VITAMIN D - A NOVEL THERAPY FOR CHRONIC DISEASES?

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Vitamin D - A Novel Therapy for Chronic Diseases?

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FOREWORD

In today's swiftly evolving world, where information is abundant and choices are vast, the quest for nutritional wisdom can seem overwhelming. Amid the myriad of dietary trends and the maze of conflicting advice, certain essentials of nutrition emerge as pillars of human health. Prominent among these is vitamin D, a nutrient that has captured the fascination of scientists and the public alike for its critical role in our well-being.

It is my distinct pleasure to present to you a comprehensive exploration of one of the most pivotal vitamins for human health: vitamin D. This book invites you on a journey through the complex world of this remarkable nutrient, shedding light on its crucial functions in the body, its varied sources, and its profound influence on health, with a particular focus on its impact on certain diseases.

The relationship between vitamin D and bone health is widely recognized, yet the scope of its benefits stretches far beyond its role in calcium metabolism. Vitamin D is instrumental in supporting immune function, enhancing mood, and potentially lowering the risk of chronic diseases, captivating researchers, and health professionals with its multifaceted effects. The evolving narrative of vitamin D is one versatility and discovery, with each chapter of research enriching our understanding of its significance.

This book is designed not only as a collection of the latest knowledge but also as a practical guide for those aiming to improve their vitamin D levels. Through clear, evidence-based recommendations and accessible explanations, it equips readers with the tools to make informed health decisions. Whether you are a healthcare professional, a nutrition aficionado, or simply someone interested in the pivotal role of nutrition in health, this book provides valuable insights that can have a lasting impact on your life.

As we venture into the following chapters, let us seize the opportunity to deepen our appreciation for vitamin D, exploring its potential to bolster our health and vitality. May this book illuminate your path to optimal health, serving as a beacon in your pursuit of well-being.

With warm regards

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PREFACE

The health of the musculoskeletal system depends on vitamin D since it controls the metabolism of calcium and phosphorus. For most people, sunlight with enough ultraviolet B (UVB) radiation is the primary source of it, as it is synthesized in the skin upon exposure. Foods and dietary supplements can also provide it. When exposure to sunlight containing UVB radiation is restricted or limited (as in the winter months), dietary sources become crucial (*e.g.*, due to lack of time spent outdoors or little skin exposure).

Vitamin D is acquired by humans through their food and exposure to sunshine. Vitamin D is found naturally in very few foods. Vitamin D3 is abundant in oily fish, including sardines, salmon, and mackerel. Vitamin D is said to be present in egg yolks, yet the concentrations are somewhat varied. Moreover, egg yolks are a poor source of vitamin D due to their high cholesterol content. Additionally, a few foods—like milk, orange juice, and some bread and cereals—are fortified with vitamin D.

In two hydroxylation steps, vitamin D is transformed into its active metabolite, 1,25-dihydroxyvitamin D (1,25(OH)2D). The primary circulating metabolite of vitamin D, 25(OH)D, is produced in the liver during the first hydroxylation of vitamin D. It is frequently utilized as a biomarker of vitamin D status. In the kidney, 25(OH)D is converted into 1,25(OH)2D during the second hydroxylation. A deficiency of vitamin D is characterized by most specialists as a level of under 20 ng for each milliliter. In 1997, the Institute of Medicine of the US National Academy of Sciences recommended new adequate intakes for vitamin D as 200 IU for children and adults up to 50 years of age, 400 IU for adults 51 to 70 years of age, and 600 IU for adults 71 years of age or older. Vitamin D deficiency can be divided based on UBV, dark skin, being old, and latitude, season, and time of the day of UBV. The other category includes medical/physical conditions or any deficiency, such as fat malabsorption, obesity, chronic kidney disease, and use of medication (*e.g.* anticonvulsant).

The chapters below discuss the most updated research data available on Vitamin D and its relation to several chronic diseases.

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CHAPTER 1

History and General Information of Vitamin D

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Abstract: The historical background of vitamin D for well-being dates to the beginning of the twentieth century. There are two types of vitamin D; ergocalciferol (D2) and cholecalciferol (D3). While D3 is mostly produced in the skin when exposed to sunshine, vitamin D2 is sourced from plant sources and is frequently utilized in fortified meals and supplements. The recommended form of vitamin D for supplementation is D3 since it has a greater potency in elevating and sustaining blood levels of the nutrient. The biochemistry of vitamin D is centered on how it becomes activated in the kidneys and liver to become its active form, which controls the metabolism of phosphorus and calcium. Although ideal serum levels might vary based on personal health considerations, recommended values generally lie between 20 and 50 ng/mL. Egg yolks, fortified dairy products, and fatty fish are good dietary sources of vitamin D; nevertheless, obtaining a sufficient intake only through food may be difficult, necessitating supplementation. However, overindulgence can result in toxicity, which is defined by hypercalcemia and associated symptoms including nausea and weakness. This emphasizes the significance of moderation in supplementing. Because vitamin D is fat-soluble, the body will keep excess rather than quickly excrete it, therefore taking too many supplements can be harmful. While vitamin D is essential for many body processes, getting the right amount of it without running the risk of negative side effects is crucial.

Keywords: Dietary intake, Food sources, Toxicity, Vitamin D history.

INTRODUCTION

Vitamin D is indeed a crucial nutrient for human health, playing a significant role in various physiological processes beyond just bone health. The primary natural source of vitamin D is through the synthesis of cholecalciferol (vitamin D3) in the skin upon exposure to UV-B radiation from sunlight. Vitamin D can also be obtained from dietary sources such as fatty fish (*e.g.*, salmon, mackerel, tuna),

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fortified foods (*e.g.*, milk, orange juice, cereals), and supplements. Vitamin D plays a crucial role in enhancing the absorption of calcium from the intestines, thereby aiding in maintaining bone health. It regulates calcium and phosphate metabolism, which is essential for bone mineralization and growth. It may also play a role in muscle function and reducing the risk of falls, especially in older adults. Vitamin D also has immunomodulatory effects, influencing both innate and adaptive immune responses. Severe vitamin D deficiency can lead to rickets in children, characterized by skeletal deformities due to impaired mineralization of bones. In adults, severe deficiency can result in osteomalacia, causing weak, soft bones and muscle weakness. Dietary recommendations for vitamin D intake vary by age, sex, and other factors. In the absence of sufficient sunlight exposure, obtaining vitamin D from diet and supplements becomes crucial. While sunlight is a natural source of vitamin D, recommendations regarding sun exposure should balance the benefits of vitamin D synthesis with the risks of skin cancer. Sunscreen use, clothing coverage, time of day, latitude, and skin type all affect the synthesis of vitamin D from sunlight. Overall, maintaining adequate levels of vitamin D is essential for overall health and well-being, and a balanced approach that includes a combination of sunlight exposure, dietary sources, and supplementation when necessary, is recommended.

HISTORY OF VITAMIN D

The story of the discovery of Vitamin D is an interesting one since it was far from a straightforward path. Several lines of research taking place between the 1700s to the 1900s led to its eventual recognition. Since the 1600s, rickets also known as the “English disease”, was rampant in different parts of the world, most notably Europe [1, 2]. This time period was marked by the advent of the Industrial revolution bringing in large amounts of air pollution from the burning of fossil fuels and mills, greatly reducing the amount of sunlight available at the ground level. Furthermore, large populations of people migrated into these crowded, air-polluted areas with little to no sunlight exposure. Concurrent to this large-scale migration, was the spread of a new, bone-softening disorder known as ‘childhood rickets’ when presenting in young children and ‘osteomalacia’ in adults [3]. Daniel Whistler from the Netherlands was first reported to have described rickets and osteomalacia in 1645 as a condition characterised by a poorly mineralized and deformed skeletal system [1]. Around that time, Franklin Glisson documented lithographic records in his book titled De Rachitide in 1650 featuring children with common symptoms such as bowing of the legs, skeletal deformities, growth retardation, enlargement of the rib cage, head, and muscle weakness [4]. The number of rachitic cases continued to rise till the 1900s. By the 20th century, between 80-90% of the children living in the US and Europe were afflicted with this bone-deforming disorder [5].

A conclusive cure for rickets remained elusive until 19th century when Sniadecki, a Polish physician scientist in 1822 [6], observed that the incidence of rickets differed between children in rural areas exposed to sunlight *versus* those in cities, suggesting that perhaps sunlight might be involved in the etiology of rickets [7]. The 20th century gave rise to much debate surrounding the possible causal factors of rickets which was proposed to be either environmental (in the form of sunlight) or dietary in nature. In 1919, Kurt Huldshinsky [8] made significant contributions to the sunlight-rickets debate by exposing children to UV radiation from a sun quartz lamp. Much to the interest of the scientific community, the X-rays of the children exposed to UV radiation showed marked increases in the mineralization of long bones [9]. It was speculated that the skin exposure to UV rays either from the sun or lamps simulating sunlight, led to a photochemical reaction producing specific products that exerted positive effects on the skeleton. Later many others such as Hess and Weinstock in 1924 experimentally tested the impact of UV irradiation on various inert foods such as lettuce and wheat successfully imparting anti-rachitic properties [10]. In the meantime, some scientists were hypothesizing a dietary etiologic factor for rickets. In 1919, Edward Mellanby, a British biochemist and nutritionist made a landmark observation, that rickets could be induced in dogs by restricting their diet to oatmeal and then reversing the rachitic symptoms by the addition of cod liver oil [11]. This observation indicated that a nutritional deficiency is a probably contributing factor in rickets. The search for the active nutrient responsible for the therapeutic activity of cod liver oil ensued and it was presumed that Vitamin A was responsible.

In Edward Mellanby's words, "Rickets is a deficiency disease which develops in consequence of the absence of some accessory food factor or factors. It, therefore, seems probable that the cause of rickets is a diminished intake of an anti-rachitic factor, which is either [McCollum's] fat-soluble factor A, or has a similar distribution to it" [12]. However, Elmer McCollum refuted that the antirachitic factor was Vitamin A. To test his theory, Elmer and his team conducted an experiment in 1922 wherein cod liver was aerated to oxidise fat-soluble factor A and subsequently heated. Since Vitamin A is highly sensitive to oxidation and heat, it was consequently destroyed in the tested sample of cod liver oil. When fed to rats with xerophthalmia and rickets, findings revealed that cod liver oil maintained its anti-rachitic properties although it lacked Vitamin A's therapeutic impact on xeropthalmia [13]. This phenomenal observation led to the discovery and naming of a new vitamin, Vitamin D. This dichotomy between the separate etiologic factors, namely UV radiation, and diet, served as an impetus to scientifically trace the common denominator. The quandary was settled independently by Harriet Chick [14] and Harry Steenbock [15] at the University of Wisconsin. Steenbock, prompted by this dichotomy, ran a series of experiments, irradiating rats with UV light. He found that the consumption of

CHAPTER 2

Vitamin D, Immunity, and Gut Health

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Abstract: The gut microbiota, a complex bacterial community within the gastrointestinal system, critically regulates human physiology. This article explores the complex interactions between the gut microbiota and vitamin D, impacting immunity and overall health. Vitamin D plays a role in immunological modulation, cell proliferation, and maintaining intestinal balance highlighting the intricate connections between gut microbiota and vitamin D in the gastrointestinal system. Recent research indicates that vitamin D receptors in the gastrointestinal tract may influence the gut microbiota's composition. Dysbiosis, an imbalance in the gut microbiota, is linked to various illnesses, including autoimmune diseases and metabolic disorders. This section examines the effects of low vitamin D levels on immunity, associating insufficient amounts with increased susceptibility to infections and autoimmune diseases like rheumatoid arthritis, multiple sclerosis, and Hashimoto's thyroiditis. Conversely, studies demonstrate that immune function relies on maintaining adequate vitamin D levels, particularly through calcitriol, the active form of vitamin D, regulating innate and adaptive immunity. Epidemiological research supports the hypothesis that sufficient vitamin D levels could reduce the prevalence of illnesses, including autoimmune diseases and osteoporosis. The chapter underscores the potential preventive benefits of adequate vitamin D intake, reviewing data from research on multiple sclerosis, Hashimoto's illness, and rheumatoid arthritis.

In conclusion, this exploration highlights vitamin D's critical role in immune system performance, gut health, and microbiota composition. While existing studies suggest the potential benefits of vitamin D for autoimmune illnesses, further research is imperative to establish conclusive evidence, especially regarding vitamin D supplementation for these ailments.

Keywords: Autoimmune disorders, Gut microbiota, Immunity, Microbiome-health relationship, Vitamin D.

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INTRODUCTION

The gut microbiota, composed of microorganisms including bacteria, viruses, and fungi, resides within the gastrointestinal (GI) tract [1]. Nowadays, there is a growing recognition of the microbiota's significance in human physiology, leading some to regard it as a distinct organ within the body [2]. Moreover, emerging evidence highlights its pivotal role in influencing human health and the development of diseases. The gut microbiota serves crucial functions in maintaining metabolic and immune well-being, aiding in the synthesis of essential vitamins, and extracting nutrients that are otherwise inaccessible from the diet, facilitating the renewal of epithelial cells, regulating fat storage, preserving the integrity of the intestinal barrier, and contributing to brain development [3 - 5]. When it comes to the gut microbiota, research has demonstrated that both vitamin D and the vitamin D receptor (VDR); which serve as mediators for the biological functions of the active form of vitamin D3 [6], are widely distributed throughout the gastrointestinal tract, and have the capacity to influence the composition of the gut microbiota [7]. They play a significant role in immune regulation, cell proliferation, as well as mantaining intestinal equilibrium [8] as shown in Fig. (**1**).

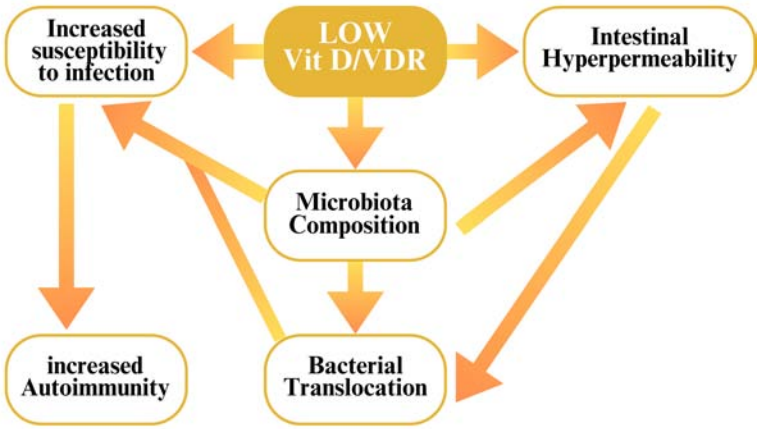

Fig. (1). Relationship of Vitamin D, autoimmunity and gut.

Vitamin D functions as an immune modulator. Notably, it stimulates the production of pattern recognition receptors, antimicrobial peptides, and cytokines, all of which play pivotal roles in initiating innate immune responses. These components are crucial for sensing the presence of the gut microbiota, preventing excessive bacterial overgrowth, and complementing the actions of vitamin D in fortifying the integrity of the intestinal barrier. Additionally, vitamin D promotes the development of tolerogenic T cells, emphasizing a less inflammatory and more immune-tolerant response [9, 10].

Both autoimmune responses and vitamin D, specifically its precursor 25-hydroxyvitamin D (25(OH)D: calcifediol) along with its active form, 1,25-dihydroxyvitamin D (1,25(OH)2D: calcitriol), have essential functions in safeguarding individuals against invading pathogens, decreasing the likelihood of autoimmune disorders, and upholding overall well-being. Conversely, having insufficient levels of 25(OH)D heightens vulnerability to infections and the development of autoimmune conditions [11].

In regard to immune cells, the regulation of both innate and adaptive immunity relies on the precise production of the active form of vitamin D, calcitriol. This process enhances the innate response, marked by the activation of monocytes or macrophages with potent antimicrobial activity [12 - 16]. Additionally, calcitriol promotes the production of immunoglobulin and enhances the stability of B-cells, by influencing B lymphocytes and plasma cells [17, 18], thereby increasing the synthesis of antimicrobial peptides [11].

Furthermore, vitamin D has a broad immunomodulatory effect on innate and adaptive immune responses, it also plays an effective role with T-helper cells, macrophages, and dendritic cells [19, 20]. Calcitriol regulates immunological responses by partially inhibiting B-cell IgE expression and increasing the anti-inflammatory Interleukin-10 expression through dendritic cells and T cells [21 - 23]. In this chapter, we will be adventuring into the benefits of vitamin D with immunity, including autoimmune disorders, the effect of deficiency and sufficiency of vitamin D on immunity and autoimmune disorders, including multiple sclerosis, Hashimoto's Thyroiditis, and rheumatoid arthritis [11].

Gut Microbiota and Vitamin D

The gut microbiome plays a crucial role in human health, influencing the course of chronic illnesses like metabolic diseases, gastrointestinal problems, and colorectal cancer. Environmental factors and dietary patterns significantly impact the establishment of gut microbiota [24 - 26]. In the human gastrointestinal tract (GI tract), approximately 200 common bacteria, viruses, and fungi undertake specific metabolic tasks essential to both health and illness [27 - 29].

The distal gut microbiome is particularly influential in maintaining host health by producing vitamins, essential amino acids, and metabolic byproducts derived from dietary components unabsorbed by the small intestine [30]. Although the gut microbial dynamics in a healthy individual tend to be stable, it is likely that the lifestyle and dietary habits of the host can influence microbial dynamics [25, 31].

A recent systematic review of *in vivo* studies investigated the association between the different levels of vitamin D and Gut Microbiota [32], the study found

CHAPTER 3

Vitamin D and Insulin Resistance

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Abstract: This chapter examines the latest research findings on the association between vitamin D levels and insulin resistance (IR) in various populations, including pregnant and postpartum women, children and adolescents, and individuals with certain health conditions such as diabetes, obesity, multiple sclerosis (MS), polycystic ovary syndrome (PCOS), non-alcoholic fatty liver disease (NAFLD), diabetic kidney disease (DKD), and diabetic peripheral neuropathy (DPN). Existing evidence suggests that Vitamin D plays a crucial role as an immunomodulator, affecting important human disorders like insulin resistance, glucose homeostasis, and mineral and bone metabolism. Extensive evidence suggests that vitamin D has a substantial impact on the development of insulin resistance (IR), through its influence on different gene variants related to vitamin D and the metabolic and immunological pathways associated with it. Supplementing with vitamin D can be beneficial in properly managing and enhancing insulin resistance. Diverse research approaches have yielded both favorable and unfavorable results on the correlation between vitamin D and insulin resistance (IR). Further research is recommended to clarify the correlation between vitamin D and insulin function, as well as to determine any variations in this association among different age groups, genders, and illnesses.

Keywords: Diabetes mellitus, Insulin resistance, Metabolic syndrome, Non-Alcoholic fatty liver disease, Vitamin D.

INTRODUCTION

Insulin is a peptide hormone (protein) produced by the beta cells of the pancreatic Langerhans islets. It is the primary anabolic hormone in the human body [1]. This hormone controls the metabolism of all dietary fuels, including carbohydrates, lipids, and proteins. It accelerates postprandial glucose absorption into hepatocytes, lipocytes, and skeletal myocytes for metabolism [1].

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As depicted in Fig. (**1**), insulin receptors are present within the cellular membranes. As a first messenger, the hormone insulin initiates a cascade of reactions when it binds to the receptor subunit. In response, myocytes and lipocytes express and insert GLUT4, and the liver and skeletal muscle tissues synthesize glycogen. GLUT4 are the primary transporter proteins involved in glucose metabolism that are activated by insulin [1].

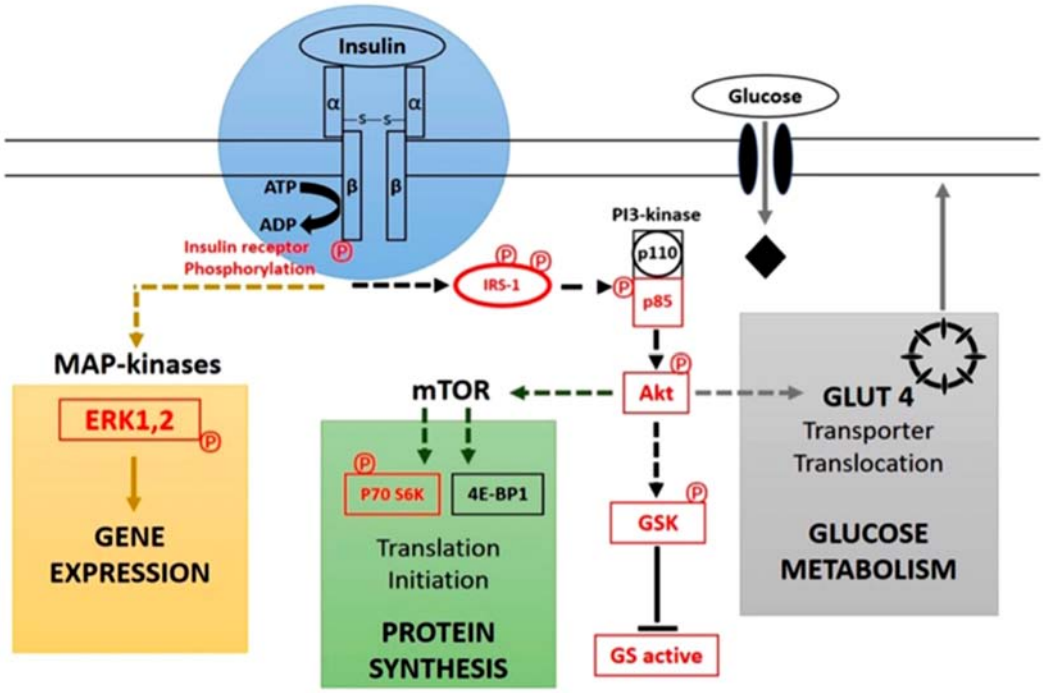

Fig. (1). Insulin signal transduction. The insulin receptor (IR) is in blue, and glucose metabolism (highlighted in grey) [1].

Insulin resistance (IR) is characterized by impaired physiological responses to insulin stimulation in certain target organs, such as the liver, muscle, and adipose tissue. It decreases the efficacy of glucose metabolism, which leads to an increase in insulin synthesis by beta cells and insulin levels [2]. As reported by the National Health and Nutrition Examination Survey (NHANES) conducted in 2021, it was found that over 40% of adults between the ages of 18 and 44 in the United States exhibited IR [2]. Various variables can contribute to the development of the condition, such as age, gender, lack of physical exercise, a significant amount of visceral fat, abdominal obesity, oxidative stress, and mitochondrial dysfunction [3]. Hyperglycemia, hypertension, dyslipidemia,

hyperuricemia, elevated inflammatory markers, impaired endothelium function, and a prothrombotic state can result from IR [2].

Comprehending the pathophysiology of IR necessitates the examination of intricate mechanisms that underpin this physiological state. It involves multiple factors and mechanisms, and the key pathophysiological aspects of IR include genetic predisposition, obesity, inflammation, dyslipidemia, adipokines and hormones, insulin signaling pathway, intracellular mechanisms, mitochondrial dysfunction, and feedback mechanisms [4]. Obesity is one of the primary risk factors for IR, which is caused by the overproduction of lipids in adipose tissue, leading to dysfunction [4]. Nevertheless, it is important to note that the issue of IR cannot be only attributed to obesity, as evidenced by the fact that many individuals with prediabetes in various countries are not classified as overweight or obese [1]. Several alternative ideas have been put forth by Aedh *et al.* [1] to provide further understanding of the biology of IR. Among these, an established correlation that has been well-documented in the literature is the strong connection between vitamin D and IR [5]. Vitamin D is classified as a steroid hormone that exerts its physiological effects through interacting with vitamin D receptors (VDRs), a part of the steroid/thyroid receptor family. Similar to insulin receptors, vitamin D receptors (VDRs) are expressed widely throughout the body. Vitamin-receptor binding translocates the complex from the cytosol to the nucleus, where it interacts with retinoid x receptors (RXR). VDR/RXR heterodimers attach to the vitamin D response element (VDRE) in the nucleus, modulating target gene transcription [5]. According to Trimarco *et al.* [5], the expression of about 200 genes is modulated by vitamin D, either upregulated or downregulated. Previous research has indicated that insufficient vitamin D levels might be regarded as either a direct or indirect outcome of IR [5].

Therefore, while the influence of genetic variables on the development and susceptibility of this morbidity is often significant, the impact of environmental events that trigger this morbidity can be substantial. During the initial phases of IR, it is feasible to impede the advancement of the pathological condition. According to Aedh *et al.* [1], oral hypoglycemic medications are the primary therapeutic approach for managing insulin resistance. The specifics pertaining to these agents are beyond the focus of this chapter and, hence, will not be covered. In addition to oral hypoglycemic drugs, research has shown that IR can be treated with methods that control the amount of insulin the body requires, such as dietary and lifestyle modifications [6]. Restoring vitamin D levels in individuals has been shown to efficiently restore insulin sensitivity and perhaps improve IR [5].

CHAPTER 4

Vitamin D and Cardiovascular Diseases

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Abstract: Vitamin D is an essential micronutrient crucial for various physiological functions in humans, notably impacting calcium metabolism, skeletal integrity, immune response, and cellular proliferation and differentiation. While predominantly synthesized through sunlight exposure, dietary intake, and supplementation also contribute to its availability. Vitamin D deficiency has been implicated as a potential risk factor for atherosclerosis, cardiorespiratory distress, and cardiovascular diseases (CVDs), including sudden cardiac death, hypertension, and stroke. Observational studies have indicated an inverse correlation between circulating vitamin D levels and the incidence of CVDs; however, causality remains ambiguous. Some evidence suggests a potential cardioprotective effect of vitamin D supplementation, however, further investigation is warranted to elucidate its precise role in cardiovascular health. This review aims to comprehensively present existing literature on the relationship between vitamin D status and CVDs.

Keywords: Atherosclerosis, Supplement, Cardiovascular disease, Hypertension, Vitamin D.

INTRODUCTION

Cardiovascular disease (CVD) is a widespread and complex group of conditions that affect the heart and blood vessels. It encompasses a range of disorders, including coronary artery disease, heart failure, stroke, and peripheral artery disease, among others [1]. CVD is a leading cause of morbidity and mortality worldwide, posing a significant public health challenge [2]. It claims the highest number of lives annually, resulting in 17.9 million deaths each year with heart attacks and strokes accounting for 85% of the total number [1].

In recent years, researchers have been increasingly exploring the relationship between vitamin D and cardiovascular health. This relationship is multifaceted,

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involving various mechanisms that affect the risk, development, and progression of CVDs. This is because almost all cells in the body, including cardiac and smooth muscle cells, express vitamin D receptors (VDRs) and are affected by their signalling [3].

One of the proposed mechanisms of vitamin D's role in calcium regulation starts from its absorption to regulating its function in the body. Calcium is essential for proper muscle contractions among other functions. Concerning the cardiovascular system, calcitriol ensures the transport of calcium intracellularly in varying concentrations for proper and rhythmic smooth muscle contractions. Imbalances in calcium handling, due to vitamin D deficiency, may lead to cardiac arrhythmias among other cardiovascular conditions [4].

Another mechanism involves the regulation of blood pressure through the renin-angiotensin-aldosterone system (RAAS). While RAAS is crucial for blood pressure homeostasis, its overactivation is the primary mechanism for the pathogenesis of hypertension [5]. Vitamin D is needed to help tightly regulate this system and prevent the prognosis of hypertension. Therefore, vitamin D deficiency has been associated with an increased risk of hypertension among other CVD [5] as will be elucidated later in the chapter.

An additional important pathophysiological mechanism is vitamin D's role in anti-inflammation. Vitamin D has been shown to reduce inflammation by activating antithrombotic and vasodilator genes and decreasing low-density lipoprotein (LDL) oxidization increasing the risk of plaque formation or atherosclerosis [6, 7].

With the growing body of evidence supporting the intricate relationship between vitamin D and cardiovascular health, this chapter aims to explore the current state of knowledge and highlight the key findings from research in this area linking vitamin D deficiency with sudden cardiac death, strokes, and CVD comorbidities including dyslipidemia, hypertension, and atherosclerosis.

Vitamin D and Cardiorespiratory Fitness

Examining the connection between vitamin D and its effect on cardiovascular health demonstrated mixed results in the previous decades. The latest reviews of this connection note that vitamin D deficiency harms the overall fitness of the CV system. For instance, it has been shown that the prevalence of vitamin D deficiency was higher in individuals with CVD compared with those without CVD [2]. Low vitamin D levels are persistent worldwide where estimates for the prevalence indicate percentages of 24% in the United States, and 37% in Canada, while in Europe, approximately 40% of residents are deficient, with over 10%

being severely deficient [8]. Such high numbers of people experiencing a lack of this vitamin are often connected to the increasing issues in cardiorespiratory systems.

Inadequate levels of vitamin D are also negatively related to the risk of developing cardiovascular problems in the future possibly through the immune system pathway although the vitamin's specific effect is unknown. For instance, vitamin D promotes immune tolerance and improves the responses from the immune system through T cell differentiation and suppression of T helper 1 and T helper 17 cells [9]. Vitamin D's presence in vascular muscle cells and cardiomyocytes is essential for cardiorespiratory fitness. Simultaneously, trials attempting to investigate the direct effect of adding supplements of vitamin D into the diet of both healthy individuals and people with CVD or hypertension (HTN) do not yield positive results.

Vitamin D and Sudden Cardiac Death (SCD) and Cardiovascular Mortality

Sudden cardiac death (SCD) is defined as a death due to a cardiovascular cause within 1 hour of the onset of symptoms [10]. Every year, 1 out of every 7.4 people die from out-of-hospital SCD in the US [11]. Although infrequent, SCD ranks as the primary non-traumatic cause of death among young athletes. The occurrence ranges between 0.47 – 1.21 per 100,000 persons among young athletes (≤35 years) and 6.64 per 100,000 persons among older athletes (>35 years) [12].

SCDs exhibit a circadian pattern as well, with a peak between 6 am and noon, and a smaller peak occurring in the late afternoon. Moreover, the overall rate of sudden cardiac death is higher on Mondays [13].

Acknowledging the complex and the heterogenous relationship between vitamin D and cardiovascular function, research has been looking into using serum vitamin D as a potential biomarker for SCD and possibly CVD [14, 15]. A recent meta-analysis of cohort studies showed a significant relationship between low circulating vitamin D levels and the risk of SCD and cardiovascular mortality among the healthy population and population with pre-existing comorbidities including CVD and chronic kidney disease with an overall hazard ratio of 1.84, 1.58, and 1.81, respectively [14]. There was one study included in the meta-analysis that looked at the risk of SCD and cardiovascular mortality rates among diabetic patients and that showed an overall HR of 1.90 [14].

Vitamin D and Ischemic Stroke Risk and Prognosis

Strokes are the second leading cause of death worldwide and the first leading cause of disability [16]. The probability of experiencing a stroke during one's

CHAPTER 5

Vitamin D and Irritable Bowel Syndrome

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Abstract: Irritable bowel syndrome (IBS) is a common gastrointestinal condition characterized by abnormal bowel habits (diarrhea, constipation, or both), poor mental health, and a reduced quality of life. Although commonly diagnosed through the Rome IV criteria, a universally agreed-upon diagnostic standard for IBS is yet to be established. Several therapeutic modalities are commonly employed to treat IBS, but the lack of a distinct biomarker for the condition makes it challenging for healthcare providers to evaluate the effectiveness of treatments. Elimination diets such as the low FODMAP diet may provide benefits to patients with IBS, however, the accompanying increased risk of nutritional deficiencies may worsen the condition's symptoms. Vitamin D (VD) supplementation may reduce symptom intensity and enhance the overall quality of life for individuals with IBS through several postulated mechanisms of action, including possible influence on gut microbiota and serotonin levels. This chapter reviews the current evidence from observational studies, systematic reviews, and meta-analyses of randomized controlled trials linking VD deficiency and/or supplementation with IBS. Four observational studies found a connection between diagnosed IBS and patients' vitamin D levels, along with a correlation with symptom severity, while two studies showed contradictory results. Systematic reviews and meta-analyses suggest a positive association between vitamin D supplementation and the relief of IBS symptoms as well as improvements in mental health. Despite these encouraging results, further large-scale clinical trials are needed to establish conclusive findings and enhance clinical approaches for effectively managing IBS.

Keywords: Deficiency, Irritable bowel syndrome, Supplementation, Vitamin D.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder that impacts 4%-10% of the global population [1]. The incidence of IBS is characterized by significant variability among different populations, as the condition tends to manifest twice as many times among women and more frequently among people under 50 [2].

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Typically, patients with IBS present with gastrointestinal complaints such as abdominal pain and a change in bowel habits, presenting as diarrhea or constipation, often occurring alternately. Concurring symptoms may include indigestion, bloating, an intense urge to have a bowel movement, a sense of incomplete evacuation, chronic pelvic discomfort, migraines, and fibromyalgia [3]. Symptoms can vary widely in intensity among patients and throughout the disease course, ranging from mild to debilitating [1, 4]. Patients with IBS are more susceptible to mental health challenges such as depression and anxiety and suffer from a lower quality of life [5].

Although a clear and universally accepted diagnostic criterion for IBS has not been defined, the Rome IV criteria are most commonly used [6]. According to Rome IV criteria, IBS is diagnosed based on recurring abdominal discomfort, bloating, constipation, or diarrhea in the absence of structural or chemical changes. For a diagnosis to be made, patients should have chronic symptoms that occurred at least once per week on average in the previous three months, lasting at least six months. Based on the prevalent bowel patterns during days with irregular bowel movements, IBS can appear in one of three primary subtypes: 1) constipation-predominant IBS, 2) diarrhea-predominant IBS, and 3) mixed IBS [7, 8] (Fig. **1**).

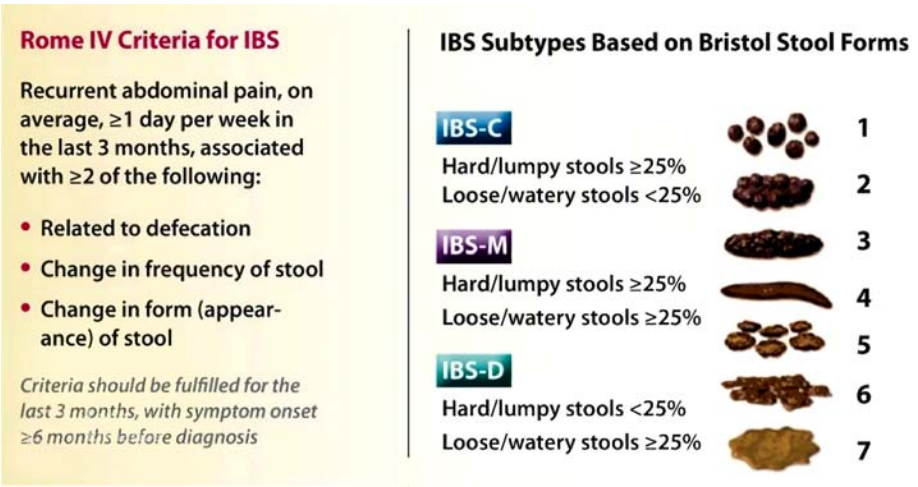

Fig. (1). IBS definition and classification. (Source: Lacy *et al.* 2016).

Patients with IBS use the healthcare system more often than other gastroenterology patients. The complexity and variability of IBS presentation make treating the condition particularly challenging [9]. For instance, IBS symptoms can resemble those of other conditions like lactose or fructose intolerance, leading to a lack of response to standard treatment. Additionally, the

absence of a specific biomarker for IBS complicates the assessment of treatment effectiveness for healthcare providers. Standard tests typically yield normal results, which can be frustrating for patients experiencing persistent symptoms [10].

In the initial phase and subsequent steps of the treatment plan, IBS therapy is tailored according to the most prominent symptom [11]. The first-line approach for treatment includes medications for the management of abdominal pain, cramping, constipation, and/or diarrhea. For patients suffering from significant psychological symptoms or several coinciding somatic conditions, utilizing a neuromodulator has been recommended as an initial treatment. Moreover, a diet that eliminates certain sugars linked to gastrointestinal discomfort, such as the low FODMAP diet, has been advocated as an alternative approach [12]. However, concerns over encountering symptoms after consuming particular foods may cause individuals with IBS to unnecessarily remove some foods from their diet, increasing their vulnerability to nutritional deficiencies. The culminating effects of these deficiencies may further worsen symptoms and quality of life among this group [6].

The current body of literature suggests a positive role of nutritional supplementation in the context of IBS. In particular, investigations into vitamin D supplementation have unveiled promising outcomes, notably in the reduction of symptom intensity and the enhancement of the overall quality of life for individuals affected by the condition [6]. Several mechanistic pathways have been postulated to underpin these effects. While the precise pathogenesis of IBS remains unclear, a growing body of research has suggested a link between gut dysbiosis and developing IBS, given its associations with heightened intestinal permeability, inflammatory processes, and altered neuronal activity [13]. Vitamin D supplementation appears to exert an influence on the gut microbiota, fostering an increase in beneficial bacterial strains such as Ruminococcus, Faecalibacterium, Akkermansia, Lactococcus, Coprococcus, and Bifidobacteria while concurrently reducing the prevalence of the Firmicutes microbial composition [14, 15]. These changes insinuate that vitamin D plays an immunomodulatory role by encouraging the generation of antimicrobial peptides, overseeing the maintenance of the integrity of intestinal epithelial cells, suppressing proinflammatory immune responses, and bolstering the adaptive immune system, as illustrated in Fig. (**2**) [16].

Moreover, serotonin receptors have been observed to have a pivotal role in gastrointestinal function, and their malfunction can give rise to IBS-related symptoms [17]. Vitamin D is involved in maintaining normal serotonin levels, potentially positively impacting the psychological well-being of IBS patients

CHAPTER 6

Vitamin D and Depression

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Abstract: This chapter discusses the relationship between vitamin D and depression, shedding light on the physiological functions of the unique characteristics of vitamin D, its synthesis, and its role in extraskeletal activities apart from its established function in bone metabolism. It further delves into the global prevalence of vitamin D deficiency and the rising incidence of depression worldwide. The link between vitamin D and depression is presented emphasizing the potential roles of vitamin D in neuromuscular and immune function. The document also discusses the purported mechanisms underlying the relationship between vitamin D and depression, including neuroinflammation, imbalance in calcium homeostasis, and deficiency in neurotransmitters. Furthermore, the document presents a comprehensive review of the existing literature on the topic, citing multiple studies and reviews to support the discussed findings. It covers various aspects, including the molecular basis of vitamin D, its impact on neurobehavioral health, and its association with depressive symptoms across different age groups primarily fetal origins, children, adolescents, adults, and older adults. Many studies suggest a possible connection between depression and vitamin D insufficiency, but the exact nature of this relationship and whether the supplementation of vitamin D could effectively treat depression remains ambiguous. Given that the link between vitamin D and depression has attracted attention, further well-designed trials are needed to establish causality, elucidate the practical consequences, and address the existing discrepancies and limitations in the evidence.

Keywords: Depression, Neuroinflammation, Neurotransmitters, Supplementation, Vitamin D insufficiency.

INTRODUCTION

Vitamin D is a lipophilic vitamin playing myriad roles in human health. It shows unique characteristics that differentiate it from other vitamins; its active form functions as a steroid hormone [1]. Vitamin D displays dual functionality as it can be ingested as Vitamin D_2 as part of dietary plant origins and Vitamin D_3 as part

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of animal origin like cod liver oil, liver eggs, external supplementation, and lastly endogenous production. Synthesizing vitamin D endogenously requires contact of the skin with the sun's ultraviolet B radiation to transform 7-dehydrocholesterol into bio-active vitamin D. Progressive hydroxylation in the liver and kidneys activates vitamin D to its bio-active form - calcitriol, chemically known as 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$) [2]. In the nucleus of cells, calcitriol behaves similarly to a steroid hormone by interlinking with a vitamin D receptor (VDR) that allows it to harness its biological functions [3]. In the musculoskeletal system, vitamin D, as part of bone metabolism, governs the absorption of phosphate, magnesium, and calcium in the intestine [4]. Vitamin D deficiency comprising low serum concentrations of 25-hydroxy vitamin D (25-OHD) remains a global epidemic. A recent comprehensive analysis was conducted worldwide amongst 7.9 million subjects to assess the prevalence of the deficiency of Vitamin D, globally. Results revealed that 15.7% of the population had serum 25-OHD levels less than 30 nmol/L while 47.9% of the population had serum 25-OHD less than 50 nmol/L [5]. Apart from Vitamin D's physiological functions, numerous investigations have indicated that it could play roles in neuropsychology—such that its deficiency may be associated with various adverse mental health outcomes [6]. According to WHO, "depressive disorder (depression) is a common mental disorder that includes a depressed mood or loss of pleasure/interest in activities for a prolonged time period" [7]. Amongst mental health illnesses, depression is the most common illness worldwide [8]. The world is witnessing a steep increase in depression with incident cases having risen exponentially by almost 50% since 1990 to 2017 [9]. Nutrition and its various facets have been linked to changes in mood, behaviour, development, and treatment of mental illness. Research on the relationship between nutrition and mental health has increased over the past decade, with some findings indicating that eating a balanced diet may help prevent the development of mental disorders [10].

Mounting data implicates Vitamin D's role in numerous extra skeletal activities such as neuromuscular and immune function [6]. Furthermore, recent findings that show depressed individuals with diminished serum concentrations of vitamin D, point to a possible link between low levels of Vitamin D in the body with an elevated risk of developing depression [11].

Vitamin D and Depression Purported Mechanisms

Evidence shows that among multiple molecular mechanisms believed to be of significance in the pathology of depression, inflammation takes precedence as a critical factor [12]. Vitamin D exhibits certain pro-neurogenic, antioxidant, neuromodulatory, and anti-inflammatory characteristics that form the basis for its

antidepressant and anxiolytic effects [11]. As outlined below in Fig. (**1**), certain mechanisms have been purported to modulate the link between vitamin D and depression.

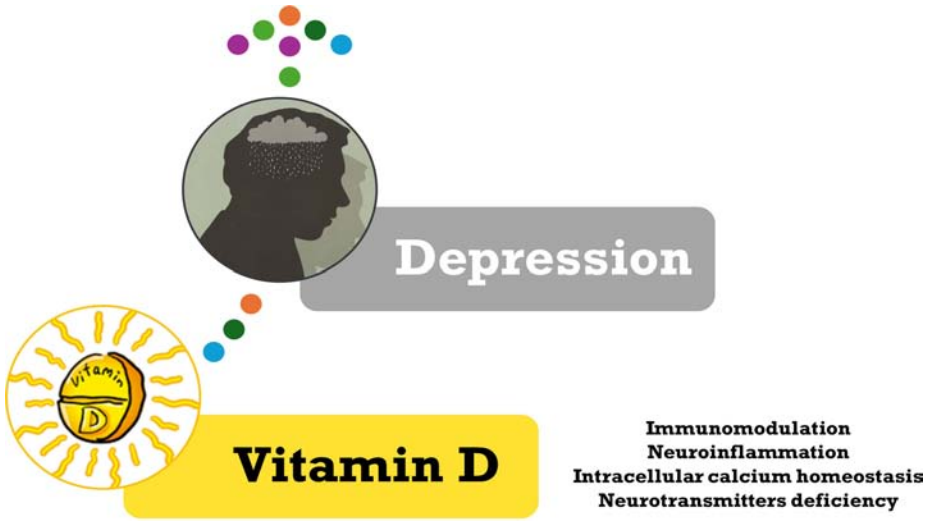

Fig. (1). Various purported mechanisms underlying Vitamin D-depression relationship.

Neuroinflammation: A Possible Mediator between Vitamin D and Depression

Neuroinflammation functions as a protective mechanism to restore the brain structure and function against physiological and infectious insults [13]. However, this protective mechanism can be detrimental and produce adverse effects in the brain when the same inflammatory process continues to be prolonged and exacerbated. Studies increasingly observe that patients with depression show elevated levels of neuroinflammatory-process-derived cytokines: IL-6, interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), which are pro-inflammatory in nature [11]. Preclinical studies on depressive rats reveal that vitamin D insufficiency could elevate inflammatory status through the production of aberrant cytokine biomarkers [14]. Thus, low serum concentrations of vitamin D could trigger inflammation. Ongoing investigations are underway to uncover the underlying mechanisms considering it still remains incompletely understood. Lowering inflammation might prove to be beneficial for patients with depression.

Imbalance in Calcium Homeostasis: A Byproduct of Vitamin D Inadequacy

There is a speculation that an inadequacy of vitamin D levels in the body could lead to a sustained elevation in Ca^{2+} levels triggering an onset of depression [15]. Calcium is required for cell signalling in the neurons, which is done by activating their inhibitory and excitatory functionalities. Excitatory neurons secrete a

CHAPTER 7

Vitamin D and Melanoma

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Abstract: Melanoma, a malignant tumor of the skin, is a major health concern worldwide, with increased incidence rates especially among fair-skinned individuals. This section investigates the complex connection between vitamin D and melanoma, offering insight to vitamin D's numerous functions in both skin health and prevention of cancer. Vitamin D, which is largely synthesized in the skin in response to ultraviolet B (UVB) radiation, has important activities beyond mineral homeostasis, such as immunological regulation and tumor suppression. Considering its potential preventive effects, the processes behind vitamin D's influence on the likelihood of melanoma and progression are complex and require further research. Observational studies indicate a possible adverse link between vitamin D levels and melanoma risk, while causality and appropriate supplementing regimens are unclear. Genetic differences in vitamin D receptors and metabolic enzymes may also influence an individual's vulnerability to melanoma. Melanoma risk reduction strategies include a broad approach, including limiting UV exposure, supplementing the diet, and considering genetics. This review summarizes the current investigation into vitamin D's complex interaction with melanoma, emphasizing the necessity for comprehensive measures to maximize its efficacy in melanoma prevention and care.

Keywords: Melanoma, Risk factor, Sunlight exposure, Vitamin D, 25-Hydroxyvitamin D.

INTRODUCTION

Malignant melanoma arises from the dermis, a layer of the skin. Despite being the third most common skin cancer, it is the primary cause of melanoma-related deaths and its incidence is increasing [1]. Its incidence is strongly connected with skin color and geographic area. Outdoor activity modifications and solar exposure over the last seventy years are significant contributors to the rising incidence of melanoma [2].

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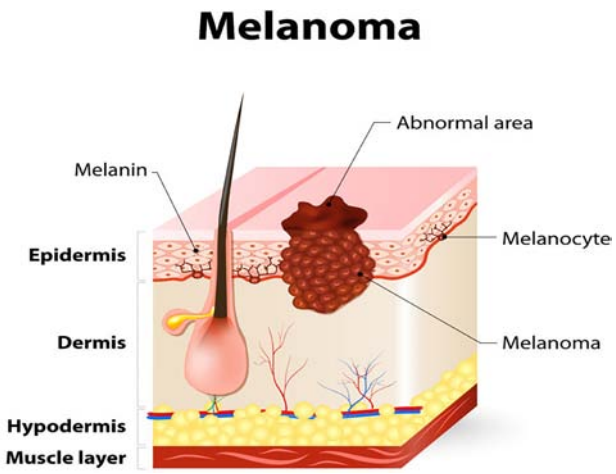

Melanoma is responsible for 1.7% of cancer occurrences worldwide and is the fifth most prominent malignancy in the United States. Melanoma in developed, fair-skinned nations has increased by over 320% in the United States. Since 2011, ten new targeted or immunotherapy agents have been approved in the United States, leading to a decrease in the mortality of nearly 30% over the past decade [3]. The different types of cancers are described below in Table **1**. [4]

Table 1. Different types of cancer and fatalities.

Rank	Typical Forms of Cancer	New Instances in 2023	Approximate Fatalities in 2023
1.	Breast Cancer Female	297,790	43,170
2.	Prostate Cancer	288,300	34,700
3.	Lung and Bronchus Cancer	238,340	127,070
4.	Colorectal Cancer	153,020	52,550
5.	**Melanoma of the Skin**	**97,610**	**7,990**
6.	Bladder Cancer	82,290	16,710
7.	Kidney and Renal Pelvis Cancer	81,800	14,890
8.	Non-Hodgkin Lymphoma	80,550	20,180
9.	Uterine Cancer	66,200	13,030

Cancer Facts Sheets, 2023 [4].

The existing treatments encompass a range of interventions such as chemotherapy, photodynamic treatment, immunotherapy, surgical interventions, and targeted therapy are all options. The treatment approach can consist of the utilization of either individual drugs or a combination of therapies, based on

factors such as the patient's overall well, tumor location and stage. The effectiveness of these interventions may be diminished because of the emergence of various resistance mechanisms [5].

Approximately 90% of vitamin D is produced in the skin when exposed to the sun, predominantly the ultraviolet type B (UVB) spectrum [6].

Vitamin D is actually a genuine hormone that the human body can produce when exposed to sunlight or through a well-rounded and nutritious diet that includes vitamin D-rich foods or supplements. Unfortunately, our prevalent indoor lifestyle, coupled with irregular and insufficient exposure to sunlight, as well as various factors like human migration, has led to a widespread deficiency of vitamin D. Ironically, this deficiency is occurring simultaneously with a rise in the prevalence of skin cancer in certain regions [7].

Maintaining a healthy level of vitamin D is essential for strong bones. D hypovitaminosis disorders, such as rickets, and osteomalacia, have been well described and should be prevented whenever possible. However, D hypovitaminosis may also be implicated in loss of bone mass, sarcopenia, falls, as well as frailty fractures in the elderly, which are major public health concerns in Europe due to their impact on morbidity, quality of life, and the cost of healthcare [8].

Vitamin D is popular for its involvement in mineral homeostasis regulation; nevertheless, D hypovitaminosis has also been related to the development and progression of certain cancer types [9].

When the skin is placed under the sun, UV B photons penetrate it and break down 7-dehydrocholesterol into pre-vitamin D3. This pre-vitamin D3 is then transformed into vitamin D3 through a process called isomerization, which is facilitated by the body's temperature. The majority of mankind have relied on the sun to meet their vitamin D needs. Factors such as skin pigmentation, sunscreen application, aging, time of day, season, and latitude have a significant impact on the synthesis of previtamin D3 [10].

Due to its high incidence and mortality rate, melanoma is a major clinical issue that affects many people. UVR, or ultraviolet light, is a major contributor to the carcinogenic alteration of melanocytes and the development of melanoma. However, UVB is needed for the cutaneous generation of vitamin D3, despite its role as a complete carcinogen in melanoma genesis [11].

In a study of 87 patients with malignant melanoma to investigate the impact that vitamin D may have on the outcome of patients with melanoma, only 11 patients

CHAPTER 8

Vitamin D and Pregnancy

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Abstract: Vitamin D insufficiency is prevalent among pregnant women and infants worldwide. Expectant mothers with a heightened risk of vitamin D deficiency may have notably low levels of 25-hydroxyvitamin D (25(OH)D) in their newborns, raising the likelihood of nutritional rickets. Numerous observational studies suggest a link between inadequate vitamin D levels during pregnancy and various adverse perinatal outcomes such as hypertensive disorders (like preeclampsia), restricted fetal growth, and premature birth. Nevertheless, the limited number of large-scale randomized controlled trials (RCTs) conducted so far have produced conflicting findings regarding the effectiveness of vitamin D supplementation in enhancing perinatal outcomes.

Keywords: Breastfeeding, Gestational diabetes, Pregnancy, Preterm, Preeclampsia, Supplement.

INTRODUCTION

Many nations have recognized vitamin D deficiency (VDD) as a public health issue; pregnant women are at a particularly high risk because their prevalence of VDD is up to 50% in the population [1]. Low vitamin D levels are common throughout pregnancy and infancy, however, there is limited information to establish dietary recommendations for vitamin D during these life stages [2]. Vitamin D is primarily responsible for preserving calcium homeostasis and promoting bone health. Furthermore, its involvement in various physiologic functions, such as immunomodulation, cell proliferation, and cell differentiation, has been established in numerous tissues and organs, including the heart, brain, and pancreas [3].

Recent research suggests that nutrition can influence immunological and metabolic programming during critical stages of fetal and postnatal development.

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Thus, modern dietary patterns may raise the risk of immunological and metabolic dysregulation, which is linked to an increase in a variety of noncommunicable diseases [4]. Vitamin D stands out among these nutrients; its impact on gene regulation and prenatal programming may describe its long list of health advantages [5].

Rickets in Newborns

Nutritional rickets remain a substantial global health concern among children, as evidenced by recent reports of its prevalence rising in numerous developed nations.

To avoid rickets, it is crucial for pregnant women and their infants to take vitamin D supplementation. Randomized controlled trials have shown that infants who receive 400 IU of vitamin D daily can reach 25-hydroxyvitamin D levels above 50 nmol/L [6].

Dental Consequences of Vitamin D

Research has shown that children whose mothers do not get enough vitamin D during the last three months of pregnancy are more likely to develop cavities in their permanent teeth by the age of six. On the other hand, there was no correlation between 25(OH)D in early life and the frequency or severity of enamel defects. In addition to bolstering the the established effects of vitamin D on bones and minerals, these findings add weight to the case for supplementation during pregnancy and the first few years of life [7].

VITAMIN D FOR MOTHER (PREECLAMPSIA, GESTATIONAL DIABETES)

There's a high prevalence of Gestational weight gain, gestational diabetes, and pregnancy-induced hypertension among women in developed countries [8, 9]. Vitamin D deficiency (VDD) poses a notable risk for pregnant women in Latin America, the Middle East, Asia, and Africa, with prevalence rates being the highest globally in these regions [10]. Maternal VDD is associated with an increased likelihood of various adverse health outcomes for both mothers and newborns. These include heightened risks of hypertension and gestational diabetes mellitus (GDM), elevated production of inflammatory cytokines of mother [11], insulin resistance, first cesarean section [12], high body mass index (BMI) of the mother as well as symptoms of postpartum depression [10].

A systematic review examined the links between maternal Vitamin D deficiency and pregnancy included six studies that utilized enzyme-linked immunosorbent

assay (ELISA) methods [13 - 17], each revealing one or more positive associations between Vitamin D Deficiency (VDD) and maternal and/or neonatal health outcomes. Two of them demonstrated positive associations between VDD and maternal GDM [18], as well as neonatal low birth weight (LBW) and small for gestational age (SGA) [19]. Two studies focused on maternal outcomes and indicated a positive relation between VDD and maternal pre-eclampsia [20, 21], while the last two studies found no significant associations at all.

Vitamin D and Preeclampsia

Pre-eclampsia is a complex pregnancy disorder affecting multiple systems, characterized by varying levels of placental mal-perfusion that result in the release of soluble factors into the maternal circulation. These factors induce injury to the maternal vascular endothelium, giving rise to hypertension and multi-organ damage. The placental involvement in this condition can lead to fetal growth restriction and, in severe cases, stillbirth. Notably, pre-eclampsia stands as a significant contributor to both maternal and perinatal mortality and morbidity, particularly in low-income and middle-income countries [22].

In a cohort study involving 13,806 pregnant women, maternal vitamin D deficiency during the gestational period of 23 to 28 weeks was found to be strongly linked to an increased risk of severe preeclampsia. After adjusting for relevant confounding factors, the odds ratio (OR) was 3.16, with a 95% confidence interval (CI) ranging from 1.77 to 5.65 [21]. Notably, current research indicates that vitamin D supplementation has the potential to enhance nifedipine treatment for preeclampsia. This supplementation is shown to reduce the time required to control blood pressure and extend the duration before the occurrence of subsequent hypertensive crises, possibly through an immunomodulatory mechanism [23]. However, despite these positive effects, data on the preventive impact of vitamin D supplementation against the onset of preeclampsia in pregnancy remain inconclusive [24].

Vitamin D and Gestational Diabetes

GDM refers to the manifestation of diabetes symptoms during pregnancy in women who had normal glucose metabolism before becoming pregnant [25]. This condition is linked to an increased likelihood of developing type 2 diabetes mellitus (T2DM), metabolic syndrome (MS) and cardiovascular disease [26].

Women with GDM have a higher probability of undergoing cesarean deliveries, and their newborns tend to have a greater birth weight [27, 28] and a higher risk of childhood asthma [29]. GDM is also correlated with elevated risks of depression [30], childhood-impaired glucose tolerance [31], and childhood

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