Ministry of Highe
Edcation Uuniversity
Hill College University
Department Medical Physics

Vitamin D

بحث مقدم إلى :

كلية الحلة الجامعة – قسم الفيزياء الطبية

وهو جزء من متطلبات نيل درجة البكالوريوس في الفيزياء الطبية

إعداد الطلبة :

علي عدنان كاظم	سجاد رياض هادي
حسين جاسم محمد	حسين محمد جاسم
حسام وهاب محمد	حميد جبار عبد

بأشراف :

م.م نورس بهاء

1445 هـ

2024 م

بسم الله الرحمن الرحيم

﴿يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ﴾

صدق الله العلي العظيم

(المجادلة: ١١)

الاهداء

إلى الكهف الحصين وغياث المضطرين المستكين
وملاذ المؤمنين سيدي ومولاي صاحب العصر
والزمان (عجل الله فرجه الشريف)

إلى صاحب السيرة العطرة والدر المستنير فلقد كان له
الفضل الأول

والدي الحبيب ...

إلى من وضعتني على طريق الحياة وجعلتني رابط
الجأش وراعتني حتى صرت كبيرا

امي الغالية ...

إلى من كان لهم بالغ الأثر في كثير من العقبات
والصعاب

إخوتي ...

شكر والتقدير

إن قلت شكرا فشكري لن يوفيكم حقا سعيكم فكان السعي مشكورا

الحمد لله الذي ذكره شرف للذاكرين وشكره فوز للشاكرين

وحمده عز للحامدين وطاعته نجاة للطائعين والصلاة والسلام على خاتم الأنبياء والمرسلين محمد وعلى ال بيته الطيبين الطاهرين

عن رسول الله (ص)

انه قال: (من لم يشكر الناس لم يشكر الله)

فبعد الانتهاء من البحث يطيب لي في مقام الشكر أسجل بأمتنان شكري وتقديري إلى الاستاذة الفاضلة

((م.م نورس بهاء))

وفي الختام اتقدم بالشكر الجزيل إلى كل من ساهم بشكل أو باخر في انجاز هذا البحث .

Summary

Vitamin D is crucial for bone health, immune function, and overall well-being. It's synthesized by the body when the skin is exposed to sunlight and is also found in certain foods and supplements. Getting enough sunlight or taking supplements can help maintain adequate vitamin D levels.the prevalence of vitamin D deficiency is widespread, affecting a significant portion of the population globally.

Vitamin D deficiency occurs when the body doesn't have enough of this essential vitamin. It can lead to various health issues, including weakened bones, increased risk of infections, fatigue, and mood disturbances. It's important to ensure adequate intake through sunlight, diet, or supplements to prevent deficiency.

Skin exposure to sunlight at wavelengths around is required for the synthesis of vitamin D. Ultraviolet B (UVB) radiation in this range penetrates the skin and converts 7-dehydrocholesterol, a precursor present in the skin, into pre-vitamin D3, which then undergoes further conversion to vitamin D3.

It's important to note that vitamin D supplementation should be done under the guidance of a healthcare professional to ensure appropriate dosage and monitoring, especially for individuals with certain medical conditions or those taking medications that may interact with vitamin D.

Addressing and correcting vitamin D deficiency through supplementation, sunlight exposure, and dietary changes can help prevent and manage these conditions, especially in high-risk populations .

NO	Subject	Page
	Summary	I
1.1	**Introdcution**	1
1	**Vitamin D**	1
2	**Prevalence of vitamin D deficiency word wid**	1
3	**vitamin D deficiency**	3
4	**Risk vitamin D deficiency**	6
5	**Skin exposure to sunlight at the regured wave length**	13
6	**Inclusion of rich source of vitamin D in the diet**	16
7	**The effect of vitamin D on other factors**	18
8	**Diagnosis and treatment of vitamin D deficiency**	26
9	**Diseases caused by vitamin D deficiency**	29
	References	37

1. Introduction

1.1 Vitamin D

VITAMIN D is an immunomodulator hormone with established effectiveness against various upper respiratory infections. Vitamin D can stall hyper-inflammatory responses and expedite healing process of the affected areas, primarily In the lung notissue. Thus, there are ecological and mechanistic reasons to promote exploration of vitamin D action In COVID-19 patients{1}.

2. prevalence of vitamin D deficiency word wid

Vitamin D deficiency is a major public health problem worldwide in all age groups, even in those residing in countries with low latitude, where it was generally assumed that UV radiation was adequate enough to prevent this deficiency, and in industrialized countries, where vitamin D fortification has been implemented now for years {2}.

The prevalence of clinical vitamin D deficiency (rickets and osteomalacia) is high in many parts of the world, and there is a resurgence of rickets among children of ethnic minority groups in Europe and Australasia {3}.

Vitamin D status and the prevalence of vitamin D deficiency and insufficiency have been addressed in many studies covering all continents. Vitamin D deficiency, when serum 25-hydroxyvitamin D is lower than 25 {4}.

Vitamin D is a fundamentally critical nutrient that the human body requires to function properly. It plays an important role in musculoskeletal health due to its involvement in the regulation of calcium and phosphorus {5}.

Vitamin D deficiency causes the bone hypomineralization disorder osteomalacia in humans and is associated with many non-skeletal disorders. We aim to estimate the global and regional prevalence of vitamin D deficiency in people aged 1 year or older from 2000 to 2022 {6}. maternal VD deficiency may lead to obesity and other obesity-related diseases among offspring later in life {7}.

It has been reported to be independently associated with stunting, obesity, and premature activation of vitamin D. Hypothalamic-pituitary-gonadal axis. The coronavirus disease 2019 (COVID-19) pandemic has led to changes in lifestyle, which could influence vitamin D status on a population level {8} .

Children's Vitamin D (VitD) fortification and supplementation are diminishing due to less outdoor exercise and insufficient VitD intake (low exogenous intake and endogenous malabsorption induced by gastrointestinal disease). Consequently, children in many developed countries suffer from VitD deficiency, which may contribute to many paediatric disorders {9}.

Vitamin D deficiency is a worldwide health problem. However, the prevalence of vitamin D deficiency in Asian populations is unclear. The aims of our study were to investigate the prevalence of vitamin D deficiency and its association with different health outcomes in Asia {10}.

Vitamin D deficiency is associated with non-communicable and infectious diseases, but the vitamin D status of African populations is not well characterised. we aimed to estimate the prevalence of vitamin D deficiency in children and adults living in Africa {11}.

Vitamin-D deficiency is linked to a wide range of chronic and infectious diseases. Body of literature suggested that the prevalence of

this deficiency can have geographical variation. Although vitamin D deficiency is frequently reported in the South Asian population {12}.

Vitamin D deficiency has a high worldwide prevalence, but actions to improve this public health problem are challenged by the heterogeneity of nutritional and clinical vitamin D guidelines, with respect to the diagnosis and treatment of vitamin D deficiency{13}.

Vitamin D status varies across all continents and countries. Vitamin D status usually is adequate in Latin America and Australia, but in contrast it is very low in the Middle East and some countries in Asia. Trends in vitamin D status, whether it improves or declines over the years, carry important messages. Trends usually are small, but can be predictors and indicators of general health {14}.

3.vitamin D deficiency

There is Increasing evidence that vitamin D has widespread tissue effects. In addition to osteoporosis, vitamin D deficiency has been associated with cardiovascular disease, diabetes, cancer, infections and neurodegenerative disease{15}.

That low vitamin D status may be associated with an increased risk of COVID-19 infection. Further studies are needed to evaluate the impact of vitamin D supplementation on the clinical severity and prognosis in patients with COVID-19{16}.

Status are young children especially those with low birth weight, adolescents, pregnant and lactating women, older persons, and non-Western immigrants. A vitamin D status can be considered adequate {17}.

VITAMIN D deficiency Is a global problem, thought to be related to lack of sunlight exposure, and usually accompanied by reduced dietary intake. This study was designed to determine vitamin D statu{18}.

VITAMIN D has an immunomodulatory role through its anti-inflammatory and anti-autoimmune actions. In the nervous system, vitamin D is involved in the regulation of calcium-mediated neuronal excitotoxicity, in the reduction of oxidative stress, and in the Induction of synaptic structural proteins {19}.

ClINICIANS may recommend supplementation but be unsure how to choose the optimal dose and type weof vitamin D and how to use testing to monitor therapy. This review outlines strategies to prevent, diagnose, and treat vitamIn D deficiency In adults{20}.

Skin pigmentation, aging, sunscreen use, all Influence the cutaneous production of vitamin D3. Vitamin D deficiency not only causes rickets among children but also precipitates and exacerbates osteoporosis among adults and causes the painful bone disease osteomalacia{21}.

ElDERly subjects are at risk of insufficient vitamin D status mainly because of diminished capacity for cutaneous vitamin D synthesis. In cases of insufficient endogenous production, vitamin D status depends on vitamin D intake{22}.

INVITAMIN D plays a vital role in successful pregnancy outcomes for both the mother and fetus. Vitamin D is bound to vitamin D binding protein (VDBP) in blood and is carried to the liver, kidneys{23}.

VITAMIN D levels may contribute to hip fractures in women, although limited data are available on vitamin D levels In US women admitted with acute hip fractures{24}.

VITAMIN D receptors have a broad tissue distribution that includes vascular smooth muscle, endothelium, and cardiomyocytes. A growing body of evidence suggests that vitamin D deficiency may adversely affect the cardiovascular system{25}.

VITAMIN D reduces the risk of autoimmune diseases including such as multiple sclerosis and type 1 diabetes mellitus, and weaker evidence for rheumatoid . Unexplained hypocalcaemia should be attributed to vitamin D deficiency in “at risk” ethnic minority groups until proved otherwise {26}.

Unexplained hypocalcaemia should be attributed to vitamin D deficiency in “at risk” ethnic minority groups until proved otherwise. VITAMIN D reduces the risk of autoimmune diseases including such as multiple sclerosis and type 1 diabetes mellitus, and weaker evidence for rheumatoid {27}.

VITAMIN D from ultraviolet-B (UVB) irradiance, food, and supplements is receiving increased attention lately for its role In maintaining optimal health{28}.

Aims/hypothesis : Low birthweight is a risk factor for type 2 diabetes but it is unknown whether low birthweight is associated with distinct clinical characteristics at disease onset. We examined whether a lower or higher birthweight in type 2 diabetes is associated with clinically relevant characteristics at disease onset{29}.

Levels of 25 (OH) D have been found negatively associated with dental caries in children, Indicating that low vitamin D levels may be considered a potential risk factor to this dental disease{30}.

VITAMIN D plays a crucial role in oral health, and Its deficiency is associated to significant changes in oral health diseases. We aimed to

explore the relationship between levels of 25-hydroxyvitamin D (25 (OH) D) and dental caries In children{31}.

Risk, to identify the dose and dose frequency most closely associated with reduced risk of falls and fractures, and to review the impact of vitamin D with and without supplemental calcium on risk of fractures{32}.

4. Risk vitamin D deficiency

Vitamin D deficiency in children will cause growth retardation and classic signs and symptoms of rickets. In adults, vitamin D deficiency will precipitate and exacerbate both osteopenia and osteoporosis and increase the risk of fracture. Muscle weakness has long been associated with vitamin D deficiency. A vitamin D receptor is present in skeletal muscle, and vitamin D deficiency has been associated with proximal muscle weakness, an increase in body sway, and an increased risk of falling. Vitamin D deficiency in adults can also cause a skeletal mineralization defect. The unmineralized osteoid provides little structural support for the periosteal covering. As a result, patients with osteomalacia often complain of isolated or global bone discomfort along with aches and pains in their joints and muscles. These patients may be misdiagnosed with fibromyalgia, dysthymia, degenerative joint disease, arthritis, chronic fatigue syndrome, and other dise {33}.

The major source of vitamin D for humans is exposure to sunlight. Anything that diminishes the transmission of solar UVB radiation to the earth's surface or anything that interferes with the penetration of UVB radiation into the skin will affect the cutaneous synthesis of vitamin D3 Melanin is extremely efficient in absorbing UVB radiation, and, thus, increased skin pigmentation markedly reduces vitamin D3 synthesis. Similarly, a sunscreen with a sun protection of 15 absorbs 99% of the

incident UVB radiation, and, thus, when topically applied properly will decrease the synthesis of vitamin D3 in the skin by 99%. African Americans with very dark skin have an SPF of 15, and, thus, their ability to make vitamin D in their skin is reduced by as much as 99%. This along with decreased milk intake are the explanations for why most African Americans who live in a temperate climate are vitamin D deficient, whereas Africans living near the equator where vitamin D3 synthesis is more efficient because of the higher flux of UVB photons are not. The angle at which the sun reaches the Earth has a dramatic effect on the number of UVB photons that reach the Earth's surface. This is why when the zenith angle is increased during the wintertime and in the early morning and late afternoon, little if any vitamin D3 synthesis occurs. The practice of purdah, whereby all skin is covered and prevented from being exposed to sunlight places those who practice it at high risk of vitamin D deficiency and explains why in the sunniest areas of the world vitamin D deficiency is very common in both children and adults. Aging is associated with decreased concentrations of 7-dehydrocholesterol, the precursor of vitamin D3 in the skin. A 70-year-old has ≈25% of the 7- dehydrocholesterol that a young adult does and thus has a 75% reduced capacity to make vitamin D3 in the skin. Because vitamin D is fat-soluble, it is readily taken up by fat cells. Obesity is associated with vitamin D deficiency, and it is believed to be due to the sequestration of vitamin D by the large {34}.

Several retrospective and prospective studies that evaluated circulating concentrations of 25(OH)D support the concept that vitamin D deficiency increases the risk of developing and dying from cancer. It has been suggested that adults with 25(OH)D of <50 nmol/L who were then followed for up to 19 y had a 30–50% increased risk of developing colorectal, breast, prostate, and many other cancers. A meta-analysis showed that increasing intake of vitamin D to 1000 IU vitamin D3/d

would be associated with a decreased risk of colorectal and breast cancer by as much as 50%. Men who ingested >400 IU vitamin D/d had a markedly reduced risk of developing several cancers, including those of the pancreas and esophagus and non-Hodgkin lymphoma. Lappe et al reported that postmenopausal women who received 1100 IU vitamin D3 and 1000 mg Ca daily for 4 years reduced their risk of developing cancer by 60%. Living at higher latitudes is associated with an increased risk of type 1 diabetes, multiple sclerosis, and hypertension. Children who received 2000 IU vitamin D/d during the first year of life and who were followed for 31 y were found to have a reduced risk of developing type 1 diabetes by 78% compared with children who were not supplemented with vitamin D. Women who received >400 IU vitamin D/d were found to have a >40% reduced risk of developing multiple sclerosis and rheumatoid arthritis. Hypertensive patients who were exposed to a tanning bed raised their blood concentrations of 25(OH)D by >180% in 3 mo and became normotensive. Patients who live at higher latitudes and are at risk of vitamin D deficiency are also more prone to developing schizophrenia, and vitamin D deficiency has been associated with depression. Vitamin D deficiency in pregnancy has also {35}.

A deficiency in vitamin D results in a decrease in the efficiency of intestinal absorption of dietary calcium and phosphorus. This causes a transient lowering of the ionized calcium, which is immediately corrected by the increased production and secretion of PTH. PTH sustains the blood-ionized calcium by interacting with its membrane receptor on mature osteoblasts, which induces the expression of RANKL. This plasma membrane receptor protein is recognized by RANK, which is present on the plasma membrane of preosteoclasts. The intimate interaction between RANKL and RANK results in increased production and maturation of osteoclasts. PTH also decreases the gene expression of osteoprotegerin (a RANKL-like receptor that

acts as a decoy) in osteoblasts, which further enhances osteoclastogenesis. The osteoclasts release hydrochloric acid and collagenases to destroy bone, resulting in the mobilization of the calcium stores out of the skeleton. Thus vitamin D deficiency- induced secondary hyperparathyroidism results in the wasting of the skeleton, which can precipitate and exacerbate osteoporosis. Vitamin D deficiency and attendant secondary hyperparathyroidism also cause a loss of phosphorus in the urine and a lowering of serum phosphorus levels. This results in an inadequate calcium × phosphorus product, causing poor or defective mineralization of the bone matrix laid down by osteoblasts. In children, the poorly mineralized skeleton under the weight of the body and gravity results in the classic bony rachitic deformities in the lower limbs (bowed legs or knocked knees). Adults have enough minerals in their skeleton to prevent skeletal deformities. However, in a vitamin D deficient state, the newly laid-down osteoid cannot be properly mineralized{36}.

Vitamin D–deficient mothers give birth to babies who are themselves deficient in vitamin D and are thus at risk of hypocalcemia and congenital rickets. Over the past 20 years, there have been numerous studies probing the potential effect of maternal vitamin D status on pregnancy complications, such as pre-eclampsia and preterm birth, and birth and early infant outcomes including low birth weight and stunting in the first year of life. The working group highlighted the importance of interactions of vitamin D with other nutrients (e.g., vitamin A, calcium, magnesium, folate, and iron) during pregnancy and lactation. It is expected that the effect of prenatal vitamin D on skeletal outcomes (including linear growth and the risk of rickets in infants) may depend on calcium nutriture. Furthermore, prenatal calcium supplementation (1–2 g/day) has been shown to reduce the risk of pre- eclampsia. Vitamin D is secreted into breast milk, but the concentration depends on

the lactating woman's regular vitamin D intake. High-dose maternal supplementation (4000 IU/day or higher) may be required to boost vitamin D content in breast milk enough to ensure that the equivalent of 200–400 IU/day is transferred to the exclusively breastfeeding infant{37}.

Strong evidence recently emerged linking vitamin D deficiency to adverse respiratory outcomes, particularly asthma exacerbations, and tuberculosis (TB) reactivation, likely mediated by the immune modulatory effects of vitamin D. Recent meta-analyses show that vitamin D supplementation can decrease the frequency of upper respiratory infections (URIs)3 and asthma exacerbations. Vitamin D may have a role in the prevention of ARI and asthma exacerbations or as an adjunctive therapy in patients receiving conventional antimicrobial treatment for TB. meta-analysis of vitamin D .supplementation trials for the management of asthma revealed a significant reduction in the frequency of asthma exacerbations that required corticosteroid treatment, as well as a significant reduction in severe episodes requiring emergency medical attention. The protective effects of vitamin D supplementation against asthma exacerbation are likely to be mediated at least in part by the induction of innate immune responses to respiratory viruses that commonly trigger such events. Vitamin D may also have a role in the prevention of Mycobacterium tuberculosis infection, prevention of active TB, or as an adjunctive therapy to enhance response to antimicrobial treatment of active TB disease{38}.

A growing body of evidence suggests that low levels of 25(OH)D may adversely affect the cardiovascular system. Cross-sectional studies show associations between decreased sun exposure or hypovitaminosis D and increased risk for myocardial infarction, stroke, heart failure, and peripheralarterial disease, and studies in rodents have shown that

vitamin D protects against cardiac hypertrophy and myocardial dysfunction. Several mechanisms may explain the link between vitamin D deficiency and cardiovascular disease. Vascular smooth muscle cells and endothelial cells express receptors for vitamin D and have the ability to convert circulating 25(OH)D into 1,25(OH)2 D. In vitro, activated 1,25(OH)2D suppresses renin gene expression and regulates the growth and proliferation of vascular smooth muscle cells and cardiomyocytes. A study verified the relationship between hypovitaminosis D and intimal medial thickening (IMT) of the common carotid artery, measured by ultrasonography among 390 type 2 diabetic patients. Hypovitaminosis D was defined as a serum 25(OH)D concentration ≤ 15 ng/mL and IMT as a focal thickening > 1.2 mm at the level of the common carotid artery. They found a strong inverse and independent association between serum 25(OH)D and carotid artery IMT. The patients with hypovitaminosis D (n = 130) had a marked increase in common carotid artery IMT (1.10 ± 0.15 vs . 0.87 ± 0.14 mm, $p < 0.001${39}.

In 1990, a case-control study showed that AMI patients had lower vitamin D levels than controls, and this difference was more pronounced in the winter-spring period. Of note, the relative risk of AMI decreased across increasing quartiles of vitamin D, suggesting an inverse correlation between vitamin D levels and AMI risk. These figures have also been confirmed in more contemporary cohorts. Among 1739 Framingham Offspring Study healthy participants, the rates of major cardiovascular events were 50% and 80% higher in those with vitamin D insufficiency and deficiency, respectively. In particular, subjects with no history of coronary artery disease and vitamin D levels < 10 ng/mL experienced a hazard ratio of 1.8 for developing a first cardiovascular event during a 5-year follow-up compared with subjects with levels > 15 ng/mL. Finally, in 18225 men in the Health Professionals Follow-up

Study, low vitamin D levels were associated with a higher risk of AMI, even after controlling for other cardiovascular risk factors and, at 10-year follow-up, subjects with normal vitamin D levels (> 30 ng/mL) had approximately half the risk of AMI. These findings have been recently confirmed in a large meta-analysis that showed an adjusted pooled relative risk of 1.52 for total cardiovascular events when comparing the lowest to the highest categories of baseline circulating vitamin D concentration. Thus, there is growing evidence suggesting that vitamin D deficiency represents a novel risk factor for AMI. In agreement with these epidemiological data, prospective reports have found a high prevalence of vitamin D deficiency in patients hospitalized with AMI. A multicenter study performed on 239 acute coronary syndrome patients showed that 96% of them had vitamin D levels < 30 ng/mL at hospital presentation[45]. In line with this, demonstrated that 74% of AMI patients had low vitamin D levels and, of note, 36% of them had a severe deficiency. reported a median serum concentration of vitamin D of 18.5 ng/mL in a cohort of 206 AMI patients (7% with STEMI), and a severe deficiency in 10% of the sample analyzed. Similar findings were also observed, who reported a prevalence of hypovitaminosis D in AMI patients of 89% and 68%, respectively{40}.

Studies have shown that vitamin D deficiency and other well-studied factors contribute to the formation and progression of DPN. For example, studies conducted at Shanghai University revealed an association between 25(OH)D levels in blood serum and the severity of neuropathy in DM2 patients. The greatest changes were found in patients with 25(OH)D levels lower than 16 ng/ml. A possible association between vitamin D deficiency and proinflammatory cytokines in patients with DM2 and DPN was also demonstrated by the results of a study conducted in Turkey—not only increased concentrations of interleukins (IL-13 and IL-17) but also a correlation

between the level of 25(OH)D in serum and the IL values. On the one hand, because of vitamin D insufficiency and deficiency, glycaemic control probably deteriorates, leading to a higher risk of microvascular complications. On the other hand, the immune-modulating properties of vitamin D and its regulation of oxidative stress suggest effects on systemic inflammation in DM patients. In addition, vitamin D deficiency leads to increased parathyroid hormone levels, the excess of which, in turn, can adversely affect tissue sensitivity to insulin and vascular remodeling parameters. In one study, a significant reduction in the painful DPN symptoms was noted in patients with DM2 20 weeks after a single intramuscular injection of 600,000 IU of vitamin D. Supplementing vitamin D at a dose of 50,000 IU per week for three months reduced HbA1c significantly in patients with DM2 and DN {41}.

5- skin exposure to sunlight at the regured wave length

The UV components of sunlight are believed to be a major cause of human skin cancer, and DNA is thought to be the principal molecular target. Alterations of the intensity and wavelength distribution of solar UV radiation reaching the surface of the earth, for example by depletion of stratospheric ozone, will change the effectiveness of solar radiation in damaging DNA in human skin{42}.

An integrated review of the transfer of optical radiation into human skin is presented, aimed at developing useful models for photomedicine. The component chromophores of epidermis and stratum corneum in general determine the attenuation of radiation in these layers, moreso than does optical scattering. Epidermal thickness and melanization are important factors for UV wavelengths less than 300 nm, whereas the attenuation of UVA (320–400 nm) and visible radiation is primarily via melanin{43}.

Penetration depth of ultraviolet, visible light and infrared radiation in biological tissue has not previously been adequately measured. Risk assessment of typical intense pulsed light and laser intensities, spectral characteristics and the subsequent chemical, physiological and psychological effects of such outputs on vital organs as consequence of inappropriate output use are examined{44}.

A theoretical treatment has been developed for the optical properties of a layered structure which absorbs and scatters light. This theory predicts that the logarithm of the inverse of reflectance (LIR) of the surface should be a useful parameter for the examination of that structure{45}.

Exposure to sunlight initiates the formation of vitamin D3 in skin as the UV B radiation in the solar spectrum causes the photoconversion of 7-dehydrocholesterol to previtamin D3. A heat-induced isomerization then converts previtamin D3 to vitamin D3 over a period of days{46}.

The photoprotective role of melanin was evaluated by comparing the transmission of ultraviolet (UV) radiation through skin samples of blacks and Caucasians, using both biologic and spectroscopic techniques{47}.

The term "exposome" describes the totality of exposures to which an individual is subjected from conception to death. It includes both external and internal factors as well as the human body's response to these factors. Current exposome research aims to understand the effects all factors have on specific organs, yet today, the exposome of human skin has not received major attention and a corresponding definition is lacking. This review was compiled with the collaboration of European scientists, specialized in either environmental medicine or skin biology. Acomprehensive review of the existing literature was performed using

PubMed. The search was restricted to exposome factors and skin aging. Key review papers and all relevant, epidemiological, in vitro, ex vivo and clinical studies were analyzed to determine the key elements of the exposome influencing skin aging. Here we propose a definition of the skin aging exposome. It is based on a summary of the existing scientific evidence for the role of exposome factors in skin aging. We also identify future research needs which concern knowledge about the interaction of distinct exposomal factors with each other and the resulting net effects on skin aging and suggest some protective measures {48}.

Multiphoton excitation microscopy at 730 nm and 960 nm was used to image in vivo human skin autofluorescence from the surface to a depth of approximately 200 microm. The emission spectra and fluorescence lifetime images were obtained at selected locations near the surface (0–50 microm) and at deeper depths (100– 150 microm) for both excitation wavelengths. Cell borders and cell nuclei were the prominent structures observed {49}.

Skin cancer is the most common type of cancer in fair-skinned populations in many parts of the world. The incidence, morbidity and mortality rates of skin cancers are increasing and, therefore, pose a significant public health concern. Ultraviolet radiation (UVR) is the major etiologic agent in the development of skin cancers. UVR causes DNA damage and genetic mutations, which subsequently lead to skin cancer. A clearer understanding of UVR is crucial in the prevention of skin cancer. This article reviews UVR, its damaging effects on the skin and its relationship to UV immunosuppression and skin cancer. Several factors influence the amount of UVR reaching the earth's surface, including ozone depletion, UV light elevation, latitude, altitude, and weather conditions. The current treatment modalities utilizing UVR (i.e.

phototherapy) can also predispose to skin cancers. Unnecessary exposure to the sun and artificial UVR (tanning lamps) are important personal attributable risks. This article aims to provide a comprehensive overview of skin cancer with an emphasis on carefully evaluated statistics, the epidemiologyof UVR-induced skin cancers, incidence rates, risk factors, and preventative behaviors & strategies, including personal behavioral modifications and public educational initiatives {50}.

6- Inclusion of rich source of vitamin D in the diet

In recent decades, interest in vitamin D has increased exponentially, particularly as a vitamin D deficit has been associated with multiple diseases and, globally, there appears to be a high vitamin D deficiency . Currently, the role of vitamin D as a hormone has been confirmed in numerous physiological and pathophysiological processes, related to various organs and systems of the human body Despite solid evidence concerning the skeletal effects of the vitamin D hormone, at all ages, there are animated discussions about the possible extra-skeletal benefits of vitamin D supplementation Nevertheless, most researchers agree that patients who have a vitamin D deficiency (or insufficiency) should receive therapy in order to maintain bone health and overall good health {51}.

This is particularly true in patients at high risk of deficiency, such as older adults (particularly those living in long-term care facilities), patients with diabetes, chronic kidney disease (CKD), and malabsorption, among others Although various guidelines recommend against supplementation with vitamin D for the primary prevention of fractures in community-dwelling, postmenopausal women in patients who already have experienced fragility fractures (secondary prevention), it is essential to obtain adequate serum concentrations of

25- hydroxyvitamin D 25(OH)D] (greater than 30 ng/mL) before starting antiresorptive or osteo-forming treatments, in order to maximize their effectiveness and to avoid hypocalcemia While there is growing awareness about the consequences of vitamin D deficiency, information on this deficiency is ambiguous and not sufficient{52}.

A general disregard of vitamin D deficiency occurs in spite of its high frequency, the ease of identifying it, and the simple, effective, and inexpensive means available to correct it{53}.

Since the identification of the chemical structure of vitamin D in 1930 by the Nobel Prize laureate Adolf Otto Reinhold Windaus, based on the knowledge acquired by several scientists who preceded him , there has been extraordinary advances in vitamin D research. Initially, the research focused on bone metabolic effects, recognizing the fundamental role of vitamin D and its metabolites in calcium homeostasis and bone metabolism. Afterwards, with the discovery of 25(OH)D in 1968 the studies expanded to other fields, including immune-mediated diseases, infections, cancer, and cardiovascular diseases]. Vitamin D is involved in the mechanisms of regulating the immune system; it regulates the actions of the suppressor T lymphocytes, the synthesis of cytokines, and acts by modulating the processes of cellular apoptosis {54}.

A recent trans-European examination of nutrient intake patterns showed dietary intakes of vitamin D to differ markedly between countries. Intakes were significantly higher in Nordic countries including Sweden, Denmark and Norway than in Mediterranean regions such as Italy and France {55}.

7 - The effect of vitamin D on other factors

Vitamin D is responsible for regulation of calcium and phosphate metabolism and maintaining a healthy mineralized skeleton. It is also known as an immunomodulatory hormone. Experimental studies have shown that 1,25-dihydroxyvitamin D, the active form of vitamin D, exerts immunologic activities on multiple components of the innate and adaptive immune system as well as endothelial membrane stability. Association between low levels of serum 25-hydroxyvitamin D and increased risk of developing several immune-related diseases and disorders, including psoriasis, type 1 diabetes, multiple sclerosis, rheumatoid arthritis, tuberculosis, sepsis, respiratory infection, and COVID-19, has been observed. Accordingly, a number of clinical trials aiming to determine the efficacy of administration of vitamin D and its metabolites for treatment of these diseases have been conducted with variable outcomes. Interestingly, recent evidence suggests that some individuals might benefit from vitamin D more or less than others as high inter-individual difference in broad gene expression in human peripheral blood mononuclear cells in response to vitamin D supplementation has been observed. Although it is still debatable what level of serum 25-hydroxyvitamin D is optimal, it is advisable to increase vitamin D intake and have sensible sunlight exposure to maintain serum 25-hydroxyvitamin D at least 30 ng/mL (75 nmol/L), and preferably at 40–60 ng/mL (100–150 nmol/L) to achieve the optimal overall health benefits of vitamin D {56}.

Vitamin D is a pleiotropic hormone that plays a vital role in regulating bone growth, maintaining calcium and phosphate homeostasis, modulating immune function, and a wide range of other pleiotrophic actions in humans, which have increased the attention for its clinical applications. Despite its importance, vitamin D deficiency is

prevalent worldwide and is related to a range of pathophysiological conditions, including an increased risk of osteoporosis and chronic and autoimmune diseases. The recommended daily doses of vitamin D vary depending on genetics, age, sex, and health status, with specific doses recommended for infants, children, adults, and those at increased risk of deficiency or specific health conditions. Maintaining adequate vitamin D levels is essential for optimal health, and together with sun exposure, appropriate supplementation strategies can help achieve this goal. Vitamin D supplementation is commonly used to maintain adequate levels, and the optimal administration strategy, such as a daily dose vs. a bolus, is still being investigated. This review aims to understand vitamin D physiology and the impact of relevant vitamin D polymorphisms and to evaluate the role of a daily dose versus a bolus in maintaining optimal vitamin D levels and clinical health outcomes. It also provides suggested clinical guidelines for clinicians based on the most recent scientific evidence {57}.

The steroid hormone vitamin D is required for normal calcium and phosphorus metabolism and is thus an important contributor to musculoskeletal health. Recent data have linked low vitamin D levels to a wide range of diseases, including cancer, cardiovascular disease, autoimmune disease and infection. Adequate levels of vitamin D are maintained through its cutaneous photosynthesis and oral ingestion. By some estimates, one billion people worldwide have vitamin D deficiency or insufficiency. A number of factors influence the photosynthesis and bioavailability of vitamin D and contribute to risk of impaired vitamin D status. These factors include variation in sun exposure due to latitude, season, time of day, atmospheric components, clothing, sunscreen use and skin pigmentation, as well as age, obesity and the incidence of several chronic illnesses. This review will focus on factors that influence vitamin D status and contribute to the prevalence of low vitamin D

levels. Key words: vitamin D; vitamin D synthesis; ultraviolet irradiation; sun exposure; vitamin D metabolism; vitamin D bioavailability; vitamin D deficiency {58}.

The bioactive vitamin D (VD) metabolite, 1,25-dihydroxyvitamin D3 regulates essential pathways of cellular metabolism and differentiation via its nuclear receptor (VDR). Molecular mechanisms which are known to play key roles in aging and cancer are mediated by complex processes involving epigenetic mechanisms contributing to efficiency of VD-activating CYP27A1 and CYP27B1 or inactivating CYP24 enzymes as well as VDR which binds to specific genomic sequences (VD response elements or VDREs). Activity of VDR can be modulated epigenetically by histone acetylation. It co-operates with other nuclear receptors which are influenced by histone acetyl transferases (HATs) as well as several types of histone deacetylases (HDACs). HDAC inhibitors (HDACi) and/or demethylating drugs may contribute to normalization of VD metabolism. Studies link VD signaling through the VDR directly to distinct molecular mechanisms of both HAT activity and the sirtuin class of HDACs (SIRT1) as well as the forkhead transcription factors thus contributing to elucidate complex epigenetic mechanisms for cancer preventive actions of VD {59}.

Vitamin D is a nutrient that, until recently, was neglected by the nutrition community. Although recognized in the early 20th century as an essential nutrient, recommendations for intake were often qualified as being needed only in the absence of sunlight. In theory (and in ancient times when early humans all lived closer to the equator), all vitamin D needs could be met by exposure to sunlight that provided ultraviolet (UV) B radiation, but only recently have we come to understand how UVB acts and what other factors—particularly environmental—mitigate cutaneous vitamin D synthesis. Studying vitamin D requirements is

difficult. Early dietary recommendations for vitamin D, such as the 1989 Recommended Dietary Allowance indicated a “relative paucity of recent controlled studies [and] … lack of data on which to base requirements.” It further stated that “clinical osteomalacia appears to be rare in the United States.” What is known today, however, is that vitamin D deficiency and insufficiency are widespread, which was not identified when the Dietary Reference Intakes (DRIs) for vitamin D were first published in 1997. In 2011, new DRIs for vitamin D reflected the need for more dietary vitamin D. While the 2011 DRI report did not set recommendations based on functions other than bone health, there remains a growing body of evidence for vitamin D’s many roles in the body {60}.

Vitamin D is a pro-hormone characterized by an intricate metabolism and regulation. It is well known for its role in calcium and phosphate metabolism, and in bone health. However, several studies have assessed a huge number of extra-skeletal functions, ranging from cell proliferation in some oncogenic pathways to antioxidant and immunomodulatory functions. Vitamin D exerts its role by binding to VDRs (vitamin D receptors), which are located in many different tissues. Moreover, VDRs are able to bind hundreds of genomic loci, modulating the expression of various primary target genes. Interestingly, plenty of gene polymorphisms regarding VDRs are described, each one carrying a potential influence against gene expression, with relapses in several chronic diseases and metabolic complications. In this review, we provide an overview of the genetic aspects of vitamin D and VDR, emphasizing the gene regulation of vitamin D, and the genetic modulation of VDR target genes. In addition, we briefly summarize the rare genetic disease linked to vitamin D metabolism {61}.

Vitamin D deficiency in children is a common nutritional issue in many populations worldwide, associated not only with skeletal malformations but, as recent studies suggest, also with the development of obesity and metabolic syndrome. The aim of this observational study was to assess the nutritional status of vitamin D in a group of Polish children with obesity and different grades of metabolic syndrome, with a consequent analysis of the correlation between vitamin D levels and the components of metabolic syndrome. For that purpose, the group of 78 participants (mean age: 14.18 ± 2.67 years) was recruited and further grouped in relation to vitamin D status into two groups of children with and without vitamin D deficiency. The biochemical parameters associated with obesity as well as anthropometric measures were assessed and analysed in search of significant differences between the groups. In the current group of children with obesity and vitamin D deficiency, HDL (45.00 ± 9.29) and adiponectin (7.21 ± 1.64) were found to be significantly lower than in their peers without vitamin D deficiency, whereas W/HtR (0.60 ± 0.04) and TG (171.31 ± 80.75) levels proved to be significantly higher. Body composition analysis using bioelectrical impedance returned no significant findings. The above findings suggest that vitamin D deficiency may influence lipid and glucose metabolism in children, leading to the development of abnormalities characteristic of the metabolic syndrome. A W/HtR parameter was shown to be a sensitive marker of abdominal obesity, which might provide an important means of assessing the correlation between vitamin D and this type of obesity. Independently, vitamin D deficiency may also influence the endocrinological function of adipose tissue, leading to lower concentrations of adiponectin. These in turn presented a linear correlation with the high results of the OGTT in the second hour of the test, hinting at its potential role in the pathophysiology of insulin resistance {62}.

1,25-Dihydroxvitamin D3 [1,25(OH)2D3] is the hormonally active form of vitamin D. The genomic mechanism of 1,25(OH)2D3 action involves the direct binding of the 1,25(OH)2D3 activated vitamin D receptor/retinoic X receptor (VDR/RXR) heterodimeric complex to specific DNA sequences. Numerous VDR co-regulatory proteins have been identified, and genome-wide studies have shown that the actions of 1,25(OH)2D3 involve regulation of gene activity at a range of locations many kilobases from the transcription start site. The structure of the liganded VDR/RXR complex was recently characterized using cryoelectron microscopy, X-ray scattering, and hydrogen deuterium exchange. These recent technological advances will result in a more complete understanding of VDR coactivator interactions, thus facilitating cell and gene specific clinical applications. Although the identification of mechanisms mediating VDR-regulated transcription has been one focus of recent research in the field, other topics of fundamental importance include the identification and functional significance of proteins involved in the metabolism of vitamin D {63}.

The active metabolites of vitamin D3 (D3) and lumisterol (L3) exert a variety of antiaging and photoprotective effects on the skin. These are achieved through immunomodulation and include anti-inflammatory actions, regulation of keratinocytes proliferation, and differentiation programs to build the epidermal barrier necessary for maintaining skin homeostasis. In addition, they induce antioxidative responses, inhibit DNA damage and induce DNA repair mechanisms to attenuate premature skin aging and cancerogenesis. The mechanism of action would involve interaction with multiple nuclear receptors including VDR, AhR, LXR, reverse agonism on RORα and -γ, and nongenomic actions through 1,25D3-MARRS receptor and interaction with the nongenomic binding site of the VDR. Therefore, active forms of vitamin D3 including its canonical (1,25(OH)2D3) and noncanonical

(CYP11A1-intitated) D3 derivatives as well as L3 derivatives are promising agents for the prevention, attenuation, or treatment of premature skin aging. They could be administrated orally and/or topically. Other forms of parenteral application of vitamin D3 precursor should be considered to avoid its predominant metabolism to 25(OH)D3 that is not recognized by CYP11A1 enzyme. The efficacy of topically applied vitamin D3 and L3 derivatives needs further clinical evaluation in future trials {64}.

The steroid hormone vitamin D is required for normal calcium and phosphorus metabolism and is thus an important contributor to musculoskeletal health. Recent data have linked low vitamin D levels to a wide range of diseases, including cancer, cardiovascular disease, autoimmune disease and infection. Adequate levels of vitamin D are maintained through its cutaneous photosynthesis and oral ingestion. By some estimates, one billion people worldwide have vitamin D deficiency or insufficiency. A number of factors influence the photosynthesis and bioavailability of vitamin D and contribute to risk of impaired vitamin D status. These factors include variation in sun exposure due to latitude, season, time of day, atmospheric components, clothing, sunscreen use and skin pigmentation, as well as age, obesity and the incidence of several chronic illnesses. This review will focus on factors that influence vitamin D status and contribute to the prevalence of low vitamin D levels. Key words: vitamin D; vitamin D synthesis; ultraviolet irradiation; sun exposure; vitamin D metabolism; vitamin D bioavailability; vitamin D deficiency {65}.

The metabolic syndrome develops in an individual with any three of the following risk factors: obesity, diabetes, inflammation, hypertension, dyslipidemia, and thrombosis. Recent evidence suggests that vitamin D may play a role in the development of some of these risk factors. The

metabolic syndrome is more common in western societies than the underdeveloped countries. Individuals in western societies usually consume a high calorie diet that lacks essential nutrients and, by virtue of being located in the northern hemisphere, they have limited sun exposures which restrict their vitamin D synthesis. Moreover, the lifestyle of these societies is considered sedentary. These dietary and environmental factors coupled with the sedentary lifestyle predispose them to metabolic syndrome risk factors. Active research revealed the role of vitamin D in the development of obesity, diabetes, inflammation, and hypertension. On the other hand, limited research has been done on the role of vitamin D in other risk factors such as dyslipidemia and thrombosis. The scientific community proposes to increase the current vitamin D fortification level in foods to reduce the risk factors of the metabolic syndrome {66}.

The prevalences of metabolic syndrome (MetS) and vitamin D deficiency are increasing dramatically worldwide. MetS is a major challenge because it can increase the risk of most non-communicable diseases. The beneficial effect of vitamin D on MetS components remains controversial, so the present review focused on the clinical effects of vitamin D supplementation on MetS components. Vitamin D can inhibit the protein expression of nuclear factor beta; improve arterial stiffness; decrease renin-angiotensin-aldosterone system activity, parathyroid hormone levels, inflammatory cytokines, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, and lanosterol 14 α-demethylase enzyme activity; increase the activity of lipoprotein lipase; alter gene expression in C2C12 cells; and improve phospholipid metabolism and mitochondrial oxidation. We tried to elucidate and analyze almost all evidence from randomized controlled trial studies of the efficacy of vitamin D supplementation in patients with MetS. The findings of the present study reported beneficial effects of vitamin D supplementation

on mentioned factors. Vitamin D supplementation is recommended in people with vitamin D deficiency even if it has no considerable effect on most MetS factors. However, existing data from interventional studies are insufficient to reach a definitive conclusion about the effect of vitamin D supplementation on MetS components in patients without vitamin D deficiency. Thus, new clinical studies are needed to test the hypothesis that vitamin D supplementation could alleviate MetS components in patients with sufficient intake of vitamin D {67}.

8- Diagnosis and treatment of vitamin D deficiency

Vitamin D has attracted considerable interest in recent years, and health care providers have reported large increases in vitamin D test requests. However, rates of diagnosis of vitamin D deficiency in clinical practice have not been investigated. We examined trends in diagnosis of vitamin D deficiency in children in England over time, and by sociodemographic characteristics {68}.

The recent discovery – in a randomised, controlled trial – that daily ingestion of 1100 IU of colecalciferol (vitamin D) over a 4-year period dramatically reduced the incidence of non-skin cancers makes it difficult to overstate the potential medical, social and economic implications of treating vitamin D deficiency. Not only are such deficiencies common, probably the rule, vitamin D deficiency stands implicated in a host of diseases other than cancer. The metabolic product of vitamin D is a potent, pleiotropic, repair and maintenance, secosteroid hormone that targets > 200 human genes in a wide variety of tissues, meaning it has as many mechanisms of action as genes it targets. A common misconception is that government agencies designed present intake recommendations to prevent or treat vitamin D deficiency. They did not. Instead, they are guidelines to prevent particular metabolic bone diseases. Official recommendations were never designed and are not

effective in preventing or treating vitamin D deficiency and in no way limit the freedom of the physician – or responsibility – to do so. At this time, assessing serum 25-hydroxy-vitamin D is the only way to make the diagnosis and to assure that treatment is adequate and safe. The authors believe that treatment should be sufficient to maintain levels found in humans living naturally in a sun-rich environment, that is, > 40 ng/ml, year around. Three treatment modalities exist: sunlight, artificial ultraviolet B radiation or supplementation. All treatment modalities have their potential risks and benefits. Benefits of all treatment modalities outweigh potential risks and greatly outweigh the risk of no treatment. As a prolonged 'vitamin D winter', centred on the winter solstice, occurs at many temperate latitudes, ≤ 5000 IU (125 μg) of vitamin D/day may be required in obese, aged and/or dark-skinned patients to maintain adequate levels during the winter, a dose that makes many physicians uncomfortable {69}.

Vitamin D deficiency is considered a major public health concern. Inadequate sun exposure, limited oral intake, and impaired intestinal absorption are common risk factors for vitamin D deficiency. An increasing amount of research is aimed at answering questions regarding the most convenient test that can assess vitamin D status, the indications for screening, and finally the utility of treatments for vitamin D deficiency. Our review outlines practical strategies to diagnose and treat vitamin D deficiency in adults. This study was undertaken in the PubMed and the Google Scholar databases in April 2018 without limitation as to the publication period. Vitamin D status is determined by measuring the 25-hydroxyvitamin D serum concentration. However, this technique has several limitations. Determining the accurate thresholds for vitamin D deficiency is still a matter of debate. Only individuals at risk for vitamin D deficiency should be screened. The symptoms of vitamin D deficiency are unspecific and very common. Therefore,

physicians may easily suspect vitamin D deficiency, measure 25-hydroxyvitamin D levels, and sometimes overprescribe supplementation. Hypovitaminosis D could rarely be treated by increasing consumption of foods naturally containing and fortified with vitamin D. Special attention should be given to vitamin D supplementation to prevent adverse effects. No safe and well-defined threshold of ultraviolet exposure allows adequate vitamin D synthesis without increasing the risk of skin cancer. Unanimous and decisive guidelines are urgently needed to improve knowledge and practices related to vitamin D deficiency {70}.

The concern about the assessment of vitamin D status is growing. Numerous publications warn about the high prevalence of vitamin D deficiency, as well as the potential role of vitamin D in non-bone health outcomes. The status of vitamin D is usually assessed by measuring serum total 25-hydroxyvitamin D (25OHD) concentration. This is the major circulating form of vitamin D and keeps an inverse correlation with serum parathyroid hormone (PTH) concentration. A value of 25OHD of 20 ng/ml is generally assumed as threshold of vitamin D sufficiency in epidemiologic studies because serum PTH tends to increase when the 25OHD concentration stands below this value. In pediatric population, very few studies have analyzed this issue and the negative relationship between serum 25OHD and serum PTH is not clear, which is the suitable circulating concentration of 25OHD and the threshold of deficiency being matters of controversy. The majority of 25OHD circulates in serum tightly bound to a globulin (DBP). According to the free hormone hypothesis, protein-bound hormones are not biologically available and it is the free form that exerts or facilitates the physiologic actions. If this is true, factors that affect DBP may alter the interpretation of total serum 25OHD measurements {71}.

Vitamin D is a fundamental mediator of skeletal metabolism. It also has important nonskeletal actions. We hypothesized that vitamin D deficiency may play an important role in skeletal morbidity and clinical outcomes in MM. We studied 148 newly diagnosed MM patients from January 1, 2004 through December 31, 2008 who had a serum 25-hydroxyvitamin D [25(OH)D] obtained within 14 days of diagnosis. Subjects with vitamin D deficiency [25(OH)D level less than 50 nmol/L (20 ng/mL)] had higher mean values of serum C-reactive protein (CRP) (2.40 mg/L vs. 0.84 mg/L, P = 0.02) and creatinine (1.75 mg/dL vs. 1.24 mg/dL, P = 0.03) and lower serum albumin values (3.12 g/dL vs. 3.39 g/dL, P = 0.003) compared to subjects without vitamin D deficiency. The prevalence of vitamin D deficiency increased in parallel with International Staging System (ISS): 16% of subjects in Stage I, 20% in Stage II, and 37% in Stage III (P = 0.03) were vitamin D deficient. No differences were detected between the two groups in terms of skeletal morbidity. Association of vitamin D deficiency with higher serum CRP, serum creatinine and ISS stage at time of diagnosis suggests that vitamin D deficiency may portend poorer outcomes in subjects with MM. Am. J. Hematol. 2009. (c) 2009 Wiley-Liss, Inc {72}.

9. Diseases caused by vitamin D deficiency

Vitamin D deficiency has been clearly linked to major chronic diseases associated with oxidative stress, inflammation, and aging, including cardiovascular and neurodegenerative diseases, diabetes, and cancer. In particular, the cardiovascular system appears to be highly sensitive to vitamin D deficiency, as this may result in endothelial dysfunction and vascular defects via multiple mechanisms. Accordingly, recent research developments have led to the proposal that pharmacological interventions targeting either vitamin D deficiency or its key downstream effects, including defective autophagy and abnormal

pro-oxidant and pro-inflammatory responses, may be able to limit the onset and severity of major cerebrovascular diseases, such as stroke and cerebrovascular malformations. Here we review the available evidence supporting the role of vitamin D in preventing or limiting the development of these cerebrovascular diseases, which are leading causes of disability and death all over the world {73}.

Vitamin D is a neurosteroid hormone crucially involved in neurodevelopment. Neural cell proliferation, neurotransmission, oxidative stress and immune function represent the main mechanisms mediated by vitamin D in the Central Nervous System. Therefore, its deficiency during pregnancy and early childhood may significantly impact on a developing brain, leading to possible adverse neuropsychological outcomes including Autism Spectrum Disorder (ASD). Significant vitamin D deficiency is described within children affected by ASD and in pregnant mothers whose offspring will later develop ASD, suggesting a possible role of the hormone as a contributing risk factor in the etiopathogenesis of ASD. We reviewed the actual literature on the potential contributing role of prenatal and early postnatal vitamin D deficiency in ASD etiopathogenesis, at both genetic and environmental levels, and the possible effect of vitamin D supplementation in autistic children. Conflicting but promising results emerged on the topic. Further Randomized Controlled Trials studies carried out during pregnancy and early infancy are necessary for better understanding the possible contribution of vitamin D deficiency in the etiopathogenesis of autism and the potential efficacy of the hormone supplementation in the improvement of ASD core symptoms {74}.

Deficiency in vitamin D (VitD), a lipid-soluble vitamin and steroid hormone, affects approximately 24% to 40% of the population of the Western world. In addition to its well-documented effects on the

musculoskeletal system, VitD also contributes importantly to the promotion and preservation of cardiovascular health via modulating the immune and inflammatory functions and regulating cell proliferation and migration, endothelial function, renin expression, and extracellular matrix homeostasis. This brief overview focuses on the cardiovascular and cerebrovascular effects of VitD and the cellular, molecular, and functional changes that occur in the circulatory system in VitD deficiency (VDD). It explores the links among VDD and adverse vascular remodeling, endothelial dysfunction, vascular inflammation, and increased risk for cardiovascular and cerebrovascular diseases. Improved understanding of the complex role of VDD in the pathogenesis of atherosclerotic cardiovascular diseases, stroke, and vascular cognitive impairment is crucial for all cardiologists, dietitians, and geriatricians, as VDD presents an easy target for intervention {75}.

The contributory roles of vitamin D in ocular and visual health have long been discussed, with numerous studies pointing to the adverse effects of vitamin D deficiency. In this paper, we provide a systematic review of recent findings on the association between vitamin D and different ocular diseases, including myopia, age-related macular degeneration (AMD), glaucoma, diabetic retinopathy (DR), dry eye syndrome (DES), thyroid eye disease (TED), uveitis, retinoblastoma (RB), cataract, and others, from epidemiological, clinical and basic studies, and briefly discuss vitamin D metabolism in the eye. We searched two research databases for articles examining the association between vitamin D deficiency and different ocular diseases. One hundred and sixty-two studies were found. There is evidence on the association between vitamin D and myopia, AMD, DR, and DES. Overall, 17 out of 27 studies reported an association between vitamin D and AMD, while 48 out of 54 studies reported that vitamin D was associated with DR, and 25 out of 27 studies reported an association

between vitamin D and DES. However, the available evidence for the association with other ocular diseases, such as glaucoma, TED, and RB, remains limited {76}.

Vitamin D exerts multiple beneficial effects in humans, including neuronal, immune, and bone homeostasis and the regulation of cardiovascular functions. Recent studies correlate vitamin D with cancer cell growth and survival, but meta-analyses on this topic are often not consistent. Methods: A systematic search of the PubMed database and the Clinical Trial Register was performed to identify all potentially relevant English-language scientific papers containing original research articles on the effects of vitamin D on human health. Results: In this review, we analyzed the antioxidant and anti-inflammatory effects of vitamin D against acute and chronic diseases, focusing particularly on cancer, immune-related diseases, cardiomyophaties (including heart failure, cardiac arrhythmias, and atherosclerosis) and infectious diseases. Conclusions: Vitamin D significantly reduces the pro-oxidant systemic and tissue biomarkers involved in the development, progression, and recurrence of chronic cardiometabolic disease and cancer. The overall picture of this review provides the basis for new randomized controlled trials of oral vitamin D supplementation in patients with cancer and infectious, neurodegenerative, and cardiovascular diseases aimed at reducing risk factors for disease recurrence and improving quality of life {77}.

Vitamin D plays an essential role in calcium and inorganic phosphate (Pi) homeostasis, maintaining their optimal levels to assure adequate bone mineralization. Vitamin D, as calcitriol (1,25(OH)2D), not only increases intestinal calcium and phosphate absorption but also facilitates their renal reabsorption, leading to elevated serum calcium and phosphate levels. The interaction of 1,25(OH)2D with its receptor

(VDR) increases the efficiency of intestinal absorption of calcium to 30–40% and phosphate to nearly 80%. Serum phosphate levels can also influence 1,25(OH)2D and fibroblast growth factor 23 (FGF23) levels, i.e., higher phosphate concentrations suppress vitamin D activation and stimulate parathyroid hormone (PTH) release, while a high FGF23 serum level leads to reduced vitamin D synthesis. In the vitamin D-deficient state, the intestinal calcium absorption decreases and the secretion of PTH increases, which in turn causes the stimulation of 1,25(OH)2D production, resulting in excessive urinary phosphate loss. Maintenance of phosphate homeostasis is essential as hyperphosphatemia is a risk factor of cardiovascular calcification, chronic kidney diseases (CKD), and premature aging, while hypophosphatemia is usually associated with rickets and osteomalacia. This chapter elaborates on the possible interactions between vitamin D and phosphate in health and disease {78}.

The global prevalence of eye diseases continues to grow, bringing with it a reduction in the activity levels and quality of life of patients, and partial or complete blindness if left untreated. As such, there is considerable interest in identifying more effective therapeutic options and preventive agents. One such agent is vitamin D, known to have a range of anti-cancer, anti-angiogenic, anti-inflammatory and anti-oxidative properties, and whose deficiency is linked to the pathogenesis of a range of cardiovascular, cancer, and inflammatory diseases. This review presents the current stage of knowledge concerning the link between vitamin D and its receptor and the occurrence of eye disease, as well as the influence of analogues of calcitriol, an active metabolite of vitamin D. Generally, patients affected by various ocular disorders have vitamin D deficiency. In addition, previous findings suggest that vitamin D modulates the course of eye diseases and may serve as a marker, and that its supplementation could mitigate some disorders. However, as

these studies have some limitations, we recommend further randomized trials to clarify the link between vitamin D and its activity with eye disease {79}.

Apart from developmental disabilities, the prevalence of chronic diseases increases with age especially in those with co-morbidities: vitamin D deficiency plays a major role in it. Whether vitamin D deficiency initiates and/or aggravates chronic diseases or vice versa is unclear. It adversely affects all body systems but can be eliminated using proper doses of vitamin D supplementation and/or safe daily sun exposure. Maintaining the population serum 25(OH)D concentration above 40 ng/mL (i.e., sufficiency) ensures a sound immune system, minimizing symptomatic diseases and reducing infections and the prevalence of chronic diseases. This is the most cost-effective way to keep a population healthy and reduce healthcare costs. Vitamin D facilitates physiological functions, overcoming pathologies such as chronic inflammation and oxidative stress and maintaining broader immune functions. These are vital to overcoming chronic diseases and infections. Therefore, in addition to following essential public health and nutritional guidance, maintaining vitamin D sufficiency should be an integral part of better health, preventing acute and chronic diseases and minimize their complications. Those with severe vitamin D deficiency have the highest burdens of co-morbidities and are more vulnerable to developing complications and untimely deaths. Vitamin D adequacy improves innate and adaptive immune systems. It controls excessive inflammation and oxidative stress, generates antimicrobial peptides, and neutralizes antibodies via immune cells. Consequently, vitamin D sufficiency reduces infections and associated complications and deaths. Maintaining vitamin D sufficiency reduces chronic disease burden, illnesses, hospitalizations, and all-cause mortality. Vulnerable communities, such as ethnic minorities living in temperate countries,

older people, those with co-morbidities, routine night workers, and institutionalized persons, have the highest prevalence of vitamin D deficiency—they would significantly benefit from vitamin D and targeted micronutrient supplementation. At least now, health departments, authorities, and health insurance companies should start assessing, prioritizing, and encouraging this economical, non-prescription, safe micronutrient to prevent and treat acute and chronic diseases. This approach will significantly reduce morbidity, mortality, and healthcare costs and ensure healthy aging {80}.

The classical clinical consequence of vitamin D deficiency is osteomalacia, presenting as rickets in children. This remains a common problem in parts of the Middle East and the Indian subcontinent, and occurs when serum 25-hydroxyvitamin D levels are <25 nmol/L. Osteomalacia remains the only problem that is unequivocally a consequence of vitamin D deficiency. Low levels of 25-hydroxyvitamin D are observed in a wide range of conditions, but consistent trial evidence of amelioration of these conditions with vitamin D is lacking. Monotherapy with vitamin D has not been found to be effective in meta-analyses of trials assessing its effects on bone density, fractures or falls. At present, supplements should be advised for individuals at risk of having serum 25-hydroxyvitamin D levels in the 25–40 nmol/L range, or below, with a view to prevention of osteomalacia {81}.

The aim of the present paper was to review the most important mechanisms explaining the possible association of vitamin D deficiency and cardiovascular diseases, focusing on recent experimental and clinical data. Low vitamin D levels favor atherosclerosis enabling vascular inflammation, endothelial dysfunction, formation of foam cells, and proliferation of smooth muscle cells. The antihypertensive properties of vitamin D include suppression of the renin-angiotensin-

aldosterone system, renoprotective effects, direct effects on endothelial cells and calcium metabolism, inhibition of growth of vascular smooth muscle cells, prevention of secondary hyperparathyroidism, and beneficial effects on cardiovascular risk factors. Vitamin D is also involved in glycemic control, lipid metabolism, insulin secretion, and sensitivity, explaining the association between vitamin D deficiency and metabolic syndrome. Vitamin D deficit was associated in some studies with the number of affected coronary arteries, postinfarction complications, inflammatory cytokines and cardiac remodeling in patients with myocardial infarction, direct electromechanical effects and inflammation in atrial fibrillation, and neuroprotective effects in stroke. In peripheral arterial disease, vitamin D status was related to the decline of the functional performance, severity, atherosclerosis and inflammatory markers, arterial stiffness, vascular calcifications, and arterial aging. Vitamin D supplementation should further consider additional factors, such as phosphates, parathormone, renin, and fibroblast growth factor 23 levels {82}.

References

1. **Mohan, M., Cherian, J. J., & Sharma, A. (2020). Exploring links between vitamin D deficiency and COVID-19. PloS pathogens, 16(9), e100887.**
2. **Palacios, C., & Gonzalez, L. (2014). Is vitamin D deficiency a major global public health problem?. The Journal of steroid biochemistry and molecular biology, 144, 138-145.**
3. **Prentice, A. (2008). Vitamin D deficiency: a global perspective. Nutrition reviews, 66(suppl_2), S153-S164.**
4. **van Schoor, N., & Lips, P. (2018). Worldwide vitamin D status. Vitamin D,15-40.**
5. **Mendes, M. M., Charlton, K., Thakur, S., Ribeiro, H., & Lanham-New, S. A. (2020). Future perspectives in addressing the global issue of vitamin D deficiency. Proceedings of the Nutrition Society, 79(2), 246-251.**
6. **Cui, A., Zhang, T., Xiao, P., Fan, Z., Wang, H., & Zhuang, Y. (2023).**
7. **Global and regional prevalence of vitamin D deficiency in population-based studies from 2000 to 2022: A pooled analysis of 7.9 million participants. Frontiers in Nutrition, 10, 1070808.**
8. **Salim, K. S., Ghassan, B., & Al-Temimi, A. A. (2023). Prevalence of Vitamin D Deficiency Among Population in Iraq. International Journal Of Medical Science And Clinical Research Studies, 3(4), 731-734.**
9. **Smaha, J., Jackuliak, P., Kužma, M., Max, F., Binkley, N., & Payer, J. (2023). Vitamin D Deficiency Prevalence in Hospitalized Patients with COVID-19 Significantly Decreased during the Pandemic in Slovakia from 2020 to 2022 Which Was Associated with Decreasing Mortality. Nutrients, 15(5), 1132.**

10. Liu, Z., Huang, S., Yuan, X., Wang, Y., Liu, Y., & Zhou, J. (2023). The role of vitamin D deficiency in the development of paediatric diseases. Annals of Medicine, 55(1), 127-135.
11. Jiang, Z., Pu, R., Li, N., Chen, C., Li, J., Dai, W., ... & Yang, G. (2023). High prevalence of vitamin D deficiency in Asia: A systematic review and meta-analysis. Critical reviews in food science and nutrition, 63(19), 3602- 3611.
12. .Mogire, R. M., Mutua, A., Kimita, W., Kamau, A., Bejon, P., Pettifor, J. M., ... & Atkinson, S. H. (2020). Prevalence of vitamin D deficiency in Africa: a systematic review and meta-analysis. The Lancet Global Health, 8(1), e134- e142.
13. Siddiqee, M. H., Bhattacharjee, B., Siddiqi, U. R., &MeshbahurRahman, M.(2021). High prevalence of vitamin D deficiency among the South Asian adults: a systematic review anmeta-analysis. BMC public health, 21, 1-18.
14. Pludowski, P., Takacs, I., Boyanov, M., Belaya, Z., Diaconu, C. C., Mokhort, T., ... & Pilz, S. (2022). Clinical practice in the prevention, diagnosis and treatment of vitamin D deficiency: a central and eastern European expert consensus statement. Nutrients, 14(7), 1483.
15. Lips, P., de Jongh, R. T., & van Schoor, N. M. (2021). Trends in vitamin D status around the world. JBMR plus, 5(12), e10585.
16. Oortgiesen, B. E., Dekens, M., Stapel, R., Alheraky, A., Dannenberg, P. D. K., Siemes, C., … & van Roon, E. N. (2023). Effectiveness of a vitamin D regimen In deficient multiple myeloma patients and its effect on peripheral neuropathy. Supportive Care in Cancer, 31(2), 138.
17. Pereira, M., Dantas Damascena, A., Galvão Azevedo, L. M., de Almeida Oliveira, T., & da Mota Santana, J. (2022). Vitamin D deficiency aggravates COVID-19: systematic review and meta-

analysis. Critical reviews in food science and nutrition, 62(5), 1308-1316..

18. Bertoldo, F., Cianferotti, L., Di Monaco, M., Falchetti, A., Fassio, A., Gatti, D., … & Chiodini, I. (2022). Definition, Assessment, and Management of Vitamin D Inadequacy: Suggestions, Recommendations, and Warnings from the Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS). Nutrients, 14(19), 4148-414.

19. Haq, A., Svobodová, J., Imran, S., Stanford, C., & Razzaque, M. S. (2016). Vitamin D deficiency: A single centre analysis of patients from 136 countries. The Journal of steroid biochemistry and molecular biology, 164, 209-213.

20. Manson, J. E., Brannon, P. M., Rosen, C. J., & Taylor, C. L. (2016). Vitamin D deficiency-is there really a pandemic. N Engl J Med, 375(19), 1817-1820.

21. need, A. G., O'Loughlin, P. D., Morris, H. A., Coates, P. S., Horowitz, M., & Nordin, B. C. (2008). Vitamin D metabolites and calcium absorption in severe vitamin D deficiency. Journal of Bone and Mineral Research, 23(11), 1859-186.

22. Kennel, K. A., Drake, M. T., & Hurley, D. L. (2010, August). Vitamin D deficiency in adults: when to test and how to treat. In mayo clinic proceedings (Vol. 85, No. 8, pp. 752-758). Elsevier.

23. Schilling, S. (2012). Epidemic vitamin D deficiency among patients in an elderly care rehabilitation facility. Deutsches Ärzteblatt International, 109(3), 33.

24. Cortet, B., Schott, A. M., Désaméricq, G., Chauny, J. V., Samama, P., Emery, C., & Fagnani, F. (2022). Trends In postmenopausal osteoporosis treatment in France during the period 2007–2016: a nationwide claims database analysis. Bone, 154, 116255.

25. LeBoff, M. S., Kohlmeier, L., Hurwitz, S., Franklin, J., Wright, J., & Glowacki, J. (1999). occult vitamin D deficiency In postmenopausal US women with acute hip fracture. Jama, 281(16), 1505-1511.
26. Ginde, A. A., Liu, M. C., & Camargo, C. A. (2009). Demographic differences and trends of vitamin D insufficiency In the US population, 1988-2004. Archives of internal medicine, 169(6), 626-632.
27. Ladhani, S., Srinivasan, L., Buchanan, C., & Allgrove, J. (2004). Presentation of vitamin D deficiency. Archives of disease in childhood, 89(8), 781-784.
28. ilverberg, S. J., Shane, E., Dempster, D. W., & Bilezikian, J. P. (1999). The effects of vitamin D insufficiency in patients with primary hyperparathyroidism. The American.
29. huang, Y., Zhu, Z., Chi, P., Zhou, H., Peng, Z., Cheng, H., … & Yu, Y. Vitamin D given daily, weekly, or monthly has similar response (116 RCTs)–meta-analysis Aug 2023.
30. Al-Oanzi, Z. H., & Elzouki, A. N. Metabolic Syndromes fought by Vitamin D In 6 ways–Oct 2023.
31. Holick, M. F. Vitamin D: 100 year anniversary of discovery–Holick Jan 2023.
32. Aljohani, N. J. (2023). FRI543 Effect Of Vitamin D Replacement On Thyroid Autoimmunity And thyroid Functions In Subclinical Hypothyroid And Vitamin D Deficient Patients: A Randomized Controlled Trial. Journal of the Endocrine Society, 7(Supplement_1), bvad114-1888.
33. Holick, M., & Chen, T. (2008). Vitamin D deficiency: a worldwide problem with health consequences.. The American journal of clinical nutrition, 87 4, 1080S-6S .

34. Lips, P. (2006). Vitamin D physiology.. Progress in biophysics and molecular biology, 92 1, 4-8 .
35. Rosen, C., Adams, J., Bikle, D., Black, D., Demay, M., Manson, J., Murad, M., & Kovacs, C. (2012). The nonskeletal effects of vitamin D: an Endocrine Society scientific statement.. Endocrine reviews, 33 3, 456-92 .
36. Holick, M. (2005). The vitamin D epidemic and its health consequences.. The Journal of nutrition, 135 11.
37. Roth, D., Abrams, S., Aloia, J., Bergeron, G., Bourassa, M., Brown, K., Calvo, M., Cashman, K., Combs, G., De-Regil, L., Jefferds, M., Jones, K., Kapner, H., Martineau, A., Neufeld, L., Schleicher, R., Thacher, T., & Whiting, S. (2018). Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries. Annals of the New York Academy of Sciences, 1430.
38. Hejazi, M., Modarresi-Ghazani, F., & Entezari-Maleki, T. (2016). A review of Vitamin D effects on common respiratory diseases: Asthma, chronic obstructive pulmonary disease, and tuberculosis. Journal of Research in Pharmacy Practice, 5, 7 - 15.
39. Griz, L. H. M., Bandeira, F., Gabbay, M. A. L., Dib, S. A., & Carvalho, E. F. D. (2014). Vitamin D and diabetes mellitus: an update 2013. Arquivos Brasileiros de Endocrinologia & Metabologia, 58, 1-8.
40. [8]: Milazzo, V., Metrio, M., Cosentino, N., Marenzi, G., & Tremoli, E. (2017). Vitamin D and acute myocardial infarction. World Journal of Cardiology, 9, 14 - 20.
41. Karonova, T., Stepanova, A., Bystrova, A., & Jude, E. (2020). High-Dose Vitamin D Supplementation Improves Microcirculation and Reduces Inflammation in Diabetic Neuropathy Patients. Nutrients, 12.

42. Freeman, S. E., Hacham, H., Gange, R. W., Maytum, D. J., Sutherland, J. C., & Sutherland, B. M. (1989). Wavelength dependence of pyrimidine dimer formation in DNA of human skin irradiated in situ with ultraviolet light. Proceedings of the National Academy of Sciences, 86(14), 5605-5609.
43. Anderson, R. R., & Parrish, J. A. (1981). The optics of human skin. Journal of investigative dermatology, 77(1), 13-19.
44. Ash, C., Dubec, M., Donne, K., & Bashford, T. (2017). Effect of wavelength and beam width on penetration in light-tissue interaction using computational methods. Lasers in medical science, 32, 1909-1918.
45. Dawson, J. B., Barker, D. J., Ellis, D. J., Cotterill, J. A., Grassam, E., Fisher, G. W., & Feather, J. W. (1980). A theoretical and experimental study of light absorption and scattering by in vivo skin. Physics in Medicine & Biology, 25(4), 695.
46. Webb, A. R., DeCosta, B. R., & Holick, M. F. (1989). Sunlight regulates the cutaneous production of vitamin D3 by causing its photodegradation. TheJournal of Clinical Endocrinology & Metabolism, 68(5), 882-887.
47. Kaidbey, K. H., Agin, P. P., Sayre, R. M., & Kligman, A. M. (1979). Photoprotection by melanin—a comparison of black and Caucasian skin. Journal of the American Academy of Dermatology, 1(3), 249-260.
48. Krutmann, J., Bouloc, A., Sore, G., Bernard, B. A., & Passeron, T. (2017).The skin aging exposome. Journal of dermatological science, 85(3), 152-161.
49. Masters, B. R., So, P. T., & Gratton, E. (1997). Multiphoton excitation fluorescence microscopy and spectroscopy of in vivo human skin. Biophysical journal, 72(6), 2405-2412.

50. Narayanan, D. L., Saladi, R. N., & Fox, J. L. (2010). Ultraviolet radiation and skin cancer. International journal of dermatology, 49(9), 978-986.
51. Norman A.W., Bouillon R. Vitamin D nutritional policy needs a vision for the future. Exp. Biol. Med. (Maywood) Exp. Biol. Med. (Maywood).
52. Haussler M.R., Haussler C.A., Jurutka P.W., Thompson P.D., Hsieh J.C., Remus L.S., Selznick S.H., Whitfield G.K. The vitamin D hormone and its nuclear receptor: Molecular actions and disease states. J. Endocrinol. 1997;154:S57–S73. doi: 10.1677/joe.0.1540057.
53. Hess A.F., Unger L.J. The cure of infantile rickets by sunlight. JAMA. 1922;78:29–31.
54. Bhan A., Rao A.D., Rao D.S. Osteomalacia as a result of vitamin D deficiency. Endocrinol. Metab. Clin. N. Am. 2010;39:321–331.
55. Zhang H.L., Wu J. Role of vitamin D in immune responses and autoimmune diseases, with emphasis on its role in multiple sclerosis. Neurosci. Bull.2010;26:445–454.
56. Charoenngam, N., & Holick, M. F. (2020). Immunologic effects of vitamin D on human health and disease. Nutrients, 12(7), 2097.
57. Sorrenti, V., Buriani, A., Davinelli, S., Scapagnini, G., & Fortinguerra, S. (2023). Vitamin D physiology, deficiency, genetic influence, and the effects of daily vs. bolus doses of vitamin D on overall health: a clinical approach. Nutraceuticals, 3(3), 403-420.
58. Bouillon, R., Carmeliet, G., Daci, E., Segaert, S., & Verstuyf, A. (1998). Vitamin D metabolism and action. Osteoporosis international, 8, S13.

59. Karlic, H., & Varga, F. (2011). Impact of vitamin D metabolism on clinical epigenetics. Clinical epigenetics, 2, 55-61.
60. Whiting, S. J., Calvo, M. S., & Vatanparast, H. (2017). Current understanding of vitamin D metabolism, nutritional status, and role in disease prevention. In Nutrition in the Prevention and Treatment of Disease (pp. 937-967). Academic Press.
61. Voltan, G., Cannito, M., Ferrarese, M., Ceccato, F., & Camozzi, V. (2023). Vitamin D: an overview of gene regulation, ranging from metabolism to genomic effects. Genes, 14(9), 1691.
62. Hofman-Hutna, J., Hutny, M., Matusik, E., Olszanecka-Glinianowicz, M., & Matusik, P. (2023). Vitamin D Deficiency in Obese Children Is Associated with Some Metabolic Syndrome Components, but Not with Metabolic Syndrome Itself. Metabolites, 13(8), 914.
63. Christakos, S., Dhawan, P., Verstuyf, A., Verlinden, L., & Carmeliet, G. (2016). Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. Physiological reviews, 96(1), 365-408.
64. Bocheva, G., Slominski, R. M., & Slominski, A. T. (2021). The impact of vitamin D on skin aging. International Journal of Molecular Sciences, 22(16), 9097.
65. Tsiaras, W., & Weinstock, M. A. (2011). Factors influencing vitamin D status. Acta dermato-venereologica, 91(2), 115-124.
66. Awad, A. B., Alappat, L., & Valerio, M. (2012). Vitamin d and metabolic syndrome risk factors: evidence and mechanisms. Critical reviews in food science and nutrition, 52(2), 103-112.
67. Faraji, S., & Alizadeh, M. (2020). Mechanistic effects of vitamin D supplementation on metabolic syndrome components in patients with or without vitamin D deficiency. Journal of Obesity & Metabolic Syndrome, 29(4), 270.

68. Basatemur, E., Horsfall, L., Marston, L., Rait, G., & Sutcliffe, A. (2017). Trends in the diagnosis of vitamin D deficiency. Pediatrics, 139(3).
69. Cannell, J. J., Hollis, B. W., Zasloff, M., & Heaney, R. P. (2008). Diagnosis and treatment of vitamin D deficiency. Expert opinion on pharmacotherapy, 9(1), 107-118.
70. Aoun, A., Maalouf, J., Fahed, M., & El Jabbour, F. (2020). When and how to diagnose and treat vitamin D deficiency in adults: a practical and clinical update. Journal of Dietary Supplements, 17(3), 336-354.
71. Alonso, M. A., Mantecón, L., & Santos, F. (2019). Vitamin D deficiency in children: a challenging diagnosis!. Pediatric research, 85(5), 596-601.
72. Ng, A. C., Kumar, S. K., Rajkumar, S. V., & Drake, M. T. (2009). Impact of vitamin D deficiency on the clinical presentation and prognosis of patients with newly diagnosed multiple myeloma. American journal of hematology, 84(7), 397-400.
73. Kim, H. A., Perrelli, A., Ragni, A., Retta, F., De Silva, T. M., Sobey, C. G., & Retta, S. F. (2020). Vitamin D deficiency and the risk of cerebrovascular disease. Antioxidants, 9(4), 327.
74. Siracusano, M., Riccioni, A., Abate, R., Benvenuto, A., Curatolo, P., & Mazzone, L. (2020). Vitamin D deficiency and autism spectrum disorder. Current Pharmaceutical Design, 26(21), 2460-2474.
75. Pál, É., Ungvári, Z., Benyó, Z., & Várbíró, S. (2023). Role of vitamin d deficiency in the pathogenesis of cardiovascular and cerebrovascular diseases. Nutrients, 15(2), 334.
76. Chan, H. N., Zhang, X. J., Ling, X. T., Bui, C. H. T., Wang, Y. M., Ip, P., ... & Pang, C. P. (2022). Vitamin D and ocular

diseases: a systematic review. International Journal of Molecular Sciences, 23(8), 4226.

77. Berretta, M., Quagliariello, V., Bignucolo, A., Facchini, S., Maurea, N., Di Francia, R., ... & Montopoli, M. (2022). The multiple effects of vitamin D against chronic diseases: From reduction of lipid peroxidation to updated evidence from clinical studies. Antioxidants, 11(6), 1090.

78. Akimbekov, N. S., Digel, I., Sherelkhan, D. K., & Razzaque, M. S. (2022). Vitamin D and phosphate interactions in health and disease. In Phosphate Metabolism: From Physiology to Toxicity (pp. 37-46). Cham: Springer International Publishing.

79. Caban, M., & Lewandowska, U. (2022). Vitamin D, the Vitamin D Receptor, Calcitriol Analogues and Their Link with Ocular Diseases. Nutrients, 14(11), 2353.

80. Wimalawansa, S. J. (2023). Controlling chronic diseases and acute infections with vitamin D sufficiency. Nutrients, 15(16), 3623.

81. Reid, I. R. (2015). What diseases are causally linked to vitamin D deficiency?. Archives of Disease in Childhood, archdischild-2014.

82. Mozos, I., & Marginean, O. (2015). Links between vitamin D deficiency and cardiovascular diseases. BioMed research international, 2015.