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Vitamin D Deficiency: Main Factors Affecting The Serum 25-Hydroxyvitamin D ([25(Oh)D]) Status And Treatment Options.

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Abstract

Vitamin D deficiency (VDD) is already recognized as a pandemic affecting over 1 billion people worldwide. The scientific debate about VDD and its complications is far from resolved because of lack of scientific based proofs in certain areas. Most observational and epidemiological trials, as well as meta-analyses report the benefits of optimal serum 25-Hydroxyvitamin D ([25(OH)D]) status. Furthermore important randomized controlled trials (RCTs) give in many cases conflicting results due to certain limitations. Moreover the debate continues whether hypovitaminosis D is cause, result or by-product of poor health. Another approach is the resilience factor hypothesis, which describes serum vitamin D status as helpful in survival of fatal conditions and therefore inversely correlated to morbidity and mortality. Endogenous and exogenous vitamin D synthesis are associated to environmental, biological and social (economical and cultural) factors. Mainly VDD is a consequence of the modern lifestyle including urbanization, indoor dwelling with work- or entertainment-based lower mobility in general population and partly profit- and mass-production-oriented farming methods resulting in products with lower vitamin D content. A healthy lifestyle with physical activity, adequate and sensible sun exposure and intake of quality nutrients, including those rich in natural vitamin D will ensure optimal serum Vitamin D concentrations.

Key words: Vitamin D; sunlight; lifestyle; age; gender; socio-economic status; adequate intake; fortification; supplementation; recommendations

Introduction

Vitamin D deficiency (VDD) is a worldwide pandemic affecting over 1 billion people worldwide [1, 2] and needs urgently to be addressed to prevent morbidity, mortality and increasing expenses related to the treatme
nt of the implicated chronic illnesses [1, 2].

The VDD pandemic, as well as under- or malnutrition are on the rise because of increasing world population, pollution, food insecurity, resource contention, degradation of agricultural land and over fishing. Other factors include population displacement due to conflicts and poverty, as well as urbanization and change in dietary patterns and lifestyles. Global climate change, soil desertification, salinization and urbanization [3] are affecting agricultural production resulting in rising food prices and fluctuations in food quality and availability. Food insufficiency, chronic hunger and malnutrition dominate large parts of the developing world [4]. Here, food insecurity mainly affects women with low or no income. As an outcome, women have the highest prevalence of VDD compared to men [2], mainly due to socio-economic factors. Education, employment and heading household are among the other factors having an impact on food insecurity [5] and result in severe VDD. Inadequate dietary energy supply and under- or malnutrition through poor diet and healthcare lead to rising obesity rates and high levels of chronic and degenerative diseases in other parts of the

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world [6]. Another important factor is the unawareness of the public on VDD, its implications and prevention strategies.

25-Hydroxyvitamin D [25(OH)D] is considered the biomarker of serum vitamin D status and is derived from cutaneous synthesis through sun exposure of the skin (vitamin D3) and dietary intake (mostly vitamin D2). During sun exposure 7-dehydrocholesterol in the skin absorbs UVB radiation, is converted to previtamin D3 and then isomerizes into vitamin D3. Vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) are precursors of the hormonally active vitamin D (calcitriol) [7]. The vitamin D3 precursor enters the blood circulation, is first transported to the liver by the vitamin D binding protein (VDBP) and is converted into 25-hydroxyvitamin D [25(OH)D]. The next conversion happens in the kidneys, where the biologically active hormone calcitriol (1,25-dihydroxyvitamin D3, [1,25(OH)D]) is formed [7].

Vitamin D is very important for building strong bones and teeth. It strengthens the immune system, maintains muscle and joint comfort, decreases cancer in organs such as breast and colon [8, 9]. There is a well-known association between VDD and reduced cancer mortality, as well as the importance of maintaining adequate serum [25(OH)D] status for cancer prevention and the possible therapeutic potential of calcitriol in oncology [8, 9].

Both endogenous (sun exposure) and exogenous (diet) synthesis contribute to the vitamin D status of the body [10]. Vitamin D produced through the skin last 2-3 times longer than diet, but only 15% of the sun rays are effective in endogenous synthesis due to environmental reasons [7]. Vitamin D status can be improved by responsible and sensible sun exposure of uncovered skin parts like face, hands, parts of arms and legs either three times weekly [7] or on daily basis on midday for 10-15 min. while protecting face and neck [11]. The duration of exposure depends on many factors. These factors can be divided into three groups. The first group depends on given environmental conditions of the habitat and includes geographical location (latitude, altitude, terrestrial environment), climate, season, temperature, time of the day and weather conditions. The second group relates to biological factors like age, gender, ethnicity, skin pigmentation, and medical condition. The last group consists of socio-economical and socio-cultural factors influencing the lifestyle, physical activity and individual choices or habits. The impact of these factors and their interconnections, as well as their influence on serum vitamin D status will be explained.

The aim of this review is to highlight the problems related to VDD, explore its reasons and outcomes. Furthermore this study provides recommendations for the development of public health strategies regarding the treatment of VDD and chronic disease prevention as well as progression. In cases where measurements are not possible or successful in raising [25(OH)D] serum status, vitamin D fortified foods, vitamin D supplementation or even heliotherapy are recommended.

Definition of VDD

Sources of Vitamin D (Sun exposure and diet)

a) Sun exposure (UVB)

The electromagnetic spectrum emitted naturally from the sun contains ultraviolet radiation (UVR), which can be divided into UVA and UVB (290-315 nm) [7]. UVB exposure is necessary for endogenous vitamin D synthesis.

Solar radiation has also non-vitamin D pathway benefits with anti-inflammatory [9, 12, 13], immunomodulatory and cancer risk reducing effects [14] through responsible and sensible sun exposure practice. There is a worldwide debate, whether VDD is a marker of major chronic diseases (causality principle), including osteoporotic diseases, cardiovascular diseases

(CVD), diabetes mellitus, some types of cancer, infections and some auto-immune conditions [15]. Furthermore sufficient serum concentrations of [1,25(OH)D] may regulate the response of the immune system when challenged by severe diseases preventing the fatal outcome of the sickness. According to this explanation, vitamin D is seen as a resilience factor helpful to survive potentially fatal conditions on associations of [25(OH)D] status with CVD, cancer and total mortality. Also low vitamin D levels result in a poorer cancer prognosis of breast or colorectal cancer patients [16]. Low vitamin D levels in elderly were associated in the ESTHER study with all case mortality and are partly a consequence of frailty and poor health status [15]. Therefore VDD may be an outcome or by-product, rather than the cause of poor health [17]. This hypothesis seems to be confirmed by the RECORD study [18], as well as the ESTHER cohort study and the CHANCES consortium [15].
In another recently published conventional cohort analysis on theoretical links between seasonal lack of sunlight, hypovitaminosis D and excess cardiovascular disease and death 13 224 Scottish Heart Health Extended Cohort participants were tested, assayed for 25-hydroxyvitamin D [25(OH)D] and followed for 22 years. As a result vitamin D's role as causal factor, or major prime mover in cardiovascular disease and mortality is questioned by this group [19]. Also according to the ESTHER cohort study and the CHANCES consortium VDD may not be a risk factor for the development of CVD and cancer but vitamin D could be a marker of resilience to fatality of potentially fatal diseases [15]. Prentice et al. even go further explaining, that serum [25(OH)D] might be a biomarker for intake but not of function [20]. According to Jorde and Grimnes, most of vitamin D research is based on observational studies (cross-sectional, prospective or ecological) and all these are still only associations or correlations, which cannot be trusted as proof of causality [21].
New randomized controlled trials (RCTs) are needed to confirm, whether low vitamin D levels are the cause or a result of ill-health. Ongoing RCTs are CAPS, VITAL, D-HEALTH, FIND, ViDA, VIDAL and J-DAVID [21-23]. Until recently, many RCTs delivered conflicting results, which in part can be blamed on limitations of the study design [21, 24, 25] as well as nonadherence and comorbidities [26].

Dangers of sun-exposure

Uncontrolled UVR exposure increases the risk of skin cancer [10]. Acute skin reactions induced by UVR exposure are erythema (skin reddening) and sunburn. DNA damage occurs by UVR-induced suntan through exposure from sun or artificial sources like sunbeds. UVR exposure is the main cause of skin cancer, especially in fair-skinned populations and seems to be most harmful during childhood [27, 28]. The sun-related cancer cases are on a rapid rise, while about 22,000 deaths from it occurred in Europe according to estimates only for 2012. This risk factor can be managed through responsible behavior, including avoidance of excessive sun exposure by seeking shade or staying indoors when the sun is most intensive, by chosing appropriate clothing, and by using sunscreens adequately if direct sunlight cannot be avoided. The beneficial effects of sun exposure like vitamin D production can still be achieved due to this responsible behaviour [27].
The recommendation of the 4th edition of the European Code Against Cancer for ultraviolet radiation is: "Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds." [27].

b) Vitamin D in diet and food fortification

The dietary sources attributed with high vitamin D content are highest in oily fish followed by egg yolk, offal, butter, some types of mushrooms,

which were exposed to sunlight and fortified products, like breakfast cereals, orange juice, diary products and [29]. Especially cold-water oily fish, tuna liver, fish oil, and cod liver oil are the richest dietary sources of vitamin D. The wild species contain more vitamin D than the farmed fish [30]. Declining ocean stock is a marker of increasing food insecurity and food inavailability. Ocean fish is rapidly depleting through over-fishing. The increase in toxins and mercury in fish through worldwide aquatic pollution lessens [31] and questions its nutritional value. The vitamin D content in food of animal origin, as well as eggs increase by feeding animals with vitamin D [32]. This process, called biofortification, permitted addition of vitamin D or 25-hydroxyvitamin D to the livestock feeds increases vitamin D and/or 25-hydroxyvitamin D contents in the animal products like eggs, milk, cultured fish, chicken, beef, lamb and pork [33].

Another practice is additional UVB-irradiation of mushrooms as well as baker's yeast which increases endogenous vitamin D2 content [33]. Slightly higher vitamin D content is achieved in egg yolk through bio-addition by UVB-exposure of hens, compared to egg yolk from free range farmed hens [34]. Anyhow, outdoor farming of livestock provides increase in vitamin D contents in animal produce and proves to be less expensive than vitamin D supplementation or UVB-irradiation [35].

Vitamin D content in meat and diary products does not decrease due to processing significantly, because it is heat and oxygen resistant, but light sensitive only [29]. The cooking method does not change the vitamin D content except in case of loss of fat, which leads to loss of vitamin D, and moisture loss resulting in an increase of vitamin D content in general [29, 36]. Butter and cream contain high vitamin D due to the high fat contents [29], but in comparison to fish and fish oil, Vitamin D content is naturally low in milk and diary products.

Food fortification is different in each country and needs to be standardized according to prevalent mean serum [25(OH)D] status in each country to fight the pandemic VDD. This is especially important because the magnitude of hypovitaminosis D may vary depending on population, ethnicity, regional and seasonal considerations [37], means environmental, biological, socio-economical and socio-cultural factors.

Vitamin D levels and deficiency

Serum 25-hydroxyvitamin D concentrations of 50 nmol/l or higher are considered as optimal vitamin D status [10].

Prevalence of vitamin D deficiency depends on definitions, which show a wide range in the literature, most of them agree on levels < 50 nmol/L [22, 24].

In a recent article the NutriProfiel project defines vitamin D deficiency for 0-4 year-olds < 20 nmol/L, for 5-64 year-olds < 30 nmol/L and for more than 65 year-olds < 50 nmol/L [38].

Vitamin D toxicity

Excessive vitamin D intake through supplements and food fortification may result in toxicity due to hypercalcemia caused by increased intestinal absorption of calcium, together with increased resorption of bones [32]. Therefore high doses of vitamin D may increase in elderly the risks of fractures and falls [39]. With long-term vitamin D intake in extremely high doses, deposition of calcium in soft tissues, especially in arterial walls and in the kidney occurs [32].

Three main predictors for VDD

Vitamin D and environmental factors

The environmental conditions of the habitat include geographical location (latitude, altitude, terrestrial environment), climate, season, temperature, time of the day and weather conditions.

The flat angle of incidence of the sun is responsible for the low intensity of the sun's rays, which depends on latitude, altitude, surface elevation, stratospheric ozone layer thickness, season and time of the day. Absorption and scattering by ozone and other atmospheric layers, cloudy or dusty weather, as well as window glass and plastic decrease or even absorb the UVB content also [7]. A long distance zenith angle forces the UVB rays to travel longer distance increasing the absorption and scattering effects and decreasing the UVB [7]. Pollution, cloudy and dusty weather conditions decrease UVR passing through the atmosphere. Dust is composed of mineral particles that also absorb and scatter sunlight decreasing UVB [40].

UVB exposure can be vertically in a partially shaded urban environment where shadows of tall buildings shade the sun, or horizontally, while exposing the skin to the sun in an open, unshaded place like a beach [41]. The amount of body surface exposed to the sun influences the endogenous vitamin D production, while temperature influences patterns of clothing and time [11]. Clothing type, texture and color of clothing may influence vitamin D status as well [42]. Sun exposure, time outdoors and physical activity are considered markers of vitamin D3 synthesis, while latitude and ambient levels of UV radiation have less importance [11, 43, 44]. Indoor dwelling due to work, study or entertainment, combined with sedentary, inactive lifestyle is a marker of obesity and increased BMI inversely associated to optimum levels of serum 25(OH)D status [43, 44]. According to a recent study there was no significant relationship between serum vitamin D status and regional latitude. The degree of hypovitaminosis D in the studied population was higher in inland rather than in coastal regions in China, linking higher fish and fish-oil consumption with higher serum [25(OH)D] values [44].

Vitamin D and biological factor in different age groups, gender, ethnicity

The biological factors are related to age, gender, ethnicity, skin pigmentation, and medical condition of the studied population.

Childhood and adolescence are times in life vulnerable to mal- or undernutrition, as well as sedentary lifestyle. Poor diets through fast food and sugar-based products leading to dental problems and increasing picky eating habits in children are the major factors of malnourishment. Adequate nutrition and physical activity is positively related to general and bone health [45], bone size and strenght [46, 47]. Overprotective measurements of parents like limiting the time spent outdoors, using highly protective sun screen and clothing result in VDD in children. This was indicated in a study in New Zealand where there may be a positive correlation of higher levels of education in parents and guardians and increased levels of vitamin D deficiency in their children [48]. There is a high unawareness of parents, caregivers, guardians and even health professionals with lack of adequate education about benefits of vitamin D supplementation in a UK-Survey with levels of 85.71% [49] compared to a Saudi Arabia-Survey with 40% [50]. Children need adequate vitamin D levels for effective bone mineralization and normal bone growth [49]. VDD may result in attention deficit hyperactivity disorders [51], hypocalcemic seizures, tetany, growth disturbances, rickets disorders [51, 52], severe early childhood caries [53], vague limb and back pain [54]. Low serum [25(OH)D] status is an indicator for reduced intestinal calcium and phosphate adsorption and increased bone resorption, which may result in a decreased bone integrity and strenght [55].

People in need of care, elderly and institutionalized individuals commonly have a passive lifestyle, limited or no physical activity outdoors and therefore limited sun exposure.

Restricted mobility is therefore a marker of reduced endogenous vitamin D synthesis [10].

Vitamin D absorption is inversely related to age because of atropic changes in skin, decreased skin thickness [56], decrease of precursor and decreased renal function. Another factor is under- or malnutrition and inadequate or no vitamin supplementation.

VDD in elderly is manifested by falls, fracture and all-cause mortality. For adults above 65 years the aim of vitamin D intake is to minimize age-related loss of bone mass and risk of fractures as result of osteoporosis [10]. At the same time vitamin D is related to muscle function and therefore relates to risk of falls and fractures [10]. Hypovitaminosis D is associated with decline in muscle function and frailty resulting in increased number of hip fractures in winter [37]. Furthermore vitamin D supplementation of 1000IU/d in elderly show a positive effect on the muscle function, but do not present a clear proof of preventing falls. Herein the supplementation has beneficial effects on muscle strength, balance and gait [37]. Intermittent high doses of vitamin D may not be effective at improving muscular strength in elderly [37].

The incidence of osteoporosis and age-related fragility fracture vary by ethnicity. The metabolic function of bone is important for Ca and P homoeostasis. Ca, P and bone metabolism are regulated by common factors, like parathyroid hormone (PTH) and 1,25-dihydroxy vitamin D [1,25(OH)2D] [57]. At the same time dark skin pigmentation with the higher melanin content blocks sunlight, therefore reducing cutaneous vitamin D synthesis and as a result requiring longer time of exposure to solar UVB to produce the same amount of vitamin D compared with individuals with light skin [58, 59]. Skin pigmentation hinders the transformation from 7-dehydrocholesterol to vitamin D. Furthermore the percentage of cutaneous 7-dehydrocholesterol is inversely correlated to age [60] and low natural cholesterol levels [61]. White caucasians have the highest risk related to osteoporosis and hip fractures when compared with African Americans, Chinese and Gambians although Caucasians have the highest intake of Ca through milk and diary products [57]. Differences in cultural preferences, socio-economic status and food availability are markers of dietary intake between ethnic groups within and between countries [57]. The interdependence of biological factors like skin pigmentation, ethnicity, body mass index (BMI) and other medical conditions on the [25(OH)D] status are still not fully understood.

Medical conditions as polymorphism (malabsorption), which is actually related to changes in nucleotide alterations in genes, as well as liver failure, nephrotic syndrome and medication (anticonvulsant, glucocorticoid, anti-rejection agents and human immunodeficiency virus therapy) are markers of hypovitaminosis D. Obesity is another independent risk factor for VDD due to vitamin D sequestration in subcutaneous fat [25].

Although gender is considered a biological factor, it is strongly associated with socio-economical and socio-cultural aspects. The impact of social, cultural and economical factors on serum [25(OH)D] concentrations is more intense on women.

Vitamin D and socio-cultural and socio-economic background

Socio-economical and socio-cultural factors include lifestyle, physical activity, employment, income status and individual choices or habits.

A sedentary lifestyle is negatively correlated to physical activity. The modern life, with mostly screen-based entertainment for all age groups, indoor dwelling due to working in offices has a negative impact on cutaneous vitamin D synthesis and overall health [44]. At the same time, mal-

and under-nutrition combined with sun-avoidance practices, increased sunscreen use and inactive lifestyle cause VDD.

The Tromsø study finds an inverse relationship between physical activity and body mineral density in boys with screen-based sedentary behaviour on weekends and a positively related association between screen time and BMI [43].

Women in all populations have generally lower serum vitamin D status compared to men. There are many factors contributing to VDD. Socio-economical, as well cultural aspects, higher impact of food insecurity, level of income and education, inadequate supplementation and poor diets caused by sedentary lifestyle and mostly physical inactivity are major contributors for women's VDD in child-bearing age.

Concerns about skin aging and development of skin cancer due to sun exposure resulted commonly in excessive use of sunscreen. Sunscreens filter 95% of UVB-radiation, which is needed to produce vitamin D [7]. This is especially true regarding the trend for fair skin complexion for women in Middle East, Asia and Northern Africa, which is one of the factors leading to VDD compared to male population. Particularly women and girls in the Middle East have low vitamin D levels compared to other women in the world, although they are living in ample sunshine conditions [2]. Here, additionally to the factors of sedentary lifestyle, inadequate supplementation and poor diets, also extreme heat in summer and harsh weather conditions as marker of temperature affect patterns of clothing and time spent outdoors [11]. Additionally excessive use of sunscreens, avoidance of sun exposure and socio-cultural sensitivities are limiting the exposure to sunshine. Worldwide, commonly indoor dwelling with limited or no physical activity in- or outdoors, especially for housebound urban women in the child-bearing age leads to hypovitaminosis D.

There are differences in the vitamin D status in rural and urban women. Rural women in Malaysia generally spent more time working outside and have higher sun exposure rates, and consequently higher serum vitamin D status than urban women, who mostly work indoors [42]. According to this, rural women have higher serum vitamin D concentrations although due to religious and cultural practices less body surface area is exposed. Hypovitaminosis D is prevalent in urban women although they have more body surface area exposed.

In conclusion, outdoor physical activity is strongly associated with endogenous vitamin D synthesis and therefore optimal serum vitamin D status in general. Indoor dwelling, combined with inactive, sedentary lifestyle are strong markers of ill health and VDD. Indoor lifestyle is also correlated to temperature and season. High temperatures with harsh weather conditions enforce mostly indoor dwelling and sun avoidance behaviours in countries with low latitudes. Patterns of clothing remain minor marker when compared to socio-economic status and lifestyle of women.

Vitamin D in pregnancy and breastfeeding mothers and their offspring

The nutritional status of pregnant and lactating woman directly affects the vitamin D status and health, especially bone mineralization [10], body structure, bone mass and physiology of the offspring [62]. Multiparity, short spacing between pregnancies, dark maternal skin pigmentation and exclusively breastfed-infants beyond 6-month of age are high risk factors for VDD of mother and child. The prevention of neonatal and childhood rickets can only be achieved through evaluation of serum Vitamin D status of future mothers. The lack of prenatal care for women is a major contributor for VDD endangering mother and offspring. Health professionals need to include a careful evaluation of important parameters in the

consultation of pregnant women, such as maternal daily vitamin D intake, serum vitamin D status, skin pigmentation, drug use and sun exposure [62]. Vitamin D content of the breast milk does not meet the requirements of the rapidly growing skeleton with very low concentrations of vitamin D [10]. Delayed introduction of solid foods, picky eating habits, and poor diet also contribute. Therefore the vitamin D status in infants and preschool children needs to be evaluated carefully to enhance a healthy development into adolescence and adulthood. This can be achieved by adequate intake of exogenous vitamin D through diet and supplementation ensuring at the same time sufficient sun exposure. Infants should not be exposed to direct sunlight, because their skin still lacks full protective mechanisms [10].

Results and Discussion

VDD Prevention and Treatment

VDD is a worlwide problem affecting millions of people, prevalent in industrialized as well as developing countries. This pandemic can only be stopped by adequate public health policies tailored for every patient in each part of the world resulting in changes in lifestyle and dietary habits. Food security, socio-economic status, local dietary costums, prevalent UVB exposure, as well as age, gender, medical condition and ethnicity are very important factors among the three above explained groups and need to be considered. Sunlight exposure alone is in most cases insufficient to generate adequate vitamin D in most people in the world, because of geographical, seasonal, environmental aspects influencing the solar UVB radiation. Diet is for most of the world population an increasingly poor source of vitamin D. Processed foods and fast food intake increased, while modern, profit-oriented techniques in agri-, aquaculture and modern farming methods of animals lead to poor quality of products containing less vitamin D. Other factors include, short or no supplies in adequate fresh food and fish products throughout the year with the seasonal variations which change the quality of the food and vitamin D content. Therefore the public awareness of a healthy lifestyle, including adequate sun exposure, physical activity and vitamin D rich diet needs to be raised dramatically through media, health authorities and healthcare providers. In individual cases recommendations to increase sunlight exposure and changing lifestyle and dietary habits may not be enough for the treatment of VDD. Patients may return to old habits after some time or are not able to follow the given recommendations due to personal limitations. Therefore, in these cases oral, long-term intake of vitamin D3 is recommended on a daily basis, after adjustment of severe VDD through high-dose vitamin supplementation orally or through injection once or twice yearly. All recommendations should be patient-tailored and patients should be followed up yearly. This approach is especially needed because even between individuals with similar ethnicity and biological factors, there is huge variability in response to equal vitamin D intake [63]. Furthermore the response to equal vitamin D supplementation varies considerably from individual to individual, depending on baseline level, body mass index (BMI) and genotype [21].

Recommendations for the public on how to increase serum vitamin D status

Recommendations of sun exposure

Sun exposure on different body parts may not result in equal cutaneous vitamin D synthesis because the density of melanocytes is variable among different body sites [60]. Moreover, BMI and scarred skin parts influence vitamin D synthesis [60]. Even there are individual differences between people with the same biological and environmental factors. Recommendations for the general public regarding sun exposure cannot be generalized.

Prolonged and unprotected sun exposure increases skin cancer risk [27]. According to the American Academy of Pediatrics, children under 6 month of age should stay out of direct sunlight and use sunscreen only on face, if protective clothing (like long-sleeved shirts, hats and long trousers from tight weaved cotton) or shade is not available [64]. Older children should be allowed to stay in the sun with adequate protective clothing, application of sunscreen (with UVA and UVB block, sun protection factor (SPF) 15-50, without ingredient oxybenzone) even on cloudy days, and limiting the time between 10 AM and 4 PM [64].

As a conclusion, protection from skin cancer incidence is through prevention of prolonged, unprotected solar exposure avoiding skin reddening, sunburn or suntan. Therefore, few minutes of exposure in the midday sun is preferable because at noon time the UVA/UVB ratio is at its highest for vitamin D synthesis [65]. Additionally, prolonged exposure initiates the photo-degradation of previtamin D3 by UVA back to 7-dehydrocholesterol and other photoproducts [7].

According to the German Nutrition Society, only 5-10 minutes in midday sun on a daily basis are needed for fair skin to produce sufficient serum [25(OH)D] status [10]. Wacker and Holick advice sensible sun exposure of uncovered skin parts like face, hands, parts of arms and legs without sunscreen for 10-15 minutes, 3 times weekly on midday sun [7]. Sun exposure can be also on daily basis at midday for 10-15 min. while protecting face and neck [11].

Recommendations for diet

Major dietary sources of vitamin D are fish, followed by eggs (egg yolk), offal, butter and fortified products, like orange juice, diary products, flour [29] and breakfast cereals.

In general, nutritionists recommend 3 portions of diary and 1 portion of fish, eggs, offal or meat per day [29]. The optimum diet should include two servings of fish in a week, in which, one serving should be oily fish like salmon, tilapia, mackerel, tuna or herring. Daily fortified cups of orange juice and milk, and additionally one serving of tuna liver, fish oil or cod liver oil in case of severe VDD. Food fortification is different in each country and needs to be standardized. Diet is and will be increasingly a poor contributor to serum vitamin D status due to food insufficiency. Intake of high vitamin D supplements like cod liver oil contain at the same time high vitamin A levels, which are maybe harmful to bone health [58]. The amount of vitamin A supplementation should not exceed 1500 IU/d [66, 67]. Vitamin A (retinol), competes with vitamin D [68] and has been associated with increased risk of hip fracture [67].

Recommendations of supplementation

A patient tailored approach has to be taken for treatment or prevention of VDD. Recommendations given for one part of the world cannot be generalized and applied for other populations with different background and circumstances. Oral vitamin D intakes recommended for the U.S., Australian or European population cannot be applied on other populations with different ethnicity, geographical location, terrestrial environment and degree of VDD. Patients with very low 25-hydroxyvitamin D levels respond more robustly to a smaller dose of vitamin D than those having a 25-hydroxyvitamin D greater than 50 nmol/L. Furthermore the response to equal vitamin D supplementation varies considerably from individual to [21] even within the same population and same ethnic background [63].

Treatment of VDD, should include a loading dose to reach optimum [25(OH)D] status followed by a maintenance dose with daily administration. This should be according to the NutriProfiel project, the optimum circulating [25(OH)D] concentration is for 0-4 year-olds 30-50 nmol/L, for 5-64 year-

olds 50-75 nmol/L and for more than 65 year-olds 75-100 nmol/L. Their recommended maintenance dose is for 0-4 year-olds 400 IU/d, for 5-64 year-olds 400-800 IU/d and for more than 65 year-olds 800 IU/d [38].

In severe cases of VDD with serum [25(OH)D] < 25 nmol/L a pharmacological high-dose vitamin D3 therapy aiming at [25(OH)D] > 50 nmol/L is needed, followed by a long term oral supplementation with vitamin D3 [69]. According to the recommendations of the Endocrine Society, depending on the patients medical history, the oral vitamin D3 long-term dose is for infants smaller than 1 year 400-1000 IU/d, children and adolescents from 1 to 18 years of age 600-1000 IU/d and all adults 1500-2000 IU/d [69].

Pregnant and lactating women, elderly patients over 70 years of age, obese, as well as institutionalized individuals, and patients with medications that increase vitamin D catabolism need to take oral supplementation of 1000-2000 IU/d. The German Nutrition Society recommends a supplemental intake of 800 IU/d for pregnant women, who do not have enough sun exposure. Their diet should include two portions of fish a week, one portion of them oily fish like salmon, herring and mackerel [10].

Combination of calcium and Vitamin D treatment is important for the elderly, those requiring osteoporosis prophylaxis, pregnant women, calcium-poor diets and lactose intolerance [70].

Oral vitamin D is potentially toxic with extremely high-dose supplements, but there is a wide safety range margin [58].

Conclusions

The VDD pandemic can only be tackled through education of the public about the importance of vitamin D in general health and the related health problems due to hypovitaminosis D. VDD may be a biomarker for the increased risk of chronic diseases. At the same time, it is a resilience factor preventing fatal outcomes when exposed to fatal conditions. Sedentary indoor lifestyle, less outdoor physical activity are the major reasons of poor endogenous vitamin D synthesis, followed by environmental, biological and socio-economical factors. Rising food insecurity and food prices, regional conflicts, poverty, subsequent displacement and hunger are markers of inadequate dietary intake. Furthermore, declining quality of food due to modern, mass production aimed farming methods and pollution reduce exogenous Vitamin D2 synthesis. Patterns of clothing remain less important in endogenous vitamin D synthesis and mostly are a result of climate and socio-cultural factors.

Public health policies are needed to ensure adequate intake through diet and food fortification, as well as supplementation, education of general public, health providers and community pharmacists. This can be also achieved through strong presence of VDD in the media, by media campaigns in TV, Internet and in community services. Governments and health authorities need to undertake public health policies ensuring to solve this problem by tailored, individual approaches in every region of the world.

Recommendations for each patient should include a comprehensive treatment and prevention strategy. Sun exposure, oily fish and fatty meat, as well as high fat diary products are the major sources of vitamin D but not enough in each individual case. Therefore drastic changes in lifestyle and dietary habits are strongly recommended and depending on individual cases daily, long term oral supplementation. Short-term high dose therapies proved to be less efficient in raising the serum [25(OH)D]. Heliotherapy is recommended for people with medical conditions, elderly in nursing homes or institutionalized individuals having no access to adequate sun exposure or diet. A free app *dminder.info* provides each user with the individual information regarding effective sun exposure related to

latitude, season, time of the day and UV index on a personalized level. This app helps patients to determine how long sun exposure is required to make enough vitamin D.

Conflict of Interests

The author(s) declare(s) that there is no conflict of interests regarding the publication of this article.

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