THE POWER OF VITAMIN D

AN UPDATE ON ITS ROLE IN HEALTH AND DISEASE

Editors:
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The Power of Vitamin D: An Update on its Role in Health and Disease

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PREFACE

Welcome to the world of Vitamin D, a fascinating nutrient with profound effects on human health. This book is a comprehensive guide to understanding the various aspects of Vitamin D, from its discovery and historical significance to its role in modern medicine and ongoing research.

Vitamin D is often referred to as the "sunshine vitamin" due to its unique synthesis in the skin upon exposure to sunlight. However, its importance goes far beyond its role in calcium metabolism and bone health. Vitamin D receptors are found in nearly every tissue and cell in the body, indicating its involvement in a wide range of physiological processes. In recent years, research on Vitamin D has expanded rapidly, uncovering its potential roles in immune function, cardiovascular health, cancer prevention, and mental well-being. The emerging evidence suggests that Vitamin D deficiency may be linked to a variety of chronic diseases, making it a subject of intense interest among scientists, healthcare professionals, and the general public.

This book is divided into several chapters, each focusing on a different aspect of Vitamin D. The first chapter provides an introduction to the history of Vitamin D, tracing its discovery and early research to the present day. The second chapter delves into the immunoregulation of Vitamin D, explaining how it is synthesized, metabolized, and immune-regulated in the body.

The third chapter explores the role of Vitamin D in ocular health. The fourth chapter discusses Vitamin D deficiency and its protective role as sunscreen against cancer-causing ultraviolet rays of sunlight and how to increase Vitamin D levels through diet, supplements, and sunlight exposure.

The fifth chapter examines the latest research on the Endocrinology of Vitamin D and its potential therapeutic applications, from preventing chronic diseases to improving overall health and well-being. The sixth chapter describes malaria known to mankind, Cerebral Malaria (CM), caused by Plasmodium falciparum, which kills ~400,000 people annually, the majority of whom are children. The seventh chapter describes the factors influencing cerebral malaria. Chapter 8 explores the role of Vitamin D against thrombosis and stroke. Finally, chapter 9 concludes with a discussion of future directions in Vitamin D research and its potential impact on public health.

Whether you are a healthcare professional seeking to deepen your understanding of Vitamin D or a curious reader interested in the latest developments in nutrition and health, this book offers a comprehensive and accessible guide to the fascinating world of Vitamin D.

We hope that you find this book informative and engaging and that it inspires you to explore the many facets of Vitamin D and its impact on human health.

Happy readings

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CHAPTER 1

Vitamin D in Human Health and Disease: An Introduction

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Abstract: Vitamin D, classified as a group of secosteroid hormones, is synthesized endogenously through ultraviolet radiation or obtained exogenously from food sources and supplements. Its primary function involves enhancing the absorption of calcium, magnesium, and phosphates in the intestines, exerting diverse biological effects. Vitamin D supplementation within the range of 75–125 nmol/L has demonstrated potential in preventing viral infections, attributed to its molecular mechanisms, including the inhibition of viral replication, anti-inflammatory properties, and immunomodulation.

To comprehensively understand the impact of Vitamin D on viral infections, further exploration through randomized controlled trials and cohort studies is imperative. This chapter addresses various aspects, including the status of Vitamin D in COVID-19 patients, its synthesis, global and Indian Vitamin D status, endocrinological aspects, and influencing factors such as gender differences, pollution, gut microbiota, and geographical variations.

Particular attention is given to the current interest in Vitamin D concerning its potential role in the ongoing COVID-19 pandemic. The chapter delves into its influence on factors contributing to immunocompetence in both innate and adaptive immunity. This comprehensive coverage is intended for inclusion in the suggested book, "The Role of Vitamin D in Human Health and Disease," encompassing a variety of topics. Looking ahead, the trajectory of biomedical research should explore Vitamin D's protective effects in diverse models of cardiovascular and infectious diseases. By delving into these areas, future studies can contribute valuable insights into the broader implications of Vitamin D for human health and its potential applications in preventing and managing various diseases.

Keywords: COVID-19, Cancer, Vitamin D endocrinology, Metabolic disorder, Neurological disorder, Ultraviolet radiation, Vitamin D status.

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VITAMIN D INTRODUCTION

Vitamin D deficiency is recognized global health concern that affects one billion people of all ethnicities, ages, infants, and pregnant women [1]. The present chapter describes the introductory part of the book that discusses vitamin D synthesis, its status in the world and India, molecular endocrinology, and its role in infertility and immunity. Various factors associated with vitamin D synthesis are age, ethnicity, pollution, diet, and ultraviolet radiation. The other topics include clinical association of Vitamin D deficiency with stroke, and a trilogy of vitamin D, COVID-19, and neurological impairment.

VITAMIN D SYNTHESIS

Vitamin D synthesis is a two-stage process that begins with the production of pre-Vitamin D after irradiation of 7-dehydrocholestrol by ultraviolet (UV) radiation. Antigen-presenting cells (macrophages and dendritic cells) synthesise the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25 (OH)2D) from its precursor 25-hydroxyvitamin D (25-OHD) *via* the enzyme 1α-hydroxylase (CYP27B1) [2]. Many factors control the probability of suitable UV photons reaching a molecule 7-dehydrocholestrol in the skin. Available solar radiation, skin pigmentation, and age are the determining factors for Vitamin D synthesis [3]. Vitamin D enters the blood circulation and binds to the vitamin D-binding proteins. Vitamin D can be broken down in the skin when the UV-irradiation increases. Two major factors influence Vitamin D synthesis such as extrinsic (environmental) pathways and intrinsic (personal) factors.

NATIONAL AND INTERNATIONAL STATUS OF VITAMIN D

The status of Vitamin D and the prevalence of vitamin D deficiency have been reported in many countries. If the serum level of 25-hydroxyvitamin D is lower than 25nm/L, it is considered a risk condition in many parts of China, the Middle East, Magnolia, and India [3, 4]. The major risk groups associated with poor vitamin D status are low birth weight children, pregnant women, old age, non-western immigrants, and post-COVID-19 patients [5 - 8]. Vitamin D Standardization Program (VDSP) was founded in November 2010 with the explicit objectives of advocating for the accuracy and comparability of 25-hydroxyvitamin D (25(OH)D) concentration measurements across different time periods. Vitamin D Standardization Program (VDSP) represents global initiatives led by the Office of Dietary Supplements at the National Institutes of Health (NIH) in conjunction with the U.S. Centers for Disease Control and Prevention (CDC). The primary goals at the program's outset included conducting a national Vitamin D survey, outlining our standardization procedure, and introducing the CDC Vitamin D Certification program [1].

MOLECULAR ENDOCRINOLOGY OF VITAMIN D

The molecular Endocrinology of Vitamin D is defined by the following events:

- The ligand 1α,25-dihydroxyvitamin D3 (1,25(OH)2D3) exhibits a strong affinity for the vitamin D receptor (VDR) located on the nuclear membrane.
- The transcription factor of the vitamin D receptor (VDR) is the exclusive target of 1α,25-dihydroxyvitamin D3 (1,25(OH)2D3) within the nucleus.
- Advanced sequencing techniques like ChIP-seq and FAIRE-seq were employed in cellular model systems to study Vitamin D signalling [3].

CANONICAL FUNCTION OF VITAMIN D

- It stimulates calcium absorption.
- It serves as a restricting factor in absorption.
- Its absorption relies on both 25(OH)-D and Calcitriol when below 80 nmol.
- The nuclear VDR has been isolated from a variety of target cells and tissues, suggesting that vitamin D compounds may have therapeutic potential throughout several body systems.
- Conducting preclinical and clinical trials for addressing diverse cancer types, osteoporosis, and immunosuppression.
- Activating the autophagy for the vitamin D production.

VITAMIN D ASSOCIATED FACTORS

Chapter 6 delves into the various factors linked to Vitamin D synthesis, including nutrient intake, diet, ultraviolet exposure, anthropometric characteristics, physical activity, signs, gender differences, diurnal and circadian rhythms, and gut microbiota. Additionally, children, adolescent girls, and pregnant women represent specific groups at risk of vitamin D deficiency.

VITAMIN D AND CLINICAL ASSOCIATIONS WITH COVID-19 PATIENTS

Implementing preventive health measures can significantly decrease the risk of infection, progression, and severity. Emerging reports highlight cases of ischemic stroke, hemorrhagic stroke, and cerebral venous sinus thrombosis (CVST) associated with the new COVID-19 variant. Notably, Spain, Italy, and Switzerland, regions where the aged population has notably low Vitamin D levels, have been grappling with the impact of COVID-19. Investigating the correlation between COVID-19 and stroke and cardiovascular diseases is crucial. There exists an unmet need to delve into the role of Vitamin D in severe COVID-19 cases and its potential as a neuroprotective and anti-inflammatory agent that may inhibit ischemic brain injury in affected patients [9]. Vitamin D has the ability to down-

CHAPTER 2

Antigen Presenting Cells: Synthesizing Vitamin D for Immune Regulation

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Abstract: Vitamin D is necessary for skeletal health, and a recent study has revealed that it is also a crucial immune system regulator in addition to its skeletal functions. Vitamin D receptors (VDR) are found in a wide range of cell types, including antigen-presenting cells (macrophages), T cells, B cells, and monocytes, indicating that vitamin D may operate as a localized endogenous regulator of immune function. At the innate level, macrophages and dendritic cells create intracrine vitamin D, which stimulates antimicrobial protein production. Vitamin D absorption by macrophages and dendritic cells appears to be important in regulating T-cell responses, ultimately inhibiting inflamed Th1 and Th17 cells and activating immune-tolerogenic T-regulatory cells. This chapter's goal is to offer an update on our current understanding of vitamin D's critical immunological activities while also emphasizing novel, lesser-known immune effects of vitamin D. In vivo studies on the role of vitamin D supplementation as an immune-boosting strategy. This has gained prominence in recent months as a result of the global coronavirus disease 2019 health disaster, highlighting critical new objectives for future vitamin D and immune function research.

Keywords: Antigen-presenting cell, Adaptive immunity, Innate, Vitamin D.

INTRODUCTION

Vitamin D has other pleiotropic activities, besides maintaining skeletal health [1]. The discovery of vitamin D has a long history, and its deficiency is a known cause of classical bone disease (rickets). Initially classified as a steroid hormone, but later reclassified as a vitamin. Vitamin D is a fat-soluble vitamin that can be obtained simply from a few food sources or by means of the photochemical reactions and thermal transformation of the cholesterol precursor 7-dehydrocholesterol in the skin *via* ultraviolet (UV) B (280-310 nm) sunlight [2 - 4]. Vitamin D production occurs productively in the skin only when the position

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of sunlight is greater than 45 degrees. Many countries in North America and Europe do not create enough vitamin D because of limitations in sunlight exposure transcription [4]. Vitamin D is accessible in two forms: D3 (cholecalciferol), which is largely produced in the skin by UV-B solar radiation, and D2 (ergocalciferol), which is obtained by the dietary intake of plant sources [5]. Vitamin D is mainly transformed into an active form in the liver *via* a hydroxylation reaction triggered by cytochrome P450 family 2 subfamily R member 1 (CYP2R1) enzymes, followed in peripheral tissues (kidney) by cytochrome P450 family 27 subfamily B member 1 (CYP27B1) enzymes. The active form of vitamin D (25hydroxyvitamin D (25D)) has a long half-life and varies periodically with skin vitamin D production. Vitamin D affects the expression of several genes *via* a nuclear receptor known as the vitamin D receptor (VDR) [4]. Furthermore, vitamin D regulates calcium and phosphate homeostasis by modulating PTH production in circulations, and an imbalance leads to rickets and osteomalacia [3]. In addition to mineral and bone advantages, vitamin D controls arterial blood pressure and avoids cardiovascular issues, modifies immune responses, regulates insulin production and prevents diabetes, protects against certain cancers, and offers renoprotection [6].

Multiple investigations have revealed that vitamin D communicates with antigen-presenting cell types (APCs) and T-lymphocyte cells (T-cells) to initiate and regulate various phases of the immune response. The kinetic model by Susmita *et al.* indicated that an adequate amount of vitamin D is crucial for the immune system's smooth functioning as well as the management of both hyper-regulation and inflammation [7]. Autoimmune illnesses such as psoriasis, rheumatoid arthritis, and uveitis have grown more common in recent years. Immunosuppressants such as methotrexate and synthetic glucocorticoids are often used in medical therapy, although they can be hazardous over time or at larger dosages. However, keeping an adequate level of vitamin D may assist in preventing autoimmune disease through regulating immune cells. This chapter addresses vitamin D's function as an immune regulator, in addition to how its presence influences both adaptive and inherent immunity.

ANTIGEN-PRESENTING CELLS

Antigen-presentation cells (APCs) are a variety of immune cell types that regulate the immune system's cellular response by processing and delivering antigens to T cell lymphocytes (dendritic cells, macrophages, Langerhans cells, and B cells). Professional APCs include dendritic cells, macrophages, and B cells, whereas non-professional APCs include thymic epithelial cells [8, 9] and stromal cells (non-epithelial cells) such as fibroblasts, endothelial cells (ECs), smooth-muscle cells (SMC), and leukocytes that function in presenting antigens for brief periods

[10]. In addition, dendritic, macrophage, and B cells are the primary cells that deliver antigens for T cells, whereas follicular dendritic cells are the primary antigen-presenting cells for B cells. APCs break down endogenous proteins into peptides, which are subsequently loaded onto MHC molecules — class I MHC molecules for CD8-expressing T lymphocytes and class II molecules for CD4-bearing cells [8].

The Effects of Vitamin D on Antigen-presenting Cells

Numerous studies conducted over the past two decades have shown the significance of vitamin D in the regulation of immunological processes/responses. In essence, these consequences may be controlled not only by the endocrine mechanisms of circulatory calcitriol but additionally by the paracrine (based on cell-cell communication that leads to the production of signal-inducing changes in nearby/adjacent cells and modulating their differentiation or behavior) and intracrine (autocrine) mechanisms of 1,25-dihydroxycholecalciferol (1,25(OH)2D3) synthesized from its precursor 25-hydroxyvitamin D3 (25(OH) [11]. Both vitamin D receptor (VDR) and 25-hydroxyvitamin D3 1--hydroxylase (CYP27B1) are expressed in a variety of immune cells including dendritic cells macrophages, and T and B cells, and can thus synthesize the bioactive form of vitamin D that modulates both the innate and adaptive immune systems and has anti-inflammatory effect [11 - 13]. Vitamin D deficiency has been linked to increased autoimmune as well as susceptibility to infection. Because immune cells in autoimmune disorders respond to vitamin D's ameliorative actions, the benefits of supplementing vitamin D-deficient persons with an autoimmune disease may extend beyond the effects on bone and calcium homeostasis [13].

Vitamin D and the Development and Function of Immune Cells

Numerous studies have found that vitamin D is closely linked to immune-related illnesses. Vitamin D receptors may be discovered in the majority of cell types involved in innate and adaptive immune responses [14]. Granulocytes, dendritic cells, monocytes/macrophages, and lymphocytes are immunological cells that regulate the immune system. Vitamin D does not govern the immune system, although it does influence monocyte and macrophage differentiation [15]. Vitamin D and the vitamin D-activating enzyme 1-hydroxylase (CYP27B1) have also been found to be expressed in dendritic cells, monocytes/macrophages, and T and B cells (Fig. **1**) [16].

CHAPTER 3

Unravelling Role of Vitamin D in Ocular Health

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Abstract: Vitamin D serves as a versatile hormone, with its well-known role in regulating calcium balance being just one aspect of its functions. Recent research highlights its involvement in various biological processes that contribute to overall health, including its local utilization within different tissues.

Notably, emerging evidence indicates a significant link between vitamin D and eye-related conditions. This chapter provides a comprehensive overview of its role in maintaining ocular health, and the connections between vitamin D and different ocular disorders, highlighting its potential therapeutic applications in these conditions.

Keywords: Dry eye disease, Diabetic retinopathy, Glaucoma, Keratoconus, Retinoblastoma, Thyroid ophthalmopathy, Uveitis, Vitamin D.

INTRODUCTION

Since the last two decades, interest has been steadily increasing in understanding how vitamin D possibly contributes to the preservation of human health and numerous bodily processes. Furthermore, alongside its role of maintaining calcium balance, other recently discovered roles include regulation of the immune system, maintenance of the barrier systems, human genome regulation, and maintenance of cellular homeostasis [1].

The momentousness of vitamin D in numerous facets of human well-being has been firmly established in the earlier chapters of the book. However, the study of vitamin D's impact on ocular tissues and diseases is also extremely relevant from a biological perspective due to the broad manifestation of vitamin D receptors (VDR) and regulatory enzymes across the entire eye. Hence, this chapter essentially explores the relation and roles of vitamin D with ocular well-being and disease processes.

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VITAMIN D IN OCULAR TISSUES

It is well understood and elaborated in the previous chapters of this book that, when subjected to ultraviolet B (UVB) rays that are received from the sun, the skin produces vitamin D, which is the body's main source of the vitamin [2]. Vitamin D must go through a couple of hydroxylation processes before getting activated physiologically, regardless of whether it is synthesised or consumed in food [3].The liver is the major site for the metabolism of vitamins in the body [4]. However, the presence of VDRs in the ocular structures such as the epithelial layer of the cornea, the endothelial layer of the cornea, ciliary body, the crystalline lens, and retinal layers including the pigment epithelium of retina (RPE), layer of photoreceptors, the retinal layer of ganglion cells (RGC) and the inner nuclear layer is indicative of local activity of the vitamin in the eyes [5, 6]. It was decades before this, when a calcium-binding protein called calbindin, which is dependent on vitamin D, was initially employed to identify vitamin D target cells in the human retina. The fact that the retina expresses this protein is suggestive of vitamin D playing an essential role in controlling cellular activities in this ocular tissue [7].

In line with these findings, it was recently established that many different ocular cell types, including the cells in the epithelium of the cornea, endothelium of the cornea, scleral fibroblasts, cells in the non-pigment epithelial layer of the ciliary body, as well as cell linings of the adult retinal pigment epithelium, have been shown to have vitamin D hydroxylases in recent investigations. This shows that the apparatus required to actuate and control the metabolism of the vitamin is available in ocular cells. Additionally, recent studies have shown that several of these cell types are capable of converting vitamin D from its inactive form, 25D3, into its biologically active form, 1,25D3, which is crucial for a number of cellular activities in the eye [8, 9].

Fascinatingly, when exposed to UVB in culture, epithelial cells at the limbus demonstrated the ability to synthesise vitamin D *de-novo*, akin to the capability observed in skin cells. This intriguing discovery suggests that these ocular cells might serve as a specialised source of the vitamin for the ocular surface. Furthermore, it is plausible that additional sources of vitamin for the eye could come from aqueous humour, tear film, and vitreous humour [9, 10]. These putative vitamin D sources show how complex and varied vitamin D metabolism is inside ocular tissues and provide important insights for comprehending its function in preserving ocular health.

FUNCTION OF VITAMIN D IN MAINTAINING OCULAR HEALTH

Due to the broad expression of its receptors and regulatory enzymes throughout the eye, vitamin D is crucial for sustaining ocular health. Some of the significant ways in which vitamin D supports ocular health are described in the subsequent subsections:

Maintaining a Healthy Ocular Surface and a Stable Tear Film

Many researchers have linked Vitamin D to maintaining a healthy ocular surface and a stable tear film, which are essential for preventing and managing dry eye disease. In line with this, it has been proven that there is a high concentration of 25(OH)D3 in the pre-corneal tear fluid [11]. Additionally, vitamin D's role in the aetiology of dry eyes and related symptomatology is clearly given that it is responsible for a variety of bodily activities, including those related to the eyes in particular, as shown in Fig. (**1**) [12].

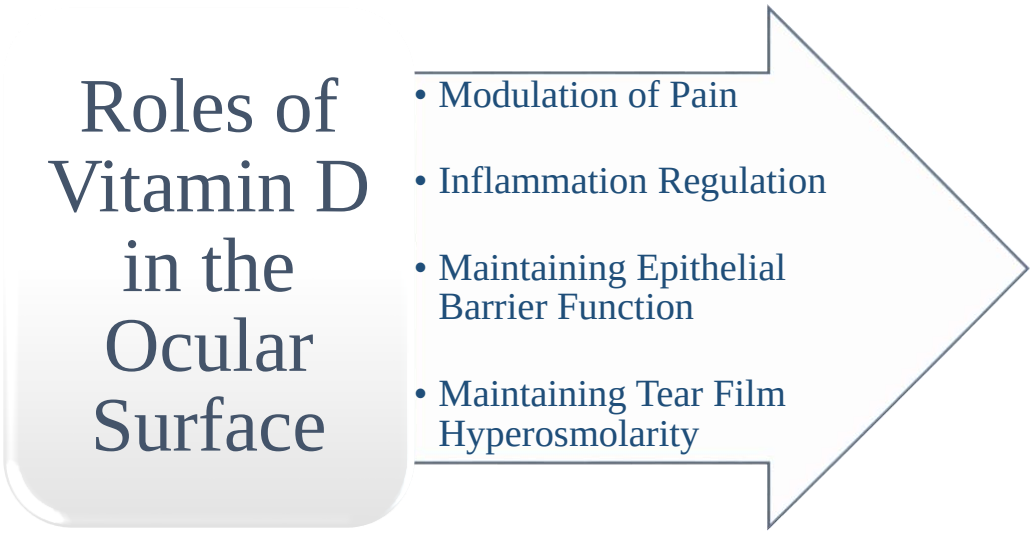

Fig. (1). Roles of vitamin D in the ocular surface.

MODULATION OF PAIN

An optimum amount of vitamin D is essential to reduce symptoms of ocular discomfort caused due to dry eyes or associated ocular inflammation. Research showing an antagonistic relationship between blood 25(OH)D3 levels and ocular surface disease index (OSDI) scores in people with evaporative dry eye also supports the pain-modulating effects of vitamin D in the eyes [13].

CHAPTER 4

Protective Role of Vitamins and Sunscreen against Cancer Causing Ultraviolet Rays of the Sun

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Abstract: Skin cancer is a universal health problem that is becoming more common due to a number of causes, such as environmental factors and lifestyle choices. Sun exposure that exposes oneself to ultraviolet (UV) rays is the main cause of skin cancer. With growing awareness of the damaging effects of UV radiation, preventive measures have become increasingly important, vitamin D and sunscreen are major weapons in the fight against skin cancer. Vitamin D can be produced by the body through ultraviolet light exposure. Only a small amount of exposed skin is needed to produce vitamin D. Deficiency of Vitamin D can lead to many chronic effects on human health. Although a small amount of vitamin D is retained in the skin, humans must synthesize vitamin D from solar radiation to maintain calcified skeletons.

Higher levels of vitamin D are associated with protection against cancer development, including melanoma. The use of sunscreen can prevent deleterious effects caused by UV radiation thus reducing the risk of skin cancer. Sunscreen inhibits the harmful radiation of sunlight in the form of UV radiation from reaching deeply into the skin thus greatly preventing UV-induced skin cancer, preventing damage to the cells below. Previous studies have shown that sunscreen use reduces the risk of squamous cell carcinoma and melanoma skin cancers. Sunscreens represent a practical approach to photoprotection for the skin. Sunscreens are capable of preventing other types of skin cancers such as SCCs in animals. Sunscreens absorb UVR with high intensity, which prompts excitation to a higher energy state and upon returning to the ground state, the absorbed energy is transformed into a longer wavelength with lower energy.

Based on the amount of UV protection they provide; chemical sunscreens can be categorized. Avobenzene, oxybenzone, meradimate, and tetraphthalydinedicamphor sulfonic acid are commonly recognized components of UVA sunscreens. Thus, this chapter examines the major role of vitamin D and sunscreen in protecting against skin cancer from the damaging effects of UV radiation in sunlight.

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Keywords: Melanoma, Skin Cancer, Sunscreens, UV-radiation, Vitamin D.

INTRODUCTION

Sun is the major source of Electromagnetic Radiations. One type of electromagnetic radiation that the sun emits is UV radiation. Three types of radiations are distinguished as: UVA, UVB, and UVC. The types of radiation that can seriously harm skin include UVA and UVB, and they can reach the surface of the Earth [1]. Exposure to harmful UV radiation has been linked to a number of skin disorders, such as sunburn, early aging, and—most frighteningly—skin cancer [2]. UV rays are a type of electromagnetic radiations measuring in the wavelength from 100 to 400 nanometres (nm) [3]. UV-A and most parts of UV-B are not absorbed by the ozone layer and penetrate deep into the skin, up to the epidermal layer where the melanocytes reside in the basal layer, and are primarily responsible for premature skin aging. Among different types of cancers, skin cancer incidence has been increasing. The total number of persons treated for all skin cancers combined increased by 44% from the period 2002–2006 to 2007–2011 [4, 5]. The US Environmental Protection Agency has developed the UV Index, tool to help individuals avoid overexposure to the sun. Occupational exposure to UV can increase the risk of skin cancer among outdoor workers. The incidence of melanoma has been increasing for several decades, with rates doubling between 1982 and 2011. Most skin cancers are caused by a combination of both non-modifiable (eg, genetic) and modifiable (eg, environmental) risk factors. The most common modifiable risk factor for skin cancer is exposure to ultraviolet radiation (UV). Genetic factors greatly influence the risk of skin cancer. The following individual characteristics increase the risk of skin cancer: having a naturally fair skin tone, light-coloured eyes, blonde or red hair, dysplastic nevi or many common moles, and skin that burns, freckles, reddens, or becomes extremely harmful after long exposure to sunlight [6, 7]. UV exposure stimulates melanocytes to produce melanin, which can appear as tanned skin, and indicates damage to the skin, skin cells, and DNA; more intense exposures can result in sunburn, indicating cell death [8]. UV radiation varies dramatically both daily and seasonally, as well as by latitude and altitude [9]. Vitamin D supplements may have a protective effect against skin cancer, especially melanoma, according to some studies [10]. The role of Vitamin D is capable of repairing the DNA damage caused by sun exposure and preventing the growth of abnormal cells [11]. However, more research data is required to estimate the optimal dose and duration of vitamin D supplementation for skin cancer prevention [12]. In experimental studies, vitamin D metabolites enhance the apoptosis of malignant cells, inhibit angiogenesis and proliferation, and increase differentiation, potentially reducing skin cancer development and improving prognosis after diagnosis. Identifying the role of vitamin D in the etiology of skin

cancer in humans is highly challenging because sunlight exposure can cause both vitamin D production and skin cancer [13]. Most of the studies are *in vitro* or on mouse models, with additional information from epidemiological and genetic studies on humans. The ingredients of the sunscreens contain chemical (organic) or physical (inorganic) compounds that are capable of blocking the harmful ultraviolet radiation from the sunlight [14, 15]. Physical sunscreen filters, such as titanium dioxide and zinc oxide, reflect or refract ultraviolet radiation away from the skin; however, experimental studies have shown that when particle sizes are very small, as in micronized sunscreens, the mechanism of action is similar to that of chemical filters [16]. More specifically, micronized zinc oxide and titanium dioxide behave as semiconductor metals, which absorb ultraviolet light throughout most of the electromagnetic spectrum. Thus, vitamin D and sunscreen are important for the prevention of skin cancer caused by UV radiation of sunlight.

Skin Cancer

Among UVR, the most damaging rays are UVB rays which affect the outer layers of the skin, causing sunburn and capable of inducing squamous and basal cell carcinomas [17]. Whereas, UVA rays penetrate deep into the skin, harming skin tissues like elastin and collagen fibers and raising the chance of melanoma, the most deadly type of skin cancer [7]. Across electromagnetic radiations, UV rays have chronic effects on skin health, emphasizing the need for preventive measures [18].

Squamous cell carcinomas and melanomas are some common types of skin cancer induced by UV rays in the sunlight [19]. Though it is not life-threatening, but if left untreated, it spreads to the other parts of the body. Amongst people with sunburns, this type of skin cancer is usually found beneath the surface of the sunburn area. Symptoms may include the presence of wart-like or mole-like structures on the skin, rough patches or sores with a scaly crust. In skin cancer, the modification in the DNA structure of the skin takes place along with biochemical changes [20]. However, skin cancers can be prevented to a large extent by using sunscreens with an SPF of 30 or more, wearing protective clothing, wearing sunglasses, often maintaining healthy skin, *etc.*

Another type of skin cancer that is life-threatening is melanoma type of cancer. It is the cancer of melanocytes, which is responsible for the production of melanin pigments in the body, which provide characteristic colour to the skin [21]. UV radiation is capable of inducing DNA damage that can lead to the formation of melanomas (Fig. **1**). Unusual moles or tanning of the skin is a symptom of melanomas. In tropical countries like India where exposure to sunlight is very

CHAPTER 5

Unraveling Role of Vitamin D in Cerebral Malaria

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Abstract: Vitamin D is classically known as a regulator of the mineral metabolism in bones particularly calcium and phosphorous; however recent research developments continue to uncover its unconventional roles. Vitamin D has a pleiotropic effect on various regulatory mechanisms that control host defense, inflammation, immunity, DNA repair, and other processes. Many studies suggest a critical role of Vitamin D in immunity and defense against pathogens. Many bacterial and viral infections are often correlate with Vitamin D deficiency or insufficiency and restoring Vitamin D levels manifests beneficial consequences. Owing to the beneficial effect of Vitamin D in diseased conditions, several studies have explored the therapeutic potential of Vitamin D against one of the deadliest diseases, malaria. The most severe form of malaria known to mankind, Cerebral Malaria (CM), caused by *Plasmodium falciparum*, kills ~400,000 people annually, the majority of whom are children. Although effective antimalarial treatment is available, the mortality rate of CM is still 15%–25% which necessitates the development of an effective adjunct therapy to combat the etiology of CM. Vitamin D deficiency has been found to be linked with higher mortality rates in many infectious diseases including malaria. Many studies on mouse model as well as human trials have indicated that Vitamin D treatment protects or reduces the severity of CM. Vitamin D insufficiency has been found to be associated with the emergence of severe malaria in humans. However, a few reports on Vitamin D treatment of malaria showed conflicting results. Studies on large cohorts are necessary to determine whether Vitamin D supplementation may help to prevent and treat CM. In this chapter, we present and discuss Vitamin D and its effect on the immune system, and on various infectious diseases. The main focus is given to studies of Vitamin D treatment, and its effect on cerebral malaria in mouse models and in human trials.

Keywords: Cerebral malaria, Infectious disease, *Plasmodium falciparum*, *Plasmodium berghei*, Vitamin D, Vitamin D receptor.

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INTRODUCTION: VITAMIN D AND CEREBRAL MALARIA

Vitamin D

The energy of sunlight has been used as a source to generate carbohydrates since the life form began to evolve in the ocean over 1 billion years ago. It is noteworthy that for more than 500 million years, ocean phytoplankton (such as *Coccolithophore* and *Emilianiahuxleyi*) have had the capability to photosynthesize Vitamin D in addition to glucose [1] while land vertebrates developed this capability ~350 million years ago [2]. Vitamin D is a group of fat-soluble secosteroids that can be synthesized only by a photochemical process. It is involved in the regulation of calcium, magnesium, and phosphate metabolism, as well as immune response, brain development, and more [3, 4]. There are five types of Vitamin D (Vitamin $D_{1\text{-}5}$) but Vitamin D_2 (ergocalciferol)and D_3 (cholecalciferol) are the most important for humans [4, 5]. Photochemically, 7-dehydrocholesterol is utilized to synthesize Vitamin D_3 (cholecalciferol) in humans and other vertebrates via ultraviolet B-rays in the skin [6]. Two different hydroxylations are needed to make a biologically active form of Vitamin D($1,25(OH)_2D$). First hydroxylation is catalyzed by the enzyme vitamin D 25-hydroxylase (encoded by human gene *CYP2R1*) at position 25 in the liver, which yields 25-hydroxycholecalciferol (calcifediol or 25(OH)D) [5, 7]. The second hydroxylation is carried out on the synthesized calcifediol by enzyme 25-hydroxyvitamin D3 1-α-hydroxylase (encoded by human gene *CYP27B1*) in the proximal tubules of the kidneys at the 1-α position to form calcitriol (1,25-dihydroxycholecalciferol or $1,25(OH)_2D$) [8]. Calcitriol is transported throughout the body (*e.g.* intestines, kidneys, and bones), and is the most potent natural ligand of the Vitamin D receptor (VDR), which mediates most of the physiological actions of Vitamin D [9]. Additionally, monocyte and macrophages can also synthesize calcitriol, which acts locally as a cytokine, modulating host defense against microbial pathogen invaders by stimulating the innate immune system [9].

Magnesium helps to activate Vitamin D and is a cofactor in enzymatic processes that take place in the liver and kidneys. It appears that magnesium is necessary for all of the enzymes that metabolize Vitamin D [10]. Deficiency of either of these two nutrients has been linked to several disorders [10]. There are two kinds of Vitamin D receptors in the cells, one located on the cell surface, protein disulfide isomers family A member 3-PDIA3, which is also known as membrane-associated rapid response steroid-binding- MARRS receptor (Fig. **1**) or as ERp57.The other is in the nucleus, a nuclear receptor called Vitamin D Receptor (VDR), (Fig. **1**). Multiple pathways in various organ systems are affected by the binding of Vitamin D to these receptors (Fig. **1**). It helps manage glucose

homeostasis by boosting pancreatic-cell function and enhancing insulin sensitivity [11, 12]. By increasing the production of nitric oxide and preserving endothelial stability, it prevents vascular endothelial dysfunction [13, 14]. Furthermore, it exerts pro-differentiation and anti-proliferation effects on keratinocytes and numerous cancer cell types [15, 16]. Numerous studies have shown links between higher levels of blood 25(OH)D concentration and lower risks of infections, and for several chronic diseases which lends credence to the broad-spectrum health benefits of VDR activation [17 - 19]. Vitamin D is also referred to as an immunomodulatory agent due to its effect on the innate and adaptive immune systems. This function of Vitamin D is discussed below in detail.

According to estimates, ~1 billion people globally, including those in advanced nations in Europe, are either Vitamin D deficient or insufficient [20, 21]. Elderly people around the world are frequently deficient in Vitamin D, as are kids and adults because of insufficient Vitamin D in their diet and inadequate sun exposure [20, 22, 23]. A blood 25(OH)D level below 12 ng/ml (30 nmol/liter) is defined as Vitamin D deficiency and a blood 25(OH)D level of 12–20 ng/ml (30–50 nmol/liter) is termed Vitamin D insufficiency [24, 25]. Populations residing outside latitudes 35° N and 35° S of the equator are more susceptible to Vitamin D insufficiency due to limited seasonal sun exposure [26]. However, Vitamin D deficiency persists even in regions with plenty of sunshine, such as parts of Africa [27, 28]. Low consumption of Vitamin D-rich dietary items (such as meat, egg yolk, offal, and oily fish) may contribute to the reported Vitamin D insufficiency in Africa [29, 30]. Also, melanin in the skin is a natural protector against excessive UV light exposure. It also prevents Vitamin D synthesis, therefore people with darker skin produce less Vitamin D [22, 31 - 33]. In the United States, Vitamin D insufficiency is widespread among Hispanic and African-American populations, with wintertime levels falling precipitously [24]. Although dark-skinned people may live in regions with abundant solar ultraviolet radiation, their genetic makeup renders them vulnerable to reliance on UV-induced Vitamin D synthesis. Therefore, food-borne Vitamin D for the African population becomes vitally important [34].

Rickets usually caused by a deficiency of Vitamin D or calcium. The antirachitic action of food exposed to ultraviolet light and cod liver oil was discovered in the early 1920s and later the active substance was identified and named “Vitamin D”. Many studies clearly observed that Vitamin D deficiency appears to have a significant role in the etiology of chronic diseases and has been linked higher severity to several infectious diseases including tuberculosis, influenza, human immunodeficiency virus (HIV), and coronavirus SARS-CoV-2 [35 - 38]. Clinical improvement upon Vitamin D treatment has been documented for pulmonary TB [39]. Improvement and protection from influenza after Vitamin D treatment has

CHAPTER 6

Factors Influencing Vitamin-D Synthesis

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Abstract: This chapter underscores the importance of understanding the multifaceted nature of vitamin D, its synthesis, biological functions, and the range of factors that influence its levels. For vitamin D to be biologically active, it must undergo several changes after being largely synthesized by sun exposure on the skin. Geographical location, skin color, age, lifestyle, food habits, and environmental conditions are important factors that affect the synthesis of vitamin D. The efficiency of vitamin D synthesis is influenced by skin color due to variations in melanin levels. In contrast, geographic location and season have an impact on UVB radiation exposure. The skin's capacity to produce vitamin D is diminished by aging, and lifestyle factors like indoor activities further restrict sun exposure. Sun exposure is essential for obtaining the necessary amount of vitamin D, as diet alone cannot provide the necessary amount. Vitamin D metabolism can be hindered by obesity and some medical conditions, which increase the risk of deficiency. Individual vitamin D levels can also be impacted by the use of particular medications and genetic variations in vitamin D metabolism. A major global health concern is the prevalence of vitamin D deficiency, relating to several diseases, including cancer, diabetes, cardiovascular, and bone disorders. A comprehensive strategy includes sufficient sun exposure, dietary modifications, and supplementation when addressing the need to treat vitamin D deficiency.

Keywords: Age, Factors, Pigment, Sunlight, Vitamin D deficiency.

INTRODUCTION

Vitamin D, is a fat-soluble secosteroid that is present in two main isoforms: vitamin D2 and vitamin D3, also called ergocalciferol, and cholecalciferol, respectively [1, 2]. Unlike conventional wisdom, vitamin D is not a vitamin. It functions as a steroidal prehormone with endocrine, paracrine, and autocrine effects [3]. The isoforms of vitamin D are inactive biologically before being transported to the liver *via* binding to VDBP (vitamin D-binding protein) and

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converted to 25(OH)D by vitamin D 25-hydroxylase. It is then metabolized, firstly in the kidney's proximal tubule, *via* 25(OH)D 1-hydroxylase to $1,25[OH]_2D$ (1,25-dihydroxy vitamin D), called calcitriol. Calcitriol is the biologically active form of vitamin D [3, 2].

The production of antioxidants, neuroimmunomodulation, and neurotransmitter expression are all aided by vitamin D [4]. To control the reabsorption, mobilization, and absorption of phosphate and calcium, calcitriol enters the bloodstream and reaches the intended tissues that are the kidney, intestine, and bone. Calcitriol performs a number of functions, such as immune system mediation, lowering inflammatory cytokine production, and fostering tolerance [5]. Calcitriol's main function is to regulate bone and calcium metabolism, but its biological actions are much wider, including the differentiation, proliferation, and regulation of a wide range of cells, including keratinocytes, lymphocytes, endothelial cells, and osteoblasts.

The most prevalent and enduring metabolite of Vitamin D found in human serum, that is calcitriol possesses a half-life of 21 days and is used as an index to assess VD levels in humans. The standard reference range for this is 30-52 ng/mL [5] (Table **1**).

Table 1. Classification based on the amount of Vitamin D present in the body [5].

Classification	Range (Ng/mL)
Deficient	0- 10
Insufficient	10-30
Sufficient	30-150
Potentially toxic	>150

According to current thinking, vitamin D deficit is linked to an advanced possibility of diabetes, high blood pressure, heart failure, peripheral artery disease, acute myocardial infarction, different kinds of cancer, bone weakening, inflammation, rickets (in children) and osteomalacia (in adults), metabolic and cardiovascular disease, type I diabetes, persistent pain, multiple sclerosis, and decreased immunity.

Sunshine and sufficient exposure are considered the most versatile elements for decreasing reliance on dietary sources and sustaining an adequate plasma level [6]. However, various factors influence (Fig. **1**) UV ray exposure dose, including exposure time, variation in season, latitude, altitude, clothing, sunscreens, skin colour, age, pollution, and medications [6].

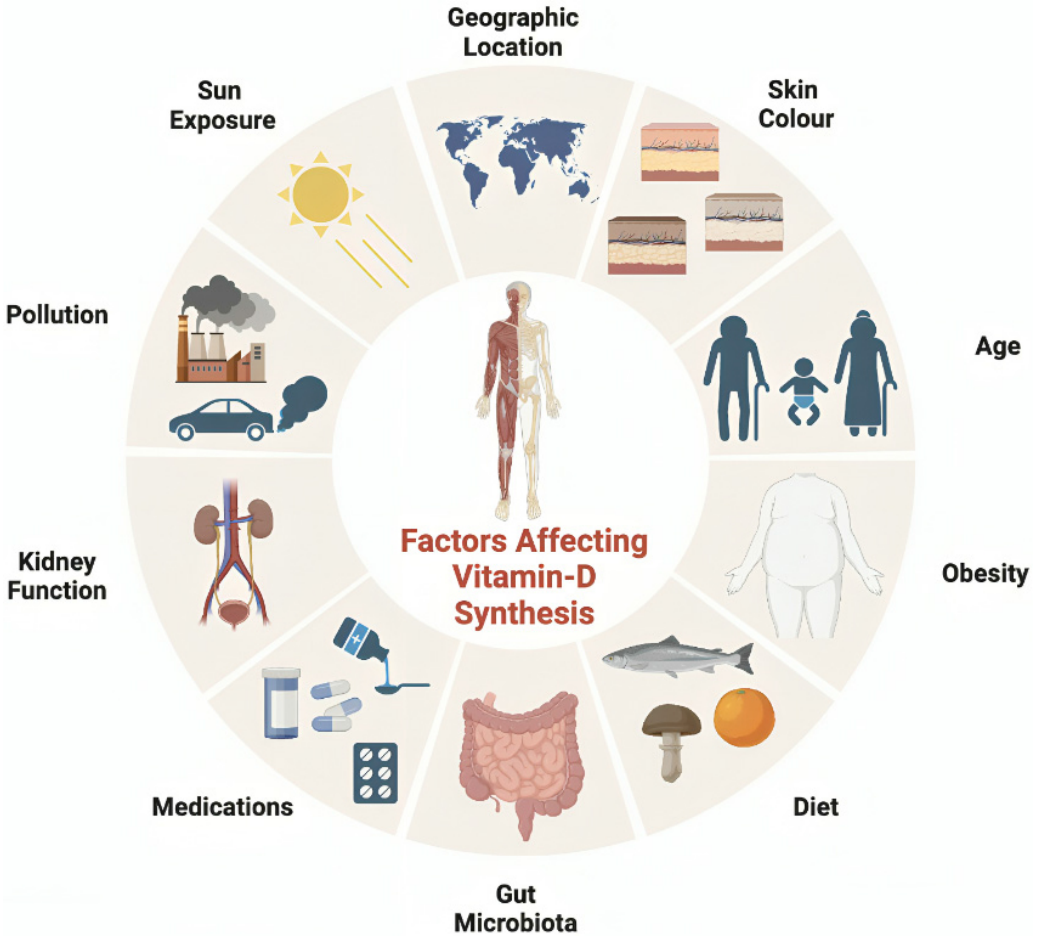

Fig. (1). This figure illustrates the multifactorial nature of Vitamin D synthesis, highlighting the diverse influences that can impact its production in the body. Factors include medication usage, kidney function, obesity, age, gut microbiome composition, sun exposure, and geographic location. Understanding the interplay of these elements is essential for optimizing Vitamin D levels and overall health.

SUN EXPOSURE

Sunlight is the natural and the most abundant source of vitamin D; after the skin gets exposed to sunlight (wavelengths 290–320 nm), the skin synthesizes vitamin D and it is absorbed *via* the intestine [7]. When exposed to UVB radiation from the sun, human skin generates vitamin D3 from 7-dehydrocholesterol (7-DHC). UV photons initiate a photochemical reaction that converts 7-DHC into pre-vitamin D3, which is then converted into vitamin D3 through a series of thermal isomerizations. Vitamin D3 reaches the target tissue, i.e, the liver, where it gets metabolized by CYP2R1 to 25(OH)D3 [25-hydroxyvitamin D3], and then to the kidney, where it develops into its active form, 1,25(OH)2D3 [calcitriol], that helps

CHAPTER 7

Role of Vitamin D in Stroke and Thrombosis

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Abstract: Vitamin D is a fat-soluble vitamin synthesized non-enzymatically by the epidermal layer of the skin and metabolized in the liver and kidneys. It regulates the immune response of the body, acts as a steroid hormone, and plays a major role in mineral homeostasis and skeletal health. Serum vitamin D levels in the range of 30-60 ng/ml (75-150 nmol/l) are considered normal. Deficiency of vitamin D has been linked to several cardiovascular diseases. It plays a substantial role in impeding the development of thrombosis, myocardial ischemia (MI), and stroke. Vitamin D in its active form of 1,25-dihydroxyvitamin D (calcitriol) exerts a vasoprotective effect on the blood vessels. Vitamin D deficiency has been observed as a common trait in most cases of cardiovascular problems. This hints toward the probable significant role played by Vitamin D in regulating cardiac health and the requirement of firm vigilance on vitamin D levels of the patients at risk. Despite growing evidence in favour of vitamin D against cardiovascular disorders, the administration of Vitamin D, over or along with other drug therapies, to patients with the deficiency and at risk for cardiovascular diseases remains debatable. This chapter aims to address the relationship between Vitamin D deficiency and major cardiovascular disorders based on the evidence emerging from various studies conducted across the globe. The process by which Vitamin D confers a protective effect, inhibiting platelet aggregation and enhancing NO production has also been discussed with an elucidation on the underlying mechanism involved in the process.

Keywords: Brain haemorrhages, Hypovitaminosis D, Pulmonary embolism, Thrombosis.

VITAMIN D AND THROMBOSIS: EXPLORING THE PROTECTIVE ROLE

Thrombosis, the formation of blood clots within blood vessels, is a critical biological response to prevent excessive bleeding following vessel damage. However, any disruption in the intricate balance of blood components can lead to

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the inappropriate formation or persistence of these clots, resulting in thromboticevents. This condition manifests in two primary forms: arterial thrombosis, characterized by blockage of an artery, and venous thrombosis or Venous Thromboembolism (VTE), involving the formation of clots in veins. Arterial thrombosis often leads to severe cardiovascular events such as heart attacks and strokes, while VTE can culminate in the development of deep vein thrombosis (DVT) or pulmonary embolism (PE). Prolonged immobility and sluggish blood flow are common contributing factors to venous thrombosis. Recent studies have illuminated the protective role of vitamin D in the prevention of thrombosis, particularly in the context of venous thrombosis. Vitamin D has been shown to possess an anti-aggregatory effect on platelets, thereby impeding the development of blood clots. Understanding the interplay between vitamin D and the complex mechanisms underlying thrombosis holds promise for the development of novel preventive and therapeutic strategies for this potentially life-threatening condition.

UNDERSTANDING THE LINK BETWEEN VITAMIN D AND THROMBOSIS: INSIGHTS FROM CLINICAL STUDIES

In Iran, an insightful case-control study highlighted the association between lower plasma 25(OH)D levels and idiopathic lower-extremity DVT, emphasizing the potential role of vitamin D in thrombotic events. Further investigations are required to discern the determinants and causative pathways of 25(OH)D in this context [1]. Similarly, a study in China underscored the independent predictive value of low serum 25(OH)D levels in DVT among patients with ischemic stroke during rehabilitation, indicating the critical involvement of 25(OH)D in DVT pathogenesis [2]. An investigation aimed at assessing the anticoagulant properties of vitamin D discovered its role in modulating the international normalized ratio (INR) with lower warfarin doses among DVT/PE patients, suggesting a potential interaction between vitamin D and conventional anticoagulant therapies [3]. In contrast, another study in Iran did not find a significant correlation between plasma 25(OH)D levels and P-selectin and hs-CRP in VTE patients, suggesting a more complex relationship between vitamin D and thrombosis [4]. In a European Population, an analysis suggested that while 25(OH)D levels might not directly influence VTE risk, the expression of key genes involved in Vitamin D metabolisms, such as the Vitamin D Receptor gene and AMDHD1 (amidohydrolase domain containing 1), displayed strong associations with VTE and PE, potentially serving as promising targets for therapeutic interventions [5]. Furthermore, a study evaluating the effects of vitamin D supplementation on thrombin generation reported potentially prothrombotic effects in individuals with vitamin D insufficiency, emphasizing the need for cautious interpretation and replication of findings in future studies [6]. Collectively, these clinical

investigations signify the pivotal role of maintaining adequate vitamin D levels as a potential preventive strategy against the development of thrombosis. By unravelling the intricate interplay between vitamin D and thrombotic processes, these studies offer crucial insights into the multifaceted relationship between vitamin D deficiency and thrombosis.

UNDERSTANDING THE IMPACT OF VITAMIN D ON PLATELET AGGREGATION

Platelets, integral components in the coagulation process, are crucial in preventing excessive bleeding following vascular injury. Arising from the fragments of megakaryocytes, these colorless, non-nucleated blood elements play a pivotal role in primary hemostasis, wherein they adhere to the site of injury, undergo activation, and ultimately aggregate to form a platelet plug. This process is intricately linked to the activation of the coagulation cascade, leading to fibrin deposition and secondary hemostasis. Notably, platelets are reservoirs for various chemicals, including serotonin, epinephrine, histamine, and thromboxane, which are released upon activation, subsequently stimulating local blood vessel constriction to facilitate clot formation. The haemostasis mechanism primarily encompasses the extrinsic and intrinsic pathways, converging at a common pathway that involves specific clotting factors. Vitamin D, known to exert a notable influence on platelet aggregation, has been implicated in various complications such as cerebrovascular accidents and ischemic heart diseases, where abnormal platelet aggregation has been identified as a contributory factor. The intricate interplay between vitamin D and platelet function underscores the significance of maintaining optimal vitamin D levels for the regulation of platelet activity and the prevention of associated cardiovascular complications. By unravelling the nuanced role of vitamin D in platelet aggregation, researchers aim to shed light on potential therapeutic strategies for managing platelet-related pathologies.

UNDERSTANDING THE LINK BETWEEN VITAMIN D AND PLATELET AGGREGATION

Studies have revealed a significant association between decreased vitamin D levels and heightened platelet activation, suggesting a potential interplay between vitamin D deficiency and increased platelet aggregation, particularly in patients with ischemic stroke and other cardiovascular disorders [7]. Findings from various research studies, including those conducted on diabetic patients undergoing dual antiplatelet therapy, further support this link, demonstrating that severe vitamin D deficiency is closely related to augmented platelet reactivity, especially in the context of ADP-mediated platelet aggregation [8]. Moreover,

CHAPTER 8

Vitamin D: The Conclusion and Future Prospective

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Abstract: Vitamin D, often referred to as the "sunshine vitamin," plays a crucial role in numerous physiological processes beyond its traditional association with bone health. It has a multifaceted role in the prevention of various diseases. Emerging research has highlighted its significance in immune modulation, cellular differentiation, and gene expression regulation, thereby influencing diverse health outcomes. A growing body of evidence suggests that vitamin D is intricately linked to immune system function, exerting both anti-inflammatory and immunomodulatory effects. Deficiency in this vitamin has been associated with an increased susceptibility to infections, autoimmune disorders, and chronic inflammatory diseases. Moreover, it has the potential to mitigate the risk of cardiovascular diseases. Vitamin D's impact on blood pressure regulation, endothelial function, and cholesterol metabolism underscores its role in maintaining cardiovascular health. The link between vitamin D deficiency and several types of cancer has garnered significant attention. Research suggests that vitamin D's anti-proliferative, pro-apoptotic, and anti-angiogenic properties may contribute to its protective effects against various cancers, including breast, prostate, and colorectal cancers. Furthermore, the role of vitamin D extends to mental health, with studies demonstrating its involvement in neurological functions and mood regulation. Deficiency has been associated with an increased risk of mood disorders such as depression and cognitive decline, emphasizing the importance of maintaining optimal vitamin D levels. This review also delves into the relationship between vitamin D and metabolic health. Vitamin D deficiency has been linked to insulin resistance, obesity, and type 2 diabetes. Adequate vitamin D levels positively influence insulin sensitivity, glucose homeostasis, and adipokine secretion. Thus, vitamin D's role in disease prevention extends far beyond its classical association with bone health. Its involvement in immune function, cardiovascular health, cancer prevention, mental well-being, and metabolic regulation highlights its multifaceted impact on various physiological systems. Public health strategies aimed at maintaining optimal vitamin D levels could have far-reaching implications for reducing the burden of chronic diseases and enhancing overall health outcomes. However, further research is warranted to elucidate the precise mechanisms underlying vitamin D's effects and to establish definitive guidelines for supplementation in disease prevention and management.

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Keywords: Cancer prevention, Chronic diseases, Immune modulation, Mental health, Obesity, Type 2 diabetes, Vitamin D.

INTRODUCTION

Vitamin D or calciferol is a crucial fat-soluble nutrient that goes beyond its conventional role in bone health. It plays an intricate and multifaceted role in various physiological processes that influence human well-being. Unlike other vitamins that primarily come from dietary sources, vitamin D exhibits a unique dual origin: it can be synthesized within the body upon exposure to sunlight, as well as acquired through certain dietary sources and supplements. This distinctive characteristic has led to a broader recognition of vitamin D as a pivotal player in maintaining overall health and preventing a spectrum of chronic diseases. Historically renowned for its role in preventing rickets, a childhood bone disorder characterized by weak and deformed bones, vitamin D's influence has now extended to encompass an array of physiological functions. From bolstering bone health by aiding calcium absorption to modulating the immune system, regulating gene expression, and potentially influencing mental health, vitamin D has garnered considerable attention from researchers, clinicians, and health enthusiasts alike. The significance of vitamin D in human health is underscored by its far-reaching implications across the lifespan. It impacts infancy, childhood, adolescence, and adulthood, exerting its effects on growth, immune response, and hormone regulation, and even potentially extending to the prevention of chronic diseases in later years. Emerging research continues to unveil the intricate mechanisms through which vitamin D contributes to a well-balanced and resilient physiology. As our understanding of vitamin D's importance evolves, so does the recognition of its potential involvement in various disease states. Links between vitamin D deficiency and conditions such as autoimmune diseases, cardiovascular disorders, diabetes, and certain types of cancer have prompted a surge of investigations into its role as both a preventive and therapeutic agent. The dynamic interplay between genetics, lifestyle, geographical location, and environmental factors further highlights the complexity of vitamin D's impact on human health. In this exploration of the importance of vitamin D in human health, we delve into its historical context, its diverse roles beyond bone health, and the compelling body of evidence linking it to a range of physiological functions and disease outcomes. By comprehending the multifaceted nature of vitamin D and its intricate influence on our well-being, we gain insights that can potentially reshape healthcare paradigms and empower individuals to make informed choices for their overall health and vitality [1, 2].

THE SIGNIFICANCE OF VITAMIN D IN BONE HEALTH

Vitamin D, a fat-soluble secosteroid, exerts a pivotal role in maintaining skeletal health through its regulation of calcium and phosphorus homeostasis, as well as its direct effects on bone cells. The integration of these mechanisms orchestrates bone mineralization, remodeling, and overall bone integrity. Vitamin D functions through its active metabolite, calcitriol (1,25-dihydroxyvitamin D or 1,25(OH)2D), which binds to the vitamin D receptor (VDR) and influences gene expression in various target tissues, particularly bone.

Intestinal Calcium and Phosphorus Absorption: Vitamin D's fundamental contribution to bone health stems from its facilitation of intestinal calcium and phosphorus absorption. Under normal physiological conditions, dietary calcium and phosphorus are absorbed in the small intestine with the assistance of vitamin D. Calcitriol enhances the expression of calcium and phosphorus transport proteins, such as calbindin-D9k and TRPV6, localized on the luminal membrane of intestinal epithelial cells. This upregulation promotes the active transport of calcium and phosphorus ions across the intestinal epithelium into the bloodstream, thereby maintaining adequate circulating levels of these minerals essential for bone mineralization [3 - 6].

Bone Remodeling Regulation: Vitamin D's impact on bone health extends to its regulatory influence on bone remodeling, a continuous physiological process that maintains bone integrity. Bone remodeling comprises two interconnected phases: bone resorption, orchestrated by osteoclasts, and bone formation, carried out by osteoblasts. Calcitriol modulates this process by indirectly regulating the differentiation and activity of osteoclasts and osteoblasts [7].

Osteoclast Regulation: Calcitriol, through its interaction with VDR, can suppress the differentiation and activity of osteoclasts, specialized cells responsible for bone resorption. This occurs *via* the inhibition of the receptor activator of nuclear factor-kappa B ligand (RANKL), a key factor involved in osteoclast formation and function. By controlling osteoclast activity, vitamin D contributes to the preservation of bone mineral density [8 - 10].

Osteoblast Stimulation: Calcitriol also promotes osteoblast activity indirectly by influencing calcium homeostasis. Adequate calcium levels are vital for osteoblast function, as these cells require calcium ions for mineral deposition during bone formation. Vitamin D's role in enhancing intestinal calcium absorption maintains the supply of calcium for osteoblast-mediated mineralization of the bone matrix.

Overall Bone Mineralization: In conjunction with parathyroid hormone (PTH), calcitriol maintains a delicate balance of calcium in the blood. When blood

SUBJECT INDEX

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Dr. Amit Kumar Tripathi is currently serving as an Assistant Professor in the Department of Biomedical Sciences, School of Bioscience and Technology, Galgotias University. He holds a master's degree in industrial biotechnology from Sardar Patel University, Gujarat, and earned his Ph.D. in Biochemistry with a specialization in stroke biology from the Council of Scientific and Industrial Research – Central Drug Research Institute (CSIR-CDRI), Lucknow, awarded by Jamia Hamdard University, New Delhi.

Dr. Tripathi's expertise encompasses a wide range of molecular techniques and animal models relevant to stroke research. His expanding publication portfolio, h-index, and citation record reflect his growing impact in the field of biomedical sciences. He has successfully mentored students across various academic levels and disciplines, including M.Sc. Medical Biotechnology, M.Tech., B.Tech. Biotechnology, and Biomedical Engineering.

He has teaching experience in subjects such as Food Nutrition and Hygiene, Stroke and Cardiovascular Biology, Nanotechnology and Biosensors, Industrial Bioprocess Technology, Molecular Therapeutics, Biomedical Sciences, and Human Values. His active involvement in education demonstrates his dedication to training students in both conventional and advanced molecular mechanisms underlying acute ischemic stroke.

Dr. Tripathi has also participated in several national and international training programs, gaining exposure to diverse cutting-edge technologies and methodologies in biomedical research

Sunil Kumar Mishra

Dr. Sunil Kumar Mishra is currently serving as an Associate Professor in the Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi. He earned his Bachelor of Pharmacy (B. Pharm.) from IT (BHU) in 1998 and completed his M. Pharm. at Birla Institute of Technology, Mesra, Ranchi, in 2003. He later earned a Ph.D. in Pharmacognosy, with a focus on medicinal plant research from IIT (BHU). Dr Mishra plays an instrumental role in propelling pharmacognosy and herbal drug technology at Department of Pharmaceutical Engineering & Technology, IIT (BHU). His expertise, spanning from plant tissue culture to herbal formulation and biological evaluation, fosters interdisciplinary research bridging botany, chemistry, and pharmacy. His growing publication record, h-index, and citation impact underscore his influence in pharmaceutical sciences. As he continues to mentor students and push research in plant-based pharmaceuticals, his contributions are vital for enhancing sustainable healthcare practices and discovering novel therapeutic agents. Dr Mishra has a strong teaching portfolio in Pharmacognosy and Herbal Pharmaceutical Science, conducting various core courses across undergraduate and postgraduate levels of Natural Drugs & Excipients, Medicinal Natural Products, Herbal Drug Technology, Evaluation of Natural Drugs, Plant Tissue Culture, General Pharmacognosy, Industrial Pharmacognosy, Medicinal Plant Biotechnology, and Herbal Drug Formulation & Standardization. His active engagement in teaching underscores his commitment to training students in traditional and modern therapeutic sciences. Dr Mishra's work significantly contributes to the validation and modernization of herbal medicine, aligning with global efforts to:

- Develop standardized plant-based pharmaceuticals.
- Employ biotechnological tools (e.g., tissue culture) to conserve rare medicinal species.
- Explore underutilized ethnopharmacological resources for new drug leads.
- Establish quality-control protocols ensuring the safety and efficacy of herbal drugs.
- Biological evaluation – in vitro and in vivo bioactivity analysis (anticonvulsant, antimicrobial, antidiabetic etc.)