization into lumisterol. Consequently, only 10-20% of the initial provitamin D3 concentrations eventually end up as previtamin D3 (Holick, 1987).

In recent years several other tissues other than the kidneys were found to possess the ability to convert calcidiol to calcitriol. Extrarenal sites of calcitriol synthesis include lymphocytes, microglia of the brain (Eyles et al., 2005), keratinocytes (Lehmann & Meurer, 2003) and respiratory epithelial cells (Hansdottir et al., 2008). In vitro studies found many other nonrenal cells, such as bone, placenta, prostata, macrophages, and various cancer cells (e.g., from lung, prostata and skin) able to convert calcidiol to calcitriol (Lehmann & Meurer, 2003).

3.2 Vitamin D from natural diet, fortified food and supplements

Vitamin D can be sourced from diet in a very small amount (30%) as only limited number of foods contain it naturally (Holick, 2004). Egg yolks oily fish, fish liver oils, seal blubber, polar bear liver and whale blubber (Bills, 1927) (Kenny et al., 2004) are good sources of vitamin D. In many countries, food items like milk, margarine, and cereal are fortified with vitamin D. Industrial revolution across all continents has reduced our exposure to sunlight, thereby increasing our dependence on dietary sources of vitamin D. Vitamin D obtained from diet are not biologically active and must undergo two hydroxylation steps to become biologically active. Vitamin D_2 and vitamin D_3 absorbed from the intestine are first hydroxylated by 25-hydroxylase in the liver (Feldman et al., 2011). 1α-hydroxylase in the kidney performs the second hydroxylation step, producing the final active metabolite.

As calcidiol and calcitriol are not considered as nutrients, they are not used for food fortification or dietary supplementation. There is evidence of ergocalciferol being too unstable for storing, and compared to cholecalciferol it has higher susceptibility to breakdown when cooked and baked. Therefore, studies concluded that the vitamin D form that ought to be considered in the context of food fortification and supplementation is cholecalciferol (Vieth, 2020).

3.3 Vitamin D Receptor (VDR)

Calcitriol exerts its effects via genomic and non-genomic pathway. The non-genomic effects (rapid responses, RR) are initiated at caveolae of the plasma membrane, whereas genomic effects are generated by binding of calcitriol to vitamin D receptor (VDR). VDR is an intracellular nuclear receptor that belongs to the thyroid hormone and retinoic acid receptor subfamily of nuclear hormone receptors. VDR can form heterodimers with retinoid X receptor (RXR) isoforms and control gene expression of variety of genes in many tissues. In these tissues VDR regulates cellular activities such as proliferation, differentiation, metabolism, ion transport, and apoptosis (Haussler et al., 2010).

VDR distribution in organs and tissues are as follows:

Cardiovascular system	Cardiomyocytes Smooth muscle cells
Endocrine system	Thyroid C-cells Parathyroid glands Langerhans islets
Epidermis	Hair follicles Keratocytes
Gastrointestinal System	Stomach Esophagus Intestine Liver
Immune System	Thymus T and B lymphocytes Bone marrow
Renal system	Ascending portion of Henle loop Juxtaglomerular cells
Respiratory system	Alveolar epithelium
Osteo-muscular system	Osteoblasts Chondrocytes Striated muscle
Reproductive system	Testis Ovary Uterus
Central nervous system	Neurons

Table 3.3: VDR distribution in organs and tissues (adapted from Vuolo et al., 2012)

3.4 Quantitation of vitamin D

In the past, vitamin D deficiency was diagnosed through clinical symptoms such as bone pain and proximal myopathy in adjunction to serum calcium, phosphate, and alkaline phosphate level quantitation (LIPS et al., 2006). More recently, advanced molecular techniques allow to assay serum vitamin D level with high level of accuracy. Clinical quantitation of vitamin D status is accomplished by measuring calcidiol, the primary circulating form of vitamin D. Serum calcidiol level is a better indicator of vitamin D status than calcitriol, because it has a relatively slower rate of clearance, and a half-life of approximately 15 days (Uribarri, 2007). Whereas the active form of vitamin D, calcitriol has a much shorter half-life (5–15 h). Additionally, conditions such as secondary hyperparathyroidism increase calcitriol concentrations making calcitriol an unreliable marker of vitamin D status (Feldman et al., 2011)

There has been poor consensus regarding definition of normal vitamin D status. Traditionally, calcidiol levels above 18-20 ng/ml were considered adequate or normal. However, due to growing body of evidence, a revised and more efficient classification has been suggested (Gómez Alonso et al., 2003). The revised cut-off levels indicated that, for a very long time wrong statistical approach was used to define "normal serum vitamin D levels". Human life begun in an ambient abundant in sunlight, and to this day, population living in such environment have a mean calcidiol concentration around 115 nmol/L (Luxwolda et al., 2013).

Vitamin D status is classified in four ranges as described below-

Vitamin D status	**25(OH)D level (ng/ml)**	**25(OH)D level (nmol/l)**
Desirable	> 40 ng/ml	> 100 nmol/l
Hypovitaminosis D	20 - 40 ng/ml	50 - 100 nmol/l
Vitamin D insufficiency	10 - 20 ng/ml	25 - 50 mmol/l
Deficient	<10 ng/ml	<25 nmol/l

Table 3.4: Classification of vitamin D status

3.5 Causes of Vitamin D Deficiency

3.5.1 Sunblock

Sunscreens are intended to absorb solar UVB radiation. A sunscreen with a sun protection factor (SPF) of 30 confers a solar UVB radiation absorption ability of nearly 95–98%. Topical application of such sunblocker will, consequently, decrease the ability of the skin to produce vitamin D by the same amount (95–98%) (T. C. Chen et al., 2007). A case control study found that topical use of sunscreen with as little as SPF 8 can cause a significant drop in vitamin D level in blood (Matsuoka et al., 1987).

3.5.2 Skin pigment

Melanin is a natural sunscreen that humans developed due to constant exposure to sunlight (N. G. Jablonski & Chaplin, 2000). Melanin's absorption spectrum is 290-700 nm and therefore competes with provitamin D3 for the UVB photons that cross the skin epidermis. This competitive action limits its photolysis 7-dehydrocholesterol (7-DHC) to previtamin D3 (Holick, 1987). Multiple experiments provide evidence to melanin's inhibitory role in vitamin D synthesis. Compared to lighter skin, darker skin, which contains more melanin, requires much more time of sun exposure to reach healthy level of vitamin D production. For example, an experiment conducted in Boston, Massachusetts found significant differences in Caucasian and black skin previtamin D_3 level after exposure to noon sunlight in the month of June (T. C. Chen et al., 2007). The differences are illustrated below-

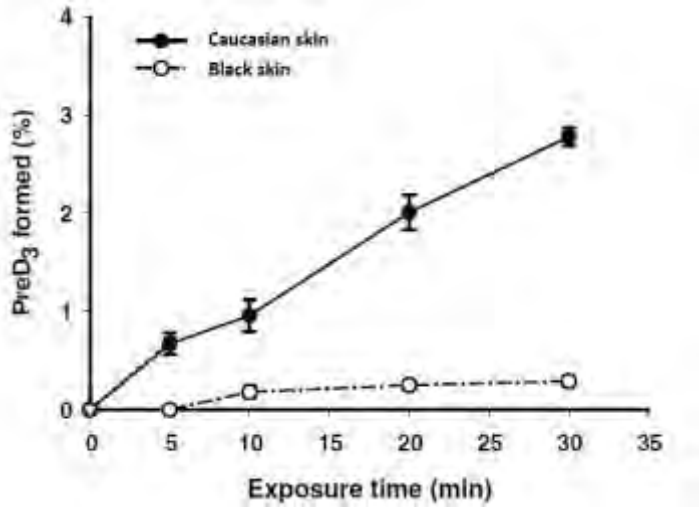

Figure 3.2: The conversion of 7-DHC to previtamin D3 in Caucasian skin versus Black skin (T. C. Chen et al., 2007)

3.5.3 Clothing

Clothes can absorb most ultraviolet radiation. Studies found that any type of clothing covering the skin with will block cutaneous synthesis of vitamin D (Matsuoka et al., 1992). A case control study found high prevalence of subclinical vitamin D deficiency among veiled Kuwaiti women (El-Sonbaty & Abdul-Ghaffar, 1996). Hypovitaminosis D was observed even among adolescent girls wearing concealing clothing in Turkey (Hatun et al., 2005).

3.5.4 Glass

Glass absorbs all UVB radiation. Therefore, skin exposed to sun UVB ray that passes through glass will not be able to produce any vitamin D. Plexiglass and plastic have similar UVB blocking effect on skin (Holick, 1994).

3.5.5 Aging

Aging decreases the capacity of human skin to synthesize vitamin D by greater than twofold. Data from clinical investigations indicate that there is an inverse relationship between age and concentrations of 7-dehydrocholesterol in human epidermis (MacLaughlin & Holick, 1985). A comparative study published in 1989 used UVB radiation in a tanning bed to compare the cutaneous synthesis of vitamin D_3 in healthy young people and older people. The results showed that the blood concentration of vitamin D in young subjects was at least three-fold higher than the older subjects (Holick et al., 1989).

3.5.6 Pollution

Air pollution has a significant and independent role in development of hypovitaminosis D. There is an inverse relationship between the level of air pollution and the amount of solar UVB radiation that can reach earth surface (Hosseinpanah et al., 2010). Therefore, less UVB can pass through more polluted areas, and as a consequence, less UVB is available for effective cutaneous vitamin D synthesis in the skin. Nitrous oxide, ozone and sulfur dioxide are some of the pollutants that absorb solar UVB radiation and decrease UVB radiation available for vitamin D synthesis (Spina Catherine Sheridan, 2005).

3.5.7 Altitude

Altitude has a dramatic impact on the extent of solar UVB that can make it to earth's surface. At high altitude the path length that UVB has to move through is shorter, thus more photons are available for skin to synthesize vitamin D (Wacker & Holick, 2013). An investigation comparing sun induced in vitro vitamin D_3 synthesis at different altitudes OF Mount Everest and Agra confirmed that higher altitude confers enhanced previtamin D synthesis. Mount Everest base camp and Agra are at same latitude but different altitude of 5300M and 169 M respectively. The results from the study demonstrated that there is an almost 5-fold increase in previtamin D_3 production in Mount Everest base camp compared to Agra (Wacker & Holick, 2013). Therefore, altitude is an independent factor that contributes to vitamin D deficiency.

3.5.8 Season and Latitude

The quality and quantity of solar radiation, especially UVB radiation, that reaches the earth's surface differs relative to latitude and season. Seasonal differences in vitamin D status of both children and adults is well documented (Holick, 2007). A study among 7437 Caucasian subjects revealed blood levels of calcidiol peaks in September (~30 ng/mL**)** and bottoms in February (~14 ng/mL) (Hyppönen & Power, 2007).

Latitude also has considerable influence on vitamin D synthesis (Webb et al., 1988). Mean circulating calcidiol in children and adults appears to be greater at equator (~40 ng/mL) and tends to drop in areas far North and South of the equator (~15 ng/mL) (Zittermann, 2006)

3.5.9 Cholecystectomy

Increased incidence of vitamin D deficiency has been reported in patients with prior cholecystectomy (Polat & Beyazal, 2018). A prior cholecystectomy confers a more than 2-fold heightened risk of deficiency (Stoker et al., 2012). This phenomenon may be due to reduced gut transit and augmented colonic passage after a cholecystectomy, resulting in suboptimal absorption (Fort et al., 1996). In addition, cholestyramine, a bile acid sequestrant often prescribed for post cholecystectomy diarrhea syndrome has been shown to impair vitamin D absorption (Thompson & Thompson, 1969).

4. Noncommunicable Diseases Linked to Hypovitaminosis D

4.1 Hypertension

The World Health Organization estimates 1.28 billion adults aged between 30-79 years to be suffering from hypertension globally. Essential hypertension, also defined as primary hypertension, is the most typical form of hypertension among hypertensive patients. Essential hypertension is often associated to low blood levels of ionized and ultrafiltrable calcium (Mccarron et al., 1987) and elevated levels of parathyroid hormone (PTH) (Jorde et al., 2005). Both of these conditions, respectively known as hypocalcemia and hyperparathyroidism, are often secondary to vitamin D deficiency (Holick, 2005; Noto & Heller, 2009). Therefore, poor vitamin D levels may lead to the development of hypertension by creating conditions conducive to hypertension.

Activation of the renin–angiotensin system (RAS) links hypovitaminosis D to hypertension (Zittermann, 2006). The renin-angiotensin system (RAS) plays an essential role in the regulation of blood pressure. Inappropriate stimulation of the RAS has been linked to development of hypertension, stroke, and heart attack. Various studies suggest calcitriol may play a key role in preventing the unfavorable over-stimulation of the RAS. In a lot of epidemiological and clinical studies of the past, high plasma renin activity and/or high blood pressure has been observed in those with low calcitriol levels (Resnick et al., 1986; Rostand, 1997). Although the exact mechanism of how calcitriol affects the renin angiotensin system was not known, results from interventional studies with calcitriol treatment had shown to reduce both plasma renin activity and blood pressure (Cheol Whee Park et al., 1999; Kimura et al., 1999). In, 2003, a study found calcitriol to function as a potent repressor of renin gene expression (Li, 2003). Therefore, vitamin D contributes in maintaining appropriate blood pressure by regulating the expression of renin. This explains why deficiency of vitamin D leads to uncontrolled renin activity and ultimately high blood pressure.

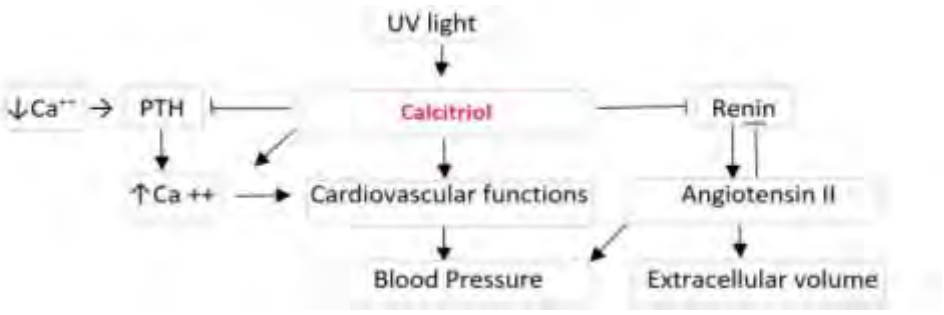

Figure 4.1: Outline of the interaction between the vitamin D and the renin–angiotensin system (RAS) leading to hypertension.

4.2 Cardiovascular Diseases

Vitamin D was first linked to cardiovascular disease in 1981, when Robert Scragg, hypothesized that the observed high CVD incidence in winter may be a consequence of low UV-B irradiation, with correspondingly low vitamin D status in that season (Scragg, 1981). After discovery of VDR in rat heart (Simpson R U et al., 1985), the relationship between vitamin D and CVD has become the focus of intense research. Numerous epidemiologic, observational, and clinical studies have found a strong relationship between serum calcidiol level and cardiovascular disease (CVD). Hypovitaminosis is consistently linked to cardiovascular events, such as myocardial infarction (MI), ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), unstable angina, ischemic stroke, cardiovascular death, and higher mortality risk after acute stroke (Surdu et al., 2021).

Vitamin D deficiency plays multiple roles in development of atherosclerosis, the first step in CVD development. Low serum calcidiol has been found to be associated with more significant stenosis in the coronary arteries of postmenopausal women (Dziedzic et al., 2021). In observational and interventional studies, poor vitamin D levels was associated with unfavorable lipid profiles, and adequate vitamin D levels correlated with better lipid profiles (Challoumas, 2014). Unfavorable lipid profile (high total cholesterol, triglycerides, LDL and low HDL) is a known risk factors for CVD. Intervention studies found vitamin D repletion correlated with improved lipid profile (Manousopoulou et al., 2015).

A critical event in the development and progression of atherosclerosis is endothelial activation and rise in adhesion molecules, which increases with vitamin D deficiency and lowers with vitamin D supplementation (Salekzamani et al., 2017). Vitamin D has the ability to increase endothelial nitric oxide (NO) production (Surdu et al., 2021). Nitric oxide acts as a vasodilator and decreases the level of reactive oxygen species (ROS) which influences the vascular tone. On the other hand, hypovitaminosis D generates oxidative stress and triggers inflammation (Förstermann et al., 2017)**.** The pathogenesis of atherosclerosis is attributed innate immune response cells (i.e., monocytes, macrophages) that cause chronic inflammation of the blood vessel walls (Wolf & Ley, 2019). Vitamin D mediates anti-inflammatory responses by reducing proinflammatory type 1 cytokines: IL-12, IL-6, IL-8, IFN-gamma, and TNF-alpha; and increasing anti-inflammatory type 2 cytokines: IL-4, IL-5, and IL-10 (Zhang et al., 2012). Vitamin D may also contribute in atherogenesis by inhibition action on proliferation of vascular smooth muscle cell (S. Chen et al., 2010).

Vitamin D action on atherosclerosis development is summarized in Table 4.1.

Lipid profile	• ↓ Total cholesterol • ↓ LDL-C • ↓ Triglycerides • ↑ HDL-C
Endothelial adhesion & activation	• ↓ Vascular cell adhesion molecule 1 (VCAM-1) • ↓ E-selectin
Vascular tone & endothelial function	• ↑ NO level • ↓ released ROS level
Inflammation & atherosclerosis	• ↓ Proinflammatory type 1 cytokines: IL-12, IL-6, IL-8, IFN-ɣ, TNF-α • ↑ Anti-inflammatory type 2 cytokines: IL-4, IL-5, & IL-10 • ↓ Oxidative stress by reducing cathepsin, IL-6 & adiponectin
Arterial smooth muscle cells	• ↓ Angiotensin II production • ↓ Oxidative stress • ↓ Tissue factor expression • Inhibits cellular senescence

Table 4.1: Vitamin D effects on atherosclerosis (adapted from Surdu et al., 2021**).**

A nested case-control study conducted over 10 years with 18,225 participants found low levels of calcidiol to be independently associated with higher risk of myocardial infarction in a graded manner, albeit other controlling for factors (Giovannucci et al., 2008). A recent experiment has shown that vitamin D is involved in lipid metabolism and diminishes the buildup of cholesterol by macrophages, making vitamin D in blood plasma a prognostic predictor of MI (Zhernakova et al., 2021). Evidence from decades of studies suggest vitamin D plays a multifactorial role in CVD development.

4.3 Cancer

The first association between cancer and sun exposure was reported in 1915 (Hoffman, 1915). The study compared cancer deaths between 1908 and 1912. The results showed that with growing distance from the equator, cancer death rate also increased. A multitude of epidemiologic studies followed these initial observations that led to the theory that vitamin D produced after sun exposure has anti-carcinogenic effects. A moderate, inverse correlation with solar radiation was observed for cancers of the organs in the digestive system including esophagus, stomach, pancreas, gallbladder, colon and rectum (Mizoue, 2004). Epidemiological data shows depleted levels of calcidiol are linked to an almost 50% increased risk of colon, prostate, or breast cancer (Garland et al., 2009; Holick, 2007). While adequate vitamin D status had a protective effect and lowered risk of cancer (Giovannucci, 2009). Epidemiological surveys have continually revealed that UVB exposure and subsequent increase in circulating levels of vitamin D are linked to decline in incidence and death in different histological types of cancer (Vuolo et al., 2012).

Although metabolizing enzymes of vitamin D are primarily located in liver and kidney, catabolic enzymes can be found in several tissues. Tissues, such as, lung, pancreas, colon, breast, and prostate can locally synthesize and degrade calcitriol and this phenomenon has been proposed to represent a key factor in numerous types of human cancer (Cross, 2007; Haussler et al., 1998; Schwartz et al., 2004). Multiple levels of evidence bolster the relationship between vitamin D and cancer (Vuolo et al., 2012):

(1) Low circulating levels of calcifediol confer increased risk for developing cancer
(2) High consumption of vitamin D is linked to a reduced risk of cancer
(3) Cancer is less aggressive in summer when the synthesis of vitamin D is higher
(4) Genetic polymorphisms of genes transcribing proteins involved in the vitamin D signal pathway influence the risk of developing cancer

In the last decades, advancement in molecular studies, allowed epidemiological data to be combined with cellular and molecular studies data to shed more light on the role of vitamin D in cancer. Calcitriol is now recognized as a powerful regulator of cell growth and differentiation. Accumulating evidence suggest it has also a role on cell death, tumor invasion, and angiogenesis. Murine models with prostate and lung metastasis, showed decreased cancer growth when treated with calcitriol (Getzenberg et al., 1997; Nakagawa, 2004).

Calcitriol is deemed to be analogous to a master switch controlling a great number of genes that modulate cell cycle progression, DNA replication and repair, etc. The antiproliferative effects of calcitriol have been repeatedly confirmed through many studies. The first instant was in 1981 where calcitriol was found to inhibit melanoma cell proliferation (Colston et al., 1981). The same year calcitriol was reported to be involved in bone marrow cell differentiation (E. Abe et al., 1981). Some studies suggest that vitamin D analogues have the ability to inhibit IGF-I signaling pathways, and therefore promote apoptosis in breast cancer cells (Xie et al., 1999).

Calcitriol shows substantial antitumoral activity *in vivo* such as human prostatic adenocarcinoma, human breast, pancreatic, and colon cancer as well as *in vitro* such as in leukemia, myeloma, and lymphoma lines (Reichel et al., 1989; Uhmann et al., 2011; Zhou et al., 1990). Calcitriol regulates transcription of several genes involved in various pathways that reduce tumorigenesis. Calcitriol's role as a potent inhibitor of inflammation farther enhances its anti-tumoral activity (Vanoirbeek et al., 2011). Calcitriol inhibits the synthesis of prostaglandin, a significant stimulus for cell growth. Calcitriol is also able to induce prostaglandin degradation, and thus significantly reduce prostaglandin activity (Moreno et al., 2005).

Vitamin D Receptor (VDR) is expressed by both benign and malignant proliferative cells (Vuolo et al., 2012). Calcitriol binds to VDR and forms heterodimers with another receptor-ligand, and together they occupy specific nucleotide sequences known as vitamin D response elements (VDREs). Along some other transcription factors this complex transcribes vitamin D responsive genes. Some genes that are implicated in cancer are transcriptionally activated by calcitriol. For example, BGLAP (osteocalcin), the growth arrest and DNA-damage-inducible gene, GADD45 gene (Deeb et al., 2007).
Vitamin D action on cancer development is summarized in Table 4.2.

Promotes	**Apoptosis**
Inhibits	Angiogenesis
	Metastasis
	Tumorigenesis

Table 4.2: Vitamin D action on cancer development

A novel cancer etiology model proposes vitamin D and calcium as elements that can prevent and even potentially arrest cancer pathogenesis (Garland et al., 2009). The model is known as DINOMIT, abbreviation of disjunction, initiation, natural selection, overgrowth, metastasis, involution, and transition. According to the model vitamin D metabolites prevent disjunction of cells and have a positive impact in other phases of DINOMIT as well (Garland et al., 2007). The reported 10 mechanisms that account for the role of vitamin D and calcium in reducing cancer rate and death and the sources is summarized in Table 4.3:

Mechanism	Studies
1. Up-regulation of adherence & signaling between epithelial cells	(Johansen et al., 2000) (Ordóñez-Morán et al., 2008)
2. Contact inhibition of proliferation	(Johansen et al., 2000) (Ordóñez-Morán et al., 2008)
3. Differentiation	(Abe et al., 1986) (Ordóñez-Morán et al., 2008) (LAMPRECHT & LIPKIN, 2001)
4. Cell cycle stabilization	(Jensen et al., 2001)
5. Promotion of apoptosis	(Welsh, 1994) (Welsh et al., 1998) (Mathiasen et al., 1999)
6. Anti-neoangiogenesis	(Majewski et al., 1996) (Pendás-Franco et al., 2008) (Mantell et al., 2000)
7. Down-regulation of glycogen synthase kinase 3 (GSK-3) *reduces proliferation of colorectal, prostate, & pancreatic cancers in vitro	(Ougolkov & Billadeau, 2006)
8. Downregulation of the canonical Wnt signaling pathway *Wnt signaling pathway is active in colorectal and other cancers	(Ordóñez-Morán et al., 2008)
9. Increased expression of DKK-1 protein *DKK-1 is a tumor suppressor protein in colon cancer cells	(González-Sancho et al., 2005)
10. Down-regulation of DKK-4 transcription *DKK-4 is up-regulated in colorectal cancer	(González-Sancho et al., 2005)

Table 4.3: Proposed mechanisms that account for the role of vitamin D and calcium in reduction of cancer rate and death

A study relying on data from observational studies and randomized trials predicted that elevation in blood vitamin D to 40-60 ng/mL would prevent nearly 58k new cases of breast cancer and 49k new cases of colorectal cancer in the USA and Canada. They also predicted such levels may cut down cancer mortality to three fourths (Garland et al., 2009).

4.4 Asthma

Asthma is a top noncommunicable disease that can afflict people at any age. In fact, it is the leading chronic illness among children. In 2019 an estimated 262 million were affected and 461000 died because of asthma ("Global Burden of Disease: GBD Cause and Risk Summaries," 2020). Last decade has seen the highest increase in asthma patients, and accumulating evidence link vitamin D deficiency to its pathogenesis and prognosis (Litonjua & Weiss, 2007). Asthma is characterized by inflammation and tightening of the muscles around the small airways causing air passages in the lungs to become narrow. In patients with asthma, vitamin D level represents a critical marker of asthma severity and treatment response.

There are many theories on the underlying mechanism of calcitriol's role in the pathogenesis of asthma. One theory points to calcitriol's impact in immune modulation. Respiratory infections are presumed to serve as trigger for a worsening of asthma and vitamin D is known to inhibit the development of respiratory infections (Urashima et al., 2010). Genetic variations in Vitamin D Receptor (VDR) have also been identified as a risk factor for asthma in patient cohorts (Poon et al., 2004).

Asthma is managed with inhaled medications such as glucocorticoids to decrease inflammation present in the air passages. However, asthma patients respond variably to inhaled corticosteroids. Results from a population-based study suggest that children with low Vitamin D levels require more inhaled corticosteroids (Brehm et al., 2009). A clinical investigation conjectured that vitamin D influences glucocorticoid response in asthma (Sutherland et al., 2010). The results from the investigation supported the theory and found that adequate levels of Vitamin D enhance glucocorticoid response. When stimulated by calcitriol, human CD^{4+} T cells increase their production of IL-10, which can potentially help overcome the poor corticosteroids responsiveness in glucocorticoid resistant (Xystrakis et al., 2006). In addition, vitamin D was found to improve lung function and decrease airway hyperresponsiveness (Sutherland et al., 2010). Accumulating evidence suggest that pregnant women can reduce the risk of early childhood asthma by almost 40% by taking vitamin D during their gestational period (Litonjua & Weiss, 2007)

4.5 Chronic Obstructive Lung Disease (COPD)

The World Health Organization (WHO) ranked Chronic Obstructive Pulmonary Disease (COPD) as third among the world's leading diseases causing mortality. In 2019 alone it was responsible for 3.23 million deaths. COPD is characterized by persistent and progressive respiratory distress including breathing difficulties, coughing, and production of phlegm. Such symptoms are result of anomaly in the small airways of the lungs that limit the airflow in and out of the lungs. The airways can become narrow due to blockage by mucus, and/or injury of the lung causing inflammation and distension of the airway lining.

Observational studies and epidemiologic evidence link COPD to vitamin D status. Adequate vitamin D status correlates to better pulmonary function (Black & Scragg, 2005) and vitamin D deficiency is predominant among patients awaiting lung transplantation (Førli et al., 2004). A study published in 2010 found high prevalence of subnormal vitamin D levels in COPD that correlates with disease severity (Janssens et al., 2010).

The mechanisms linking vitamin D depletion with the development of COPD are mostly hypothetical. Vitamin D deficiency is known to cause osteoporosis and fractures. Alterations in the thoracic skeleton may result in malfunction of the respiratory muscles which is conducive to the pathophysiology of COPD. In women, multiple thoracic vertebral fractures was found to decline vital capacity as well as total lung capacity (Leech et al., 1990). Another study of COPD patients observed a strong link between COPD severity and fractures (Nuti et al., 2009).

COPD is exacerbated by growth of an abnormal flora composed of viruses or bacteria or a combination of both (Papi et al., 2006). Vitamin D deficiency may alter host immunity of the lung, allowing the growth of such microbes which ultimately trigger inflammation.

Calcitriol maintains the extracellular matrix homeostasis of bone tissue and the lung. Matrix metalloproteinasis-9 (MMP-9) has been suggested contribute in the development of COPD (Culpitt et al., 2005). In induced sputum of subjects suffering from COPD, MMP-9 was found to be elevated. Adequate levels vitamin D in keratinocytes inhibits TNF-alpha from inducing upregulation of MMP-9 (Bahar-Shany et al., 2010). Therefore, it is possible that deficiency of vitamin D decreases the attenuation of MMP-9 activity, subsequently increasing degradation of lung parenchyma.

4.6 Diabetes

Diabetes is one of the four major non communicable diseases. It has long been noticed that as humans age, serum calcifediol falls (McKenna, 1992) and serum glucose rises (Harris et al., 1998). Comparative studies revealed calcifediol concentration in blood is lower in subjects diagnosed with type 2 diabetes compared to nondiabetic control subjects (Pietschmann et al., 1988; Scragg et al., 1995). A study published in 1995 revealed that patients at risk for diabetes had lower calcifediol levels compared to those who were not at risk for diabetes (Boucher et al., 1995). The same study also found that among subjects at high risk for diabetes, poor vitamin D levels was associated with impaired insulin secretion. In a prospective population-based study of elderly men, hypovitaminosis D was linked to hyperresponsive insulin secretion after an oral glucose tolerance test (Baynes et al., 1997). Consequently, vitamin D has long been suspected of contributing to the pathogenesis of type 2 diabetes by triggering insulin resistance and reducing insulin secretion (Boucher, 1998).

It has been long established that onset of insulin resistance triggers diabetes. When cells become resistant to insulin, β-cells release more insulin in an attempt to prevent hyperglycemia. As this hyperactivity grows, β cells experience acute elevation in Ca^{2+} and reactive oxygen species (ROS) signaling that ultimately results in cell death and marks the beginning of diabetes (Newsholme et al., 2016). In normal physiological condition, vitamin D acts to preserve the normal levels of both Ca^{2+} and ROS that increase in β-cells during diabetes (Berridge, 2015). Therefore, in hypovitaminosis D, with depleted reserves, vitamin D cannot efficiently reduce inflammation, which eventually initiates insulin resistance.

The discovery of VDR in pancreatic β cells and Vitamin D dependent calcium-binding proteins (calbindins) in pancreatic tissue, suggested a role for vitamin D in insulin secretion (Johnson et al., 1994). Currently numerous VDR gene polymorphisms have been recognized to be associated to type 2 diabetes mellitus and insulin release (Ortlepp et al., 2001). It has been hypothesized that vitamin D affects several pathways involved in insulin secretion. According to one experimental data, calcitriol affects β-cell insulin secretion and synthesis by increasing intracellular concentration of calcium through non-selective voltage-dependent calcium channels (Sergeev, 2016). Vitamin D, likely, also assists in maintaining β-cell calcium-dependent endopeptidases involved in cleavage of proinsulin to insulin (Boucher, 1998). Calcium not only helps with insulin exocytosis but also with β-cell glycolysis, which signals concentration of glucose in circulation (Boucher, 1998)

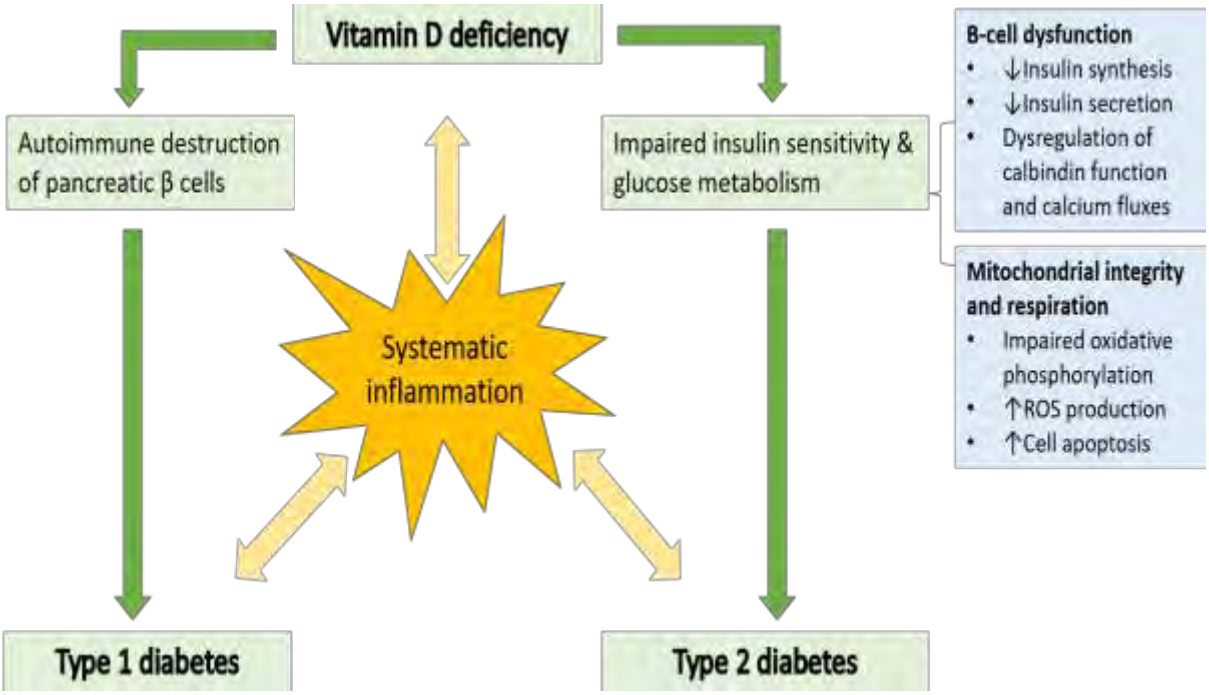

Figure 4.2: Vitamin D deficiency and development of diabetes

Vitamin D plays a significant role in preserving the epigenome (Berridge, 2017). Epigenetic alterations are a hallmark of diabetes where hypermethylation inactivates many diabetes-related genes. Vitamin D prevents hypermethylation of several gene promoter regions of numerous diabetes-related genes by enhancing the expression of the enzyme DNA demethylase.

Vitamin D repletion has been shown to ameliorate and even prevent type 1 diabetes mellitus (Stene et al., 2000; The EURODIAB Substudy 2 Study Group, 1999). More recent studies found that Vitamin D supplementation may be able to prevent the onset of diabetes type 2 (Wimalawansa, 2018). Supplementation with active vitamin D_3 might help improve the insulin resistance and decrease risk in predisposed patients (Berridge, 2017). In diabetic patients with established hypovitaminosis D, vitamin D replenishment was found to improve both glycemia and insulin secretion (Kumar et al., 1994). Frequent replenishment with large enough doses of vitamin D was able to enhance insulin sensitivity among insulin resistant and vitamin D deficient patients (von Hurst et al., 2010).

4.7 Bone diseases (Osteoporosis, Osteomalacia, Rickets)

Because of its key role in calcium metabolism, Vitamin D sufficiency is critical for maintaining skeletal health. Chronic inadequacy of calcitriol leads to (Lips, 2001)-

- Secondary hyperparathyroidism
- High bone turnover
- Progressive bone loss
- Mineralization defects
- Fragility fractures

Among numerous functions attributed to vitamin D, the main function is to aid the processes necessary to maintain healthy, mineralized bones. Vitamin D enhances intestinal absorption of calcium and phosphorus, therefore depleted vitamin D levels cause calcium malabsorption. Combined results from multiple studies establish that at serum calcidiol concentrations below ~80 nmol/L there is calcium malabsorption and thus enhanced risk of fracture (Heaney, 2004). Osteoporosis, osteomalacia and rickets are major hypovitaminosis D related bone diseases. The figure below depicts the relationship between the level of serum calcidiol concentration and the risk of various hypovitaminosis D related bone disease.

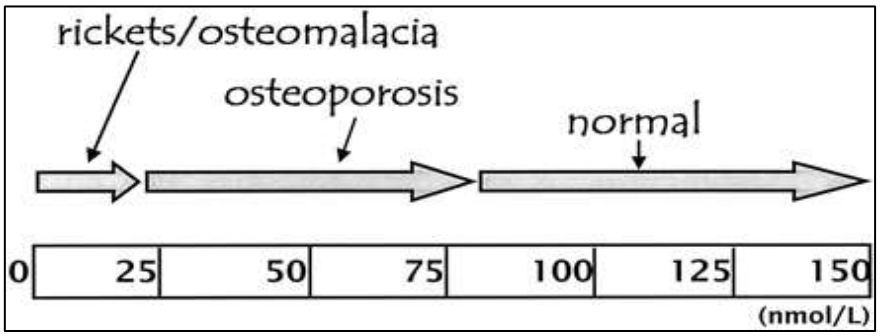

Figure 4.3. Proposed mapping of hypovitaminosis D induced bone diseases onto the serum calcidiol concentration continuum (Heaney, 2004)

Osteoporosis is a major NCD and the most prevalent bone disease, globally present at rate of in 1 in 3 among women and 1 in 5 among men above the age of 50 (Kanis et al., 2000; Melton et al., 1992, 1998). Osteoporosis results in fragility fractures that often led to other conditions such as myocardial infarction, cancer or death. In children, severe vitamin D deficiency leads to rickets, a bone disease characterized by bone pain and skeletal deformities. In adults, severe vitamin D deficiency leads to the development of a condition named osteomalacia. Osteomalacia is characterized by incomplete osteoid mineralization (Lips et al., 2006).

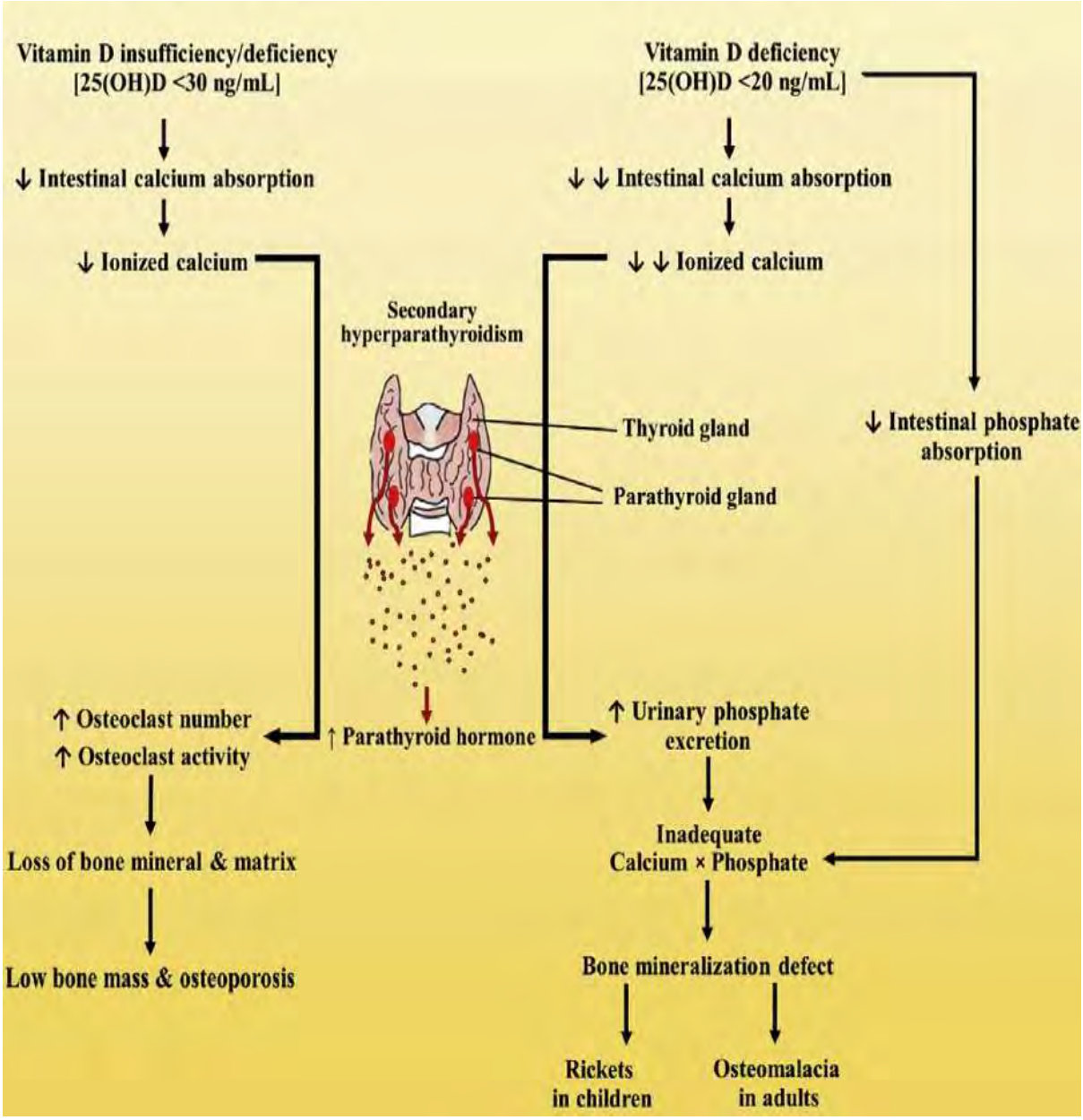

Figure 4.4: Vitamin D deficiency pathway to Osteoporosis, osteomalacia and Rickets development (Charoenngam et al., 2019)

There is strong consensus over necessity of vitamin D in preventing rickets and osteomalacia (Anderson & Atkins, 2008). Vitamin D's most studied action is its ability to maintain physiological levels of serum calcium and phosphate through calcium and phosphate absorption, renal tubular calcium reabsorption, and calcium mobilization from the bone (Charoenngam et al., 2019). Calcitriol is a strong stimulant for active transport of calcium in the intestine (O'Loughlin & Morris, 1998) and its primary role on bone is to mediate fluctuations in the extracellular fluid (ECF) concentration of calcium and phosphate, which indirectly impacts bone mineralization.

Decreased calcium and phosphate absorption due to vitamin D deficiency elevates parathyroid hormone (PTH) causing secondary hyperparathyroidism. These events trigger the release of calcium from the bones in order to maintain calcium homeostasis in a process known as bone resorption (Lips, 2001). During bone resorption, existing bone is broken down by osteoclasts, and replaced with new bone by osteoblasts (Jilka, 2003; Parfitt, 2002; Zaidi, 2007). Calcitriol and PTH stimulate osteoblasts to express RANKL, which in turn activates osteoclasts. Increased osteoclast activity results in enhanced bone resorption, loss of bone mineral and matrix, and ultimately decreased bone mass and causes osteoporosis (Charoenngam et al., 2019). Incessant bone turnover and resorption weakens bone architecture and increases fracture risk (Lips, 2001). Increase of PTH has a phosphaturic effect in the body, i.e., increase in phosphate excretion trough urine. Decline in intestinal phosphate absorption combined with urinary phosphate excretion results in inadequate calcium-phosphate product, leading to defective bone mineralization and development of osteomalacia and rickets (Charoenngam et al., 2019).

It is difficult to assess whether beneficial effect of vitamin D on skeletal health is solely due to this "calcemic effect". In vivo, administration of calcium and phosphate alone can correct the effects of vitamin D deficiency on skeleton (Underwood & DeLuca, 1984). Such finding signifies that at least for bone mineralization, calcitriol is not an absolute requirement. However, calcitriol may exert a direct response on cartilage and bone by stimulating normal skeletal development and turnover (Bikle, 2014). Increasing evidence suggest that vitamin D plays a direct role throughout normal bone metabolism by regulating bone cell activity (Atkins et al., 2007; Driel et al., 2006).

Supplementation with vitamin D suppresses PTH function and therefore bone turnover (Prestwood et al., 1996). Results from a meta-analysis of multiple randomized controlled trials suggest a positive dose response association between supplementation with vitamin D and prevention of fractures (Bischoff-Ferrari et al., 2009). Although vitamin D has not been proved to directly cause bone diseases, it is evident that maintaining adequate vitamin D level throughout life is critical to prevent osteomalacia, and to reduce or avoid the onset of osteoporosis in old age.

4.8 Chronic Liver Disease

Hypovitaminosis D is a common phenomenon in subjects with chronic liver disease, manifested by 92% of all patients (Arteh et al., 2010). Cholestatic liver disorders cause impaired intestinal absorption, hence, in the past, hypovitaminosis D was believed to be predominant only in cholestatic liver disorders (Collier et al., 2002). Growing body of evidence, however, demonstrate its widespread presence in chronic liver disease, irrespective of etiology.

Non-alcoholic fatty liver disease (NAFLD) has long surpassed viral hepatitis and alcoholic fatty liver disease as the most common form of chronic liver disease (Lazo & Clark, 2008). NAFLD encompasses an extensive spectrum of liver damage conditions including steatosis, fibrosis and cirrhosis that can advance to liver failure and hepatocellular carcinoma (Marchesini, 2003). NAFLD pathogenesis is incompletely understood but it has been hypothesized that a number of diverse parallel processes involving extrahepatic factors may lead to the development and progression of liver inflammation (Tilg & Moschen, 2010). One of those extrahepatic factors is vitamin D level. A study confirmed that relative to control subjects, subjects with biopsy-proven NAFLD have lower serum 25-hydroxycholecalciferol concentrations (Targher et al., 2007). Another study showed that, irrespective of sex, age, BMI, race, history of diabetes, peripheral vascular disease, renal disease, liver diseases and hypertension, there is an inverse relationship between low serum 25-hydroxycholecalciferol levels and NAFLD (K. L. Jablonski et al., 2013)

Vitamin D deficiency has been recognized as an independent risk factor for severe liver fibrosis (Petta et al., 2010). Serum levels of 25-hydroxyvitamin D represent a critical marker predicting mortality in advanced liver cirrhosis (Paternostro et al., 2017).

Intervention studies with vitamin D supplementation, however, have failed to provide enough evidence on the positive effect of vitamin D supplementation on liver related morbidity and quality of life (Bjelakovic et al., 2017).

While it is evident that a relationship between vitamin D and liver disease exists, it is unclear whether it's deficiency of vitamin D that confers an enhanced risk to liver disease or it's the other way around where disease of the liver causes vitamin D deficiency.

4.9 Chronic Kidney Disease

Chronic kidney disease (CKD) is an emerging non communicable disease and one of the most important predictors of premature cardiovascular disease. Patients with CKD exhibit dramatically high rate of severe vitamin D deficiency, which is further exacerbated by the reduced ability to convert calcifediol into the hormone form calcitriol (Jones, 2007). The kidneys have a significant role in vitamin D metabolism. They not only offer the enzymatic system for the calcitriol synthesis but they are also involved in the uptake of filtrated calcifediol from the urine (Nykjaer et al., 1999). Consequently, it is not surprising that impaired renal function leads to vitamin D deficiency. In fact, even early-stage CKD patients experience vitamin D deficiency (Levin et al., 2007). While it is unclear whether hypovitaminosis D triggers kidney disease, it is certain vitamin D deficiency accelerates the progression of kidney disease. Growing body of evidence have established a relationship between vitamin D deficiency and progression of CKD, and they have also recognized plasma vitamin D status to be an independent inverse predictor of disease progression and mortality in patients with chronic kidney disease (S. Williams et al., 2009). Vitamin D and its receptor are involved in regulation of the renin–angiotensin system (RAS) (Li et al., 2004) and the nuclear factor (NF)-κB pathway (Sun et al., 2006). Both pathways are involved in a broad range of pathological process affecting the kidneys. Vitamin D has been recognized for its impressive therapeutic effects in prevention and intervention of various kidney diseases. Strong data suggest that adequate replenishment of vitamin D in deficient populations could potentially reduce premature morbidity and mortality in chronic kidney disease (Li, 2010).

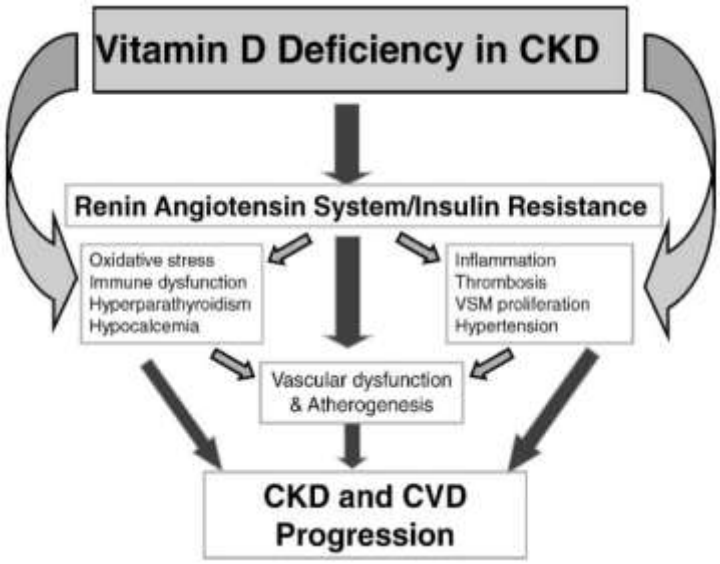

Figure 4.5: Major pathways linking vitamin D deficiency to CKD progression and complications (S. Williams et al., 2009)**.**

4.10 Irritable Bowel Syndrome (IBS)

Irritable bowel syndrome (IBS) is a prevailing gastrointestinal disorder experienced by millions of individuals worldwide. IBS patients are often diagnosed with hypovitaminosis D (Khayyat & Attar, 2015). Data from epidemiological and clinical studies suggest that poor vitamin D levels might be accountable for IBS pathogenesis. However, there is poor consensus on the exact role of Vitamin D in IBS pathogenesis. It is generally assumed that Vitamin D improves the IBS by improving the factors involved in the development of IBS. In the gut vitamin D is known to modulate function of intestinal microbiota, regulate expression of antimicrobial peptide and exert a protective effect on epithelial walls of the intestinal mucosa (Akimbekov et al., 2020).

Some hypotheses draw a relationship between vitamin D and IBS through calcium. It has been long known that Vitamin D promotes gastrointestinal absorption of calcium and its subsequent entry into the circulation. From the circulation, calcium is carried to various tissues. In the skin tissue, calcium plays a role in decreasing the reactivity of skin to inflammatory stimuli (Klauder & Brown, 1929). It has been proposed that, calcium may have a similar role in the epithelial cells of the large intestine, where it effectively reduces the inflammatory response to gut flora and other agents in colon lumen (Garland & Garland, 1980). According to this model, people likely experience IBS due to inadequate intracellular calcium levels caused by depleted reserve of vitamin D. Another study, conducted more recently, attempted to identify potential gene expression-based biological signatures and biomarkers of IBS (Dussik et al., 2018). Their investigation was able to identify potential IBS genes, and calcitriol, the active version of vitamin D, was found to be a regulator of a subset of potential IBS genes. Such findings provide evidence to support the theory that pathological gene expression of IBS biomarkers may be initiated due to low circulating vitamin D levels. In line with this assumption, it can also be assumed that an increase in serum vitamin D status may ameliorate IBS symptoms by reversing pathological gene expression of the identified IBS biomarkers. An inverse relationship between serum vitamin D level and IBS symptom severity has also been extensively reported (C. E. Williams et al., 2018). In light of that, intervention studies have been conducted to assess the effect of vitamin D supplementation in IBS population. Most of the trials found Vitamin D supplementation to ameliorate the symptoms and quality of life in patients with IBS (Jalili et al., 2019; Abbasnezhad et al., 2016). Although the underlying mode of action of vitamin D in the pathogenesis of IBS lacks clear understanding, maintaining an ideal vitamin D status seems to have a positive effect in gut health.

4.11 Multiple Sclerosis

Multiple sclerosis (MS) is a noncommunicable neurodegenerative disorder that impacts the central nervous system (CNS). It is chronic, inflammatory, and of probable autoimmune origin. In multiple sclerosis there is a recurring or progressive demyelination and degeneration of the central nervous system. The demyelination and degeneration are believed to be caused by an erroneous immune response. Hypovitaminosis D has been identified as an environmental factor that increases susceptibility of developing MS. The role of vitamin-D in the development of MS has been the focus of intense research. A prospective nested case-control study with data from more than 7 million US military personnel records found that high serum concentrations of calcidiol confers decreased MS risk (Munger et al., 2006). Another prospective study conducted 6 years later confirmed these findings and stated that calcidiol level over 75 nmol/L lowers the risk of developing MS later in life (Salzer et al., 2012). Vitamin D intake from supplements has a protective effect and is inversely associated with the risk of MS (Munger et al., 2004). Extensive number of studies suggest that vitamin D is not only protective against the development MS, but it may also have a beneficial role in disease progression. In case of relapsing-remitting MS depletion of vitamin D increases risk of exacerbation whereas repletion may a beneficial effect on disease activity (Simpson et al., 2010; Runia et al., 2012).

Relapsing-remitting and secondary-progressive forms of multiple sclerosis are often treated with interferon-β, a cytokine in the interferon family. Vitamin D influences the prognosis of relapsing-remitting MS patients being treated with interferon-β (Simpson et al., 2010). It has been reported that, among patients undergoing interferon-β treatment, the lowest rate of new lesions was observed in patients with 25-hydroxyvitamin D levels over 100 nmol/L (Fitzgerald et al., 2015).

The involvement of Vitamin D in the pathogenesis and progression of MS does not seem to be straightforward. After the development of new genetic tools such as next-generation sequencing, and the fast growth of epigenomics, scientists have realized that the association between vitamin D and MS might be based on the widespread and typical genomic binding of the vitamin D receptor (VDR) (Lu et al., 2018).

5. Discussion and Conclusion

The unique conditions of the twenty-first century have let chronic noncommunicable diseases surpass infectious diseases as the major killers worldwide. NCDs are deemed as the most "democratic" diseases as they can affect anyone regardless of their socioeconomic or geographical background. As the burden of NCDs increases, it is important to identify and address any risk factor that contributes to the growing number. For more than a century, academics have been reporting an inverse correlation between latitude and many chronic diseases like diabetes, hypertension, common cancers, and numerous autoimmune diseases. By now, it is clear that vitamin D deficiency is a shared risk factor among many chronic non-communicable diseases. In this review, several lines of evidence were presented, suggesting that hypovitaminosis D has direct and indirect actions on non-communicable disease development.

Vitamin D is unique amid many vitamins and hormones in that its production is not enzymatic but depends on photo radiation. Solar UVB is capable to transform 7-dehydrocholesterol (7-DHC) into previtamin D_3, which undergoes thermal isomerization to form cholecalciferol. Vitamin D can also be obtained to some extent from dairy food and wild fatty fish, such as salmon and mackerel. Both vitamin D produced in the skin from 7-DHC or absorbed from food or supplement, must be activated first to calcidiol and then to its active form calcitriol. Photoproduction of calcitriol is limited by environmental conditions such as season, latitude, altitude, clothing, sunscreen, pollution and physiological conditions such as skin pigmentation, aging.

Vitamin D is remarkable considering the numerous cellular activities maintained by its active form, calcitriol. When vitamin D level is inadequate, many of these activities begin to decline, thereby setting the stage for the onset of many non-communicable diseases. Calcitriol influences a variety of biological pathways in parallel. In addition, basic mechanism of action that leads to the development of most NCDs is still not clear. Therefore, calcitriol's involvement in their molecular pathogenesis pathways is likely difficult to prove.

Most cells in the body, including most cancerous cells, express Vitamin D receptor. Most tissues have not only VDRs, but also the hydroxylase enzyme that converts calcidiol to the active form, calcitriol. Calcitriol is a key calciotropic hormone. It's calciotropic activities have immense significance in maintaining skeletal health. Poor vitamin D levels and subsequent

poor calcium and phosphate levels pave the way for non-communicable bone diseases such as osteoporosis, osteomalacia and in children, rickets.

Current data demonstrate that calcitriol activities extend beyond maintaining skeletal health. The effects of calcitriol extend to tissues that are not necessarily involved in calcium and phosphate homeostasis. Receptors for vitamin D have been detected in respiratory, renal, cardiovascular, gastrointestinal, reproductive, nervous and immune system. Thereby many chronic NCDs such as COPD, asthma, diabetes, cancer, CVD, hypertension, MS, chronic kidney disease, chronic liver disease have been linked to vitamin D deficiency.

When the levels are adequate, calcitriol acts to reduce inflammation, and inflammation is the first step in the pathway of pathogenesis of many NCDs. Poor vitamin D levels not only increases inflammation but also oxidative stress, and expression of immune cells, i.e., monocytes and macrophages. Vitamin D also maintains normal mitochondrial activity by supporting respiratory chain's physiological electron flow, thus preventing the formation of ROS. Additional molecular mechanisms that are directly or indirectly regulated by calcitriol are the critical elements that coherently modulate the cell cycle progression. In fact, calcitriol was found to have the ability to inhibit proliferation and induce terminal differentiation of tumor cells and various other cells. The antiproliferative effects of calcitriol have been repeatedly confirmed in many laboratories.

For most NCDs discussed in this paper, vitamin D supplementation in deficient population was found to have beneficial effect on disease progression and in some cases even potentially prevent disease incidence. In some cases, the effects have been proven in vitro or in animal trials in vivo but not in humans. For example, numerous animal studies have showed that calcitriol or its analogs can reduce cancer growth in vivo, yet clinical trials in humans are still missing.

Although a multitude of epidemiological studies suggest an inverse relationship between vitamin D status and a large number of NCDs, such relations have not been universally confirmed. Conclusive data from clinical and interventional studies are missing for many of these disease entities. Study limitations limit the extent to which inverse relations can be attributed to vitamin D, and additional studies are needed to further understand the nature of this association. The long-term outcome of cholecalciferol therapy in patients with various chronic NCDs needs further exploration through long-term intervention studies.

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