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Review

Non-musculoskeletal benefits of vitamin D

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ABSTRACT

The aim of this study is to determine and critically evaluate the plausible relationships of vitamin D with extra-skeletal tissues in humans. Severe vitamin D deficiency results in rickets in children and osteomalacia in adults; these beneficial effects in the musculoskeletal system and certain physiological functions are well understood. Nevertheless, mounting reports support additional beneficial effects of vitamin D, outside the musculoskeletal system. This review explores the recent advances in knowledge about the non-skeletal effects of vitamin D. Peer-reviewed papers were extracted from research databases using key words, to assess correlations between vitamin D and extra-skeletal diseases and conditions. As per the guidelines of the Preferred Reporting Items for Systematic Reviews (PRISMA); general interpretations of results are included; taking into consideration the broader evidence and implications. This review summarizes current knowledge of the effects of vitamin D status on extra-skeletal tissues with special attention given to relationships between vitamin D status and various diseases commonly affecting adults; the effects of intervention with vitamin D and exposure to sunlight. Evidence suggests that vitamin D facilitates the regulation of blood pressure; and cardiac; endothelial; and smooth muscle cell functions; playing an important role in cardiovascular protection. In addition; $1,25(OH)_2D$ improves immunity; subdues inflammation; and reduces the incidence and severity of common cancers; autoimmune diseases and infectious diseases. Almost all adequately powered; epidemiological and biological studies that use; adequate doses of vitamin D supplementation in D-deficient populations have reported favorable outcomes. These studies have concluded that optimizing 25(OH)D status improves the functionality of bodily systems; reduces comorbidities; improves the quality of life; and increases survival. Although accumulating evidence supports biological associations of vitamin D sufficiency with improved physical and mental functions; no definitive evidence exists from well-designed; statistically powered; randomized controlled clinical trials. Nevertheless, most studies point to significant protective effects of vitamin D in humans when the minimum 25(OH)D serum level exceeds 30 ng/mL and is maintained throughout the year.

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1. Introduction

1.1. Factors affecting Vitamin D levels

Skin synthesis and dietary intake of vitamin D are the two natural ways of obtaining vitamin D by humans. Vitamin D and its precursors are present in only a few foods and even then occur in small amounts. Therefore, supplements may be necessary for those who cannot or do not sufficiently expose their skin surfaces to sunlight and for those living in northern climates during the winter months. For the vast majority of people, it is impossible to attain vitamin D sufficiency by the commonly consumed diets [1]. Therefore, for those who have inadequate sun exposure, especially during the winter months, and those who live in northern and southern latitudes, supplementation becomes a necessity [2].

Sunlight causes the photo-production of vitamin D_3 in the skin. Exposure to sunlight is a major source of vitamin D for most people, yet public health advice focuses overwhelmingly on avoiding exposure of unprotected skin, because of the risks of erythema and potential skin cancer [3]. Meanwhile, humans are expected to generate 80% of their daily vitamin D requirement though exposure to sunlight. Moreover, not everyone has the capacity to generate similar amounts of vitamin D following exposure to ultraviolet B (UVB) rays (280–315 nm). The efficiency of cutaneous generation of vitamin D is dependent on the intensity of sunlight, amount of skin exposed, duration of exposure to UVB rays, the zenith angle of the sun, thickness of the skin, and the skin color [2,4].

Considering the abundance of sunshine, one would expect most inhabitants living near the equator (as in south Asia and GULF countries), to be vitamin D sufficient. However, this is not the case [5–7]. In addition, there are several barriers for vitamin D synthesis in the skin, including time of day of the exposure (*i.e.*, exposures to early morning and late afternoon exposures to sunshine generate less vitamin D) and having darker skin, which is a barrier to UVB penetration. In certain conditions, the synthesis of vitamin D may not occur at all [8–11].

1.2. Dietary sources of vitamin D are insufficient

Many people do not ingest or generate the estimated needed daily requirement for vitamin D from dietary sources, including society seeking comfort and fewer outdoor activities, a sedentary lifestyle, and limited sun exposure, public health efforts should be geared to encouraging safe sun-exposure and prioritizing food fortification and adequate oral vitamin D intake, as well as interventions to increase physical activity [12].

Most foods do not contain meaningful amounts of vitamin D. Despite stipulations and regulations, fortified food contains variable ad sub-optimal amounts of vitamin D. Thus, safe exposure to sunlight provides the most reliable and optimal way to obtain the daily vitamin D requirement [13]. However, aging, sun avoidance, the use of sunscreen, and the change in the zenith angle of the sun (time of the day) can markedly change the body's cutaneous production of vitamin D_3.

Dietary sources of vitamin D are inadequate and thus, insufficient for the daily requirement. In addition, many dietary sources are inadequately fortified with vitamin D (including milk) and some do not provides the amount stated on the label [14]. Among commonly consumed fish, only salmon and mackerel have reasonable amounts of vitamin D, but the contents within species can vary markedly. For example, farmed salmon had approximately 25% of the vitamin D content as wild salmon [14].

1.3. Generation of vitamin D with reference to geographical location

Europeans living in northern latitudes have higher levels of serum vitamin D than do those living in southern latitudes and closure to the equator [1,15–17]. The discrepancy is due in part to the sun-avoidance behaviors of those who live closer to the equator and the greater consumption of eating fatty fish by those who live in northern latitudes. Still, in both populations, the median serum 25(OH)D levels are less than the optimal [9]. In the case of those who live near the equator, having hypovitaminosis D is attributable in part, (A) sun avoidance because of excessive heat and fear of erythema, sunburns and cancer, (B) darker skin pigmentation and (C) personal and cultural habits [16,18].

1.4. Evolution, generation of vitamin D, and survival

In evolutionary terms, thousands of years ago, when the original human inhabitants of tropical central Africa with darker skin started to migrate from Africa to more northern climates, they were exposed to less sunlight [2]. They had a major survival

disadvantage (*i.e.*, the inability to produce adequate amounts of vitamin D with lesser amounts of available sun). Consequently, as a survival advantage, genetic mutations in skin cells occurred, leading to the production of less melanin. Because such mutation-dependent skin color changes occur over many generations, during this migratory period, almost all of these people likely experienced vitamin D deficiency [19].

The degree of skin pigmentation reduces the penetration of UV radiation and consequently, the photosynthesis of 25(OH)D. Despite living in higher latitudes and altitudes and exposure to less sunlight, people who developed lighter skin colors were able to produce more vitamin D than were those with darker skins [20,21]. Those who developed lighter skin through mutations of melanin and other genes also had a major reproductive and procreative advantage [22–24] because adequate amounts of vitamin D are essential for male and female reproductive functions, as well as the safe delivery of an infant. Meanwhile, a small study (n = 17) concluded that there are no ethnic differences in the synthesis of 25(OH)D between Caucasian and south Asians [25], which contradicts most other published data.

The reproductive health declined in the migrants who moved northward from africa, and continued to have darker skin. Those with hypovitaminosis D had fewer offspring, and succumbed to infectious diseases such as tuberculosis, more often than did those who experienced mutation to lighter skin. In addition, in Northern countries, the conception rate is higher during the summer period when there is a seasonal increase in blood 25(OH)D levels, which further support this theory [26,27].

The effects of vitamin D on endometrial and oocyte development may be a part of the explanation for decreased female fertility. In addition, *in vitro* studies have reported that the ovarian production of progesterone, estradiol and estrone, and anti-Müllerian hormone expression in granulosa cells are stimulated by $1,25(OH)_2D$ [28]. Even today, those with darker skin who live in northern climates generate significantly less vitamin D than do those with lighter skin [16,18,27].

1.5. The importance of adequate skin exposure to sunlight

In a person, the amount of vitamin D generated *in vivo* is relatively proportionate to the surface area of the skin exposure to UVB, time of day, and duration of exposure. Therefore, unless an adequate area of skin is exposed to sunlight for a reasonable amount of time, the production of vitamin D is likely to be insufficient.

The duration of exposure needed in individual person depends on the skin pigmentation, presence of sun blockers (clothing, creams, *etc.*) and the inherent ability of the skin to generate vitamin D. Other factors that influence vitamin D generation includes, the intensity of sunlight, time of day (the direction of the UV rays), and health of the skin and age of the person, and cultural and personal habits (*e.g.*, the sun blocking effects of clothing) [29–31].

The exposure required to gain the oral-equivalent doses of vitamin D, as functions of latitude, season, skin type and skin area exposed, expressed in minimum erythema doses has been investigated. A daily intake of 400 IU can be readily achieved through casual sun exposure in the midday "lunch hour" (casual sun exposure without the risk of erythema, for all latitudes). However, to generate a dose of 1000 IU during lunchtime sun exposure requires a greater exposure of skin areas, but a daily dose in excess of 4000 IU is hardly achievable with such short exposure [3].

The regular use of sunscreen and the strength of the sunscreens are major factors that reduce or prevent the ability of the skin to produce vitamin D [29,30,32]. It has been shown that sunscreens with sun-protection factor (SPF) greater than 15 would completely cut off the UVB skin penetration [33–35], but other studies contradict that finding [36,37]. Nevertheless, human physiology is designed to derive most of the daily need of vitamin D through sun exposure (Fig. 1).

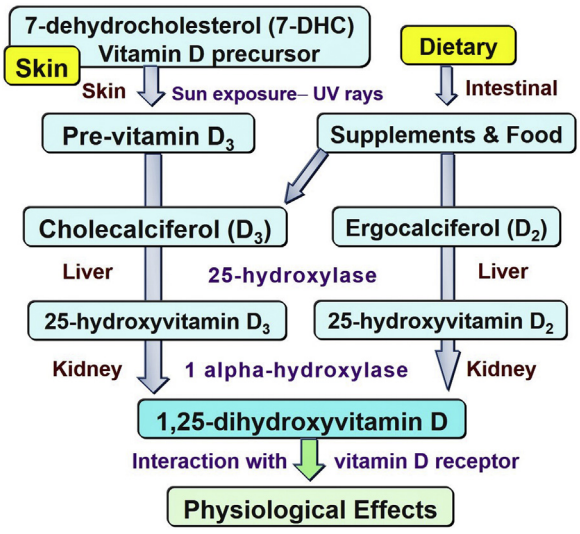

Fig. 1. Pathways of generation and activation of vitamin D.
Generation and activation of vitamin D. The activation of cholecalciferol and ergocalciferol into, 25(OH)D in the liver and $1,25(OH)_2D$, and interacting with the vitamin D receptors (VDRs) in target tissues, leading to physiological actions [modified from Wimalawansa [1].

2. Vitamin D—physiology

2.1. Physiological importance of vitamin D

Vitamin D has many functions in humans, including calcium and phosphate homeostasis. Once absorbed from the gut or produced in the skin, vitamin D is hydroxylated in the liver into 25-hydroxyvitamin D [25(OH)D] and then in the kidney into 1,25-dihydroxyvitamin D [1,25(OH)2D]. Thereafter, the active metabolite circulates through the blood stream, enters cells and binds to the vitamin D receptor (VDR) in a vitamin D-responsive gene, such as that of calcium-binding protein producing its action of assisting calcium absorption.

Vitamin D deficiency causes growth retardation and rickets in children, and precipitate and exacerbates osteopenia, and osteoporosis, and increases the risk of fractures in adults [38,39]. In addition, the affinity of vitamin D-binding protein, circulating half-lives, enzymatic transformations of vitamin D metabolites, and so forth modulate its biological and physiologic actions, in a given tissue [40]. In the longer-term, the levels of 25(OH)D in the circulation required to activate some of its functions vary depending on the tissue [17,41]. Fig. 2 illustrates the estimated serum 25(OH)D levels needed to alleviate various disease states.

Intestinal calcium absorption varies depending on the serum ionized calcium levels, activity of the calcium binding proteins, and serum 1,25(OH)2D [42]. Vitamin D also regulates the secretion of parathyroid hormone (PTH), which in turn controls calcium homeostasis and bone turnover [2,43]. Severe vitamin D deficiency leads to a failure of skeletal calcification and thus leads to accumulation of osteoid tissues [43]. Unless treated, this can lead to rickets in children and osteomalacia in adults.

The key function of vitamin D is to provide adequate calcium and phosphorus to the body and body fluids to maintain optimal metabolic functions [44]. Vitamin D deficiency also impairs

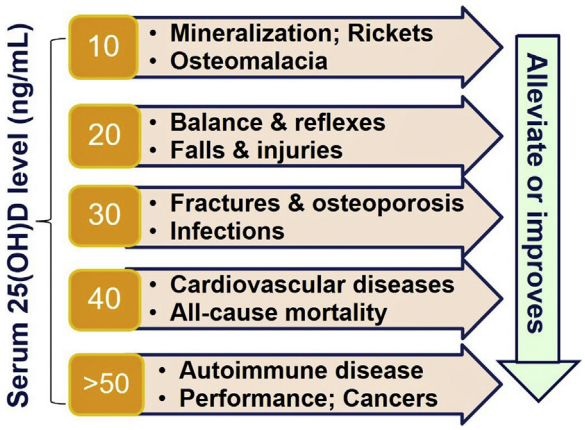

Fig. 2. Different minimum serum 25(OH)D levels are needed to overcome diverse diseases.
The relationships between various disease states and the approximate median serum 25(OH)D levels needed to improve various conditions.

fertility and reproductive success [22–24]. Vitamin D modulates the transcription of cell cycle proteins that decrease cell proliferation and increase cell differentiation, such as in osteoclastic precursors, enterocytes, and keratinocytes; these actions of vitamin D are reflected in bone resorption, intestinal calcium transport, and skin cell turnover, respectively [43]. In the case of the latter, the cell-differentiation and immuno-modulatory properties of vitamin D have led to the topical use of vitamin D and its metabolites in the treatment of psoriasis and other skin disorders.

Circulating vitamin D, the parent compound, likely plays an important physiological role with respect to the vitamin D endocrine/autocrine system, including providing as a substrate to produce its active hormone [40]. Based on emerging data from the laboratory, clinical trials, and studies on circulating 25(OH)D, accumulated during past few years, we can conclude, it is likely that for the optimal functioning of these systems, significant amount of vitamin D should be available on a daily basis to ensure, stable circulating concentrations [40].

Thus, the unphysiological variations (e.g., fluctuations) of 25 (OH)D levels in blood secondary to infrequent vitamin D dosing (*i.e.*, administration every 3 months to yearly) could lead to negative outcomes as reported in clinical trials. This is in part because of the shorter circulating half-life of intact vitamin D and the marked fluctuation of bio-available vitamin D in the circulation and within cells [40,45]. Reported negative outcomes in certain clinical studies represent (poor) failure of the study designs, not necessarily the lack of efficacy of vitamin D.

2.2. The physiological blood level of 25(OH)D

Having physiological levels of vitamin D over a long period, decreases the incidence and severity of type 1 and type 2 diabetes, insulin resistance, metabolic syndrome, cardiovascular diseases (CVDs), depression, and certain cancers, including cancer of the breast, colon, and prostate [44,46–55]. Fig. 3 illustrates the different mean serum 25(OH)D levels in four different ethnic groups.

Based on these data from the United States, more than 90% of the non-Hispanic African Americans (15 ng/mL) and Hispanics (mean level of 20 ng/mL) have hypovitaminosis D [55,56], whereas non-Hispanic Whites have mean serum 25(OH)D levels of 26 ng/mL. Dark-skinned people in central Africa living in traditional cultures had mean serum 25(OH)D levels of 46 ng/mL. The latter should be considered as the true physiologic level of 25(OH)D in humans [55,56]. In addition, a variety of data have been reported on the relationships among ethnicity, skin color, and serum 25(OH)D levels [19,57–59].

In addition to the aforementioned, it has been suggested that the socioeconomic factors are the strongest determinant of skin-color based health disparities in the United States (and perhaps other) population [60]. Fig. 4 illustrates the odds ratios of 25(OH)D deficiency in relation to the lowest quartile of serum 25(OH)D levels by race [58]. Data presented were from the National Health and Nutrition Survey III. Compared with non-Hispanic Whites, non-Hispanic African Americans are 10-times likely to be vitamin D deficient ($p < 0.001$).

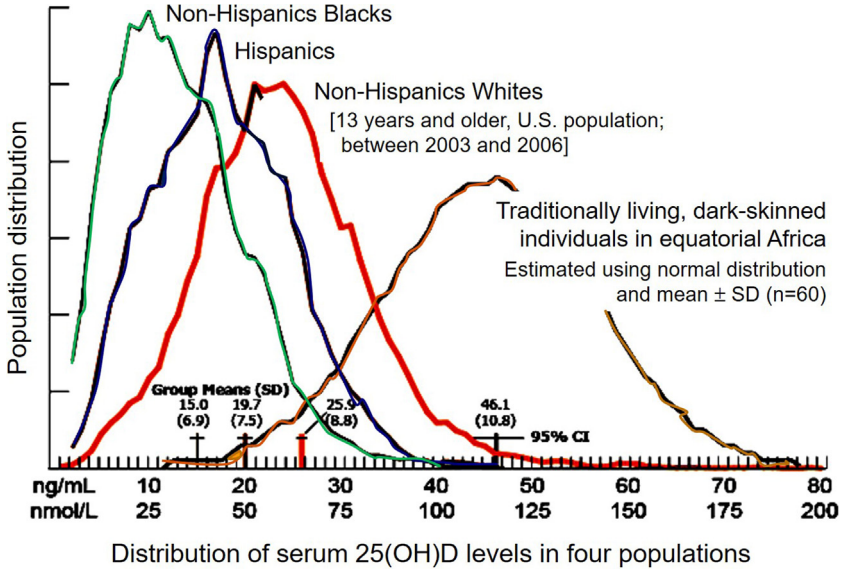

Fig. 3. The physiological mean serum 25(OH)D level is above 40 ng/mL.
The distribution of serum vitamin D levels in different groups of populations are illustrated. The traditional-living populations in East Africa, where humans originated, have mean 25(OH)D serum levels of approximately, 45 ng/mL. This is about twice the mean value of the adult, non-Hispanic and the white population in the United States and elsewhere. From an evolutionary perspective, the higher level is likely the one that is optimal/ physiological for humans (modified from Luxvolda et al., 2012) [55] and Weishaar & Vergili, 2013 [56].

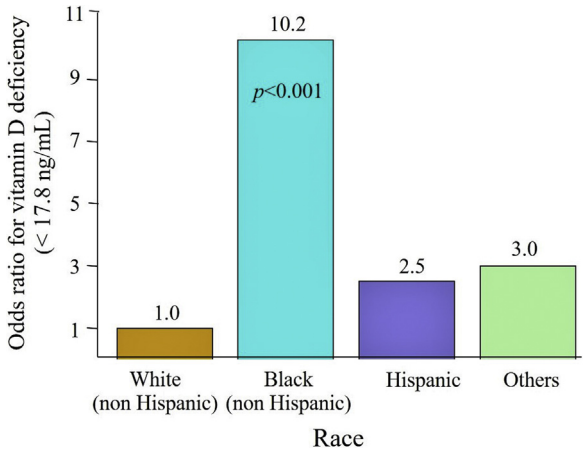

Fig. 4. People in minority ethnic groups have significantly lower vitamin D blood levels than do Caucasians.
Data presented as odds ratios of 25(OH)D deficiency below 17.8 ng/mL (the lowest quartile) by race; data from the National Health and Nutrition Survey III (n = 13,331). Non-Hispanic Blacks are 10-times more likely to be vitamin D deficient ($p < 0.001$) (modified from Melmed) [58].

2.3. Vitamin D: associations and comorbidities

Vitamin D plays an essential role in developing and maintaining a healthy skeleton for humans and other land vertebrates. The major biological function of $1,25(OH)_2D$ is to keep the serum calcium and phosphorus concentrations within the normal range. It is essential to maintaining cellular functions and, enzymatic activities, and promoting mineralization of the skeleton [13].

Associations have been reported between vitamin D intake and dose-dependent risk reduction for falls and osteoporosis [61,62], diabetes [63,64], multiple sclerosis [65], rheumatoid arthritis [66], and cancer [32,67]. Published reports indicate that those who live in higher latitudes not only have low serum 25(OH)D levels that are associated with the increased prevalence of hypertension [68], autoimmune diseases, type 1 diabetes [69] and multiple sclerosis [70,71].

Recent data from epidemiological, cross-sectional, and longitudinal studies suggest that vitamin D adequacy can minimize or prevent many of the aforementioned chronic diseases. Such associations include reduction in the risks of diabetes [63,64,72,73], multiple sclerosis [65], rheumatoid arthritis [66], osteoporosis [61,74], and certain types of cancer [75,76]. However, none of these studies was designed to use vitamin D supplementation as the primary intervention or address specific disease risk reduction as the primary end point.

Therefore, evidence reported through these ecological/observational studies, although demonstrating strong associations, also includes confounders. These include, failures in study design, randomization bias, inadequate statistical power, drug interferences that are not controlled between groups, variations of body mass index, age and gender disproportions, variability of taking diet and supplements, nutritional status, sun exposure, smoking and alcohol use, physical activities, and skin pigmentation, etc. The lack of control over these confounders can influence the outcome of these associations. Therefore, the resulting data cannot be fully relied upon nor can be used to make firm or overreaching conclusions or policy making.

2.4. Consequences of vitamin D deficiency

In people of all ages, vitamin D deficiency negatively affects health outcomes. Recent studies have confirmed that during fetal life, maternal vitamin D deficiency causes a reduction in fetal bone mineralization and development of fetal rickets [77–79], and perhaps suboptimal brain development [80–84]. Long-term vitamin D insufficiency can lead to other effects, such as type 1 diabetes, cancer, and multiple sclerosis, and several other diseases [32,82–84]. Table 1 identifies some common diseases and conditions that are associated with vitamin D deficiency.

Signs and symptoms of vitamin D deficiency include lethargy, increased vulnerability to bacterial and viral infections, exacerbation of existing chronic diseases, the inability to lose weight and visceral obesity, insulin resistance, low back pain, proximal muscle weakness muscle aches, and spontaneous throbbing bone pain. Painful skeletal sites at times can be identified as pseudo-fractures using routine plain x-rays.

2.5. Benefits of vitamin D in the musculoskeletal systems

Vitamin D plays an important role in stimulating the intestinal absorption of calcium and maintaining physiological blood levels of calcium and phosphorous, bone development and ossification, mineralization, and preservation. Vitamin D deficiency increases muscle weakness and falls and thus fractures [62,85,86]. Studies have shown that vitamin D supplementation will aid in maintaining bone strength, and reduce the risk of falls, fractures, and bone loss in elderly individuals, especially those with inadequate calcium and/or vitamin D intake [39,87–90].

Vitamin D adequacy not only supports healthy bone development and growth in children and adults but also can promote healthy remodeling and rebuilding of new bones. Hypovitaminosis D has profound effects on pancreas, leading to prediabetes and diabetes [91,92], and in the brain causing neurocognitive dysfunction and impairment of balance [93]. There is strong evidence for the protective effects of vitamin D in muscular system

Table 1
Diseases and conditions that are associated with or aggravated by vitamin D deficiency.

• Osteomalacia/osteoporosis	• Parathyroid diseases
• Muscle function and falls	• Polymyalgia rheumatic
• Autoimmune disorders	• Autism
• Tuberculosis/infections	• Peripheral vascular disease
• Cancer (breast, colon, skin, pancreas, prostate)	• Chronic pain
	• Fibromyalgia
• Celiac disease	• Chronic fatigue syndrome
• Cystic fibrosis	• Cardiovascular mortality
• Multiple sclerosis	• Demyelinating diseases
• Hypertension	• Infections
• Type 2 diabetes	• Athletic performance
• Inflammatory bowel disease	• Seasonal affective disorder
• Rheumatoid arthritis	• Depression
• Migraine headaches	• Obesity
• Incontinence	• Rheumatoid arthritis
• Macular degeneration (AMD)	• Parkinson's disease
• Cognitive impairment	• Psoriasis
• Cardiovascular events	• Overall mortality

From Wimalawansa [1].

[11,94–97], including prevention of falls [62,85,98] and fractures [39,99]. Nevertheless, in the elderly in particular, it is necessary to reduce the fall risks from other factors, such as arthritis, disabilities, poor balance [90,100], impaired vision and hearing; unsafe home setting; peripheral neuropathy; and environmental hazards [1,9].

It is common to find vitamin D deficiency in those who are having increased falls and impaired physical function [101]. Although some data suggest that serum 25(OH) D levels greater than 15 to 20 ng/mL are adequate to prevent rickets and osteomalacia [102], other data including recent cohort reports, animal data, and a number of epidemiological studies indicate that much higher serum 25(OH)D levels are required for cancer prevention and protective immune responses [79,103].

3. Non-skeletal effects of vitamin D deficiency

Non-skeletal effects of vitamin D can be broadly categorized into (A) regulatory effects on the endocrine and immune systems; (B) cardiovascular functions, metabolic syndrome–obesity, and diabetes; (C) sarcopenia and gait; (D) memory and neurological dysfunction; and (E) cancer and chronic kidney diseases. VDR knock-out mice cell-based models, and genome-wide association studies have provided some insight to a variety of non-skeletal effects of vitamin D.

Because vitamin D is an important mediator of calcium metabolism, its actions have been implicated in the pathophysiology of several extra-skeletal conditions. Some of the extra-skeletal benefits (non-calciotropic functions) such a cell proliferation, hypertension, renal disease, and insulin resistance, apoptosis and immunity of vitamin D arising from extra-renal synthesis; autocrine and paracrine effects of the active metabolite, 1,25 $(OH)_2D$ [104].

Statistically significant inverse associations between 25(OH)D levels and CVD risk factor were reported in dose-responses (an inverse association exhibiting a linear biological gradients, and cellular-level causative mechanisms and biological pathways with increased risk for CVD with mediators, such as dyslipidemia, hypertension and diabetes mellitus n the with hypovitaminosis D [105]. Table 2 illustrates common conditions that are thought to aggravate vitamin D deficiency.

As per the VitaminDWiki [www.vitamindwiki.com], vitamin D reduces the severity of more than 70 different diseases. Some of these key diseases and conditions incudes, rickets, osteomalacia, falls, hip fractures, diabetes, metabolic syndrome, influenza, certain cancers (breast, colon and prostate cancer), pregnancy risks, chronic kidney disease, cystic fibrosis, rheumatoid arthritis, osteoarthritis, tuberculosis, respiratory and urinary tract infections, lupus erythematosus, multiple sclerosis, congestive heart failure, asthma, chronic obstructive airways disease, depression, fibromyalgia, allergy, chronic hives, weight gain and loss, vertigo, restless legs syndrome, preeclampsia, irritable bowel syndrome, perinatal depression [http://www.vitamindwiki.com/VitaminDWiki].

3.1. Vitamin D inadequacy and cancer incidences

In many industrialized countries, cancer is the second most common cause of death. Vitamin D is involved in control of the cell cycle and thus likely is a key mechanism in cancer reduction [106,107]. Consequently, low vitamin D status is associated with increased risks of various cancers. Among those who live at higher latitudes in the United States, an increased risk of dying of common cancers has been documented [108,109], including the risk of developing and dying of colon, breast, prostate, and other cancers [108–112]. Correlations also have been reported between an inability to produce vitamin D_3 through the skin and living at higher latitudes [113–115].

The mechanisms and effects of vitamin D on cancer are complicated. Moreover, VDR polymorphisms may also have an association with cancer, which suggests gene-environment interactions for such outcomes but data are inadequate to make firm conclusions [116–120]. It is possible that the genetic variations of vitamin D effector system or the VDR pleomorphism, together with epigenetics, may further modify cancer incidence [116,121].

In addition, vitamin D metabolism and perhaps its effects also are influenced by diet, medications, the balance between energy intake and expenditure, and environmental pollutants [122]. Many research gaps exist in this area that needs to be addressed via large randomized controlled clinical trials (RCTs). Without such definitive studies, it is not possible to effectively predict or guide treatments, or modify the susceptibility of people/communities to protect them using dietary and vitamin D interventions.

In addition, evidence supports the relation between vitamin D deficiency and the incidence of certain cancers. Data from ecological studies demonstrate significant inverse correlations between solar UVB doses and the incidence of a number of cancers as well as the mortality rate associated with them [123–126]. Whether this is in part attributable to sun avoidance or some other phenomenon, such as frailty and aging, is remains unknown.

Epidemiological studies have suggested links between exposure to sunlight and low mean serum 25(OH)D levels, with higher incidences of breast [127–129], colon (digestive tract), prostate, and ovarian cancers, and non-Hodgkin's lymphoma and certain leukemias [46,94,130–133]. However, it is unknown whether the risks of cancer would decrease with normalization of vitamin D

Table 2
Skeletal and non-skeletal effects of vitamin D.

Musculoskeletal effects	Non-skeletal effects
• Essential for calcium homeostasis	• Improved immunity
• Enhanced GI absorption of calcium	• Decrease severity of autoimmunity and neurological disorders
• Enhanced osteoblast function	• Prevention of type 1 and type 2 diabetes
• Necessary for bone mineralization	• Prevention of cancer
• Prevent rickets and osteomalacia	• Decreased cardiovascular diseases
• Decrease sarcopenia	• Decreased all-cause mortality
• Improve balance and prevention of falls	• Decreased pulmonary morbidities
• Prevention of osteoporosis and fractures	• Less morbidities and improved survival

From Wimalawansa [1].

status in the longer term [134,135]. Vitamin D decreases cell proliferation and increase cell differentiation, decrease angiogenesis, and has anti-inflammatory effects; impeding cancer cell growth [136] and decreasing cancer metastasis [137–140]. Nevertheless, it is not clear whether hypovitaminosis D itself, leads to increase incidence of certain cancers, but most studies support this notion.

Epidemiological studies have suggested an inverse association between increased sunlight exposure [surrogate for an increase in serum 25(OH)D levels] and decreased incidences of several types of cancers, including those of the breast [127–129,141,142], colon, prostate, and ovaries, as well as certain leukemias and non-Hodgkin's lymphoma [46,94,120,126,130–133,143]. Recent data point to increasing incidences of similar types of cancers in those who live in northern latitudes [124,144–148]. Thus, it is tempting to postulate that this increasing incidence of cancer is at least in part attributable to the prevailing high incidence of vitamin D deficiency.

One study reported that postmenopausal women who received 1100 IU vitamin D_3 and 1000 mg calcium daily (*i.e.*, dual effect) experienced 60% fewer cancers over a 4-year period [149–151]. These data have been supported by meta-analyses demonstrating that increasing the intake of vitamin D_3 by 1000 IU a day was associated with a 50% reduction in colorectal and breast cancer risks [152–154]. Those who increase their vitamin D intake modestly (*e.g.*, 400 IU vitamin D/day) also had reduced risk of certain cancers, such as pancreatic and esophageal [155], and non-Hodgkin's lymphoma [156–161].

In the Women's Health Initiative study, women supplemented with calcium and vitamin D had a significantly lower risk of total breast and invasive breast cancers (14–20%), and non-significant reduction in the risk of colorectal cancer (17%) [162]. The mechanisms whereby vitamin D reduces the risk of cancer are complex. These include, reducing inflammation, effects on cellular differentiation, apoptosis, reduced angiogenesis around tumors and reduced metastasis [125,163]. Data from experimental studies suggest that VDR activation exerts anti-cancer effects on virtually all steps of carcinogenesis [134].

A series of reports indicates that those who are exposed to more sunlight throughout their lives (not just one summer) were less likely to die of cancer [50–54]. This concept was supported by prospective and retrospective studies that have documented circulating 25(OH)D levels [135]. For example, a 30% to 50% risk reduction of colorectal, breast, prostate, and several other cancers in adults over two decades was reported in those with serum 25 (OH)D levels more than 20 ng/mL (50 nmol/L) [164–168]. Fig. 5 illustrates associations between serum vitamin D levels and various diseases.

Not every study finds positive relationships between vitamin D and cancer. For example, in the United Kingdom [where approximately, 600,000 deaths from cancer occur each year [169]] a community-based study compared 100,000 IU of vitamin D_3 administered every 4 months (less than 1000 IU a day, given on an infrequent basis) with a placebo in 2686 men and women aged 65 to 85 years; there were no differences between the interventional and placebo groups (RR, 1.09; 95% CI, 0.86 to 1.36) and total cancer mortality (RR, 0.86; 95% CI, 0.61 to 1.20) for the two groups was statistically comparable after 5 years of follow-up [170]. In this study, the dose provided was inadequate to attain the minimum levels necessary to have a meaningful reduction in cancer incidence [*i.e.*, mean serum level beyond 30 (or 40) ng/mL], and the administration (*i.e.*, the dosing schedule) was too infrequent, preventing the possibility of a positive outcome.

Nevertheless, the overall evidence from ecological and RCTs suggests that having serum 25(OH)D concentration above 30 ng/mL (75 nmol/L) is likely to reduce the risks of having cancer and improve the survival, if cancer is developed [124,154]. On a population basis, to achieve such serum level, in the presence of casual exposure to sunlight, one needs to ingest vitamin D, approximately 2000 IU/day [171].

3.2. Cardiovascular effects of vitamin D

Evidence is also emerging with reference to associations between vitamin D deficiency and an increased incidence of cardiovascular mortality and all-cause mortality [172–177]. Vitamin D has anti-inflammatory and cardiovascular protective effects [178,179]. Its cardiovascular protective effects are mediated through lowering blood pressure and vascular tone [180,181], preventing vascular calcification [41,177,182,183], improving cardiac and smooth muscle cell functions, and maintaining the health of the endothelium [184–186].

The association between CVD and serum 25(OH)D is based on both, longitudinal and cross-sectional observational studies [187]. Such studies have reported associations between serum 25(OH)D levels and cardiovascular risk, including stroke, myocardial infarction, heart failure, and the ensuing cardiovascular mortality [79,187]. Increased PTH levels are known to promote insulin resistance, weight gain, left ventricular hypertrophy, hypertension, and the inflammatory–acute phase responses, which further increase the risk for cardiac arrhythmias and cardiovascular mortality [188].

The increased PTH levels in blood (secondary hyperparathyroidism) that are common in those with vitamin D deficiency have been suggested to be a contributor to the progression of CVD [187], but, no such correlation has been found between blood vitamin D and lipid levels [189,190]. However, others have fund beneficial

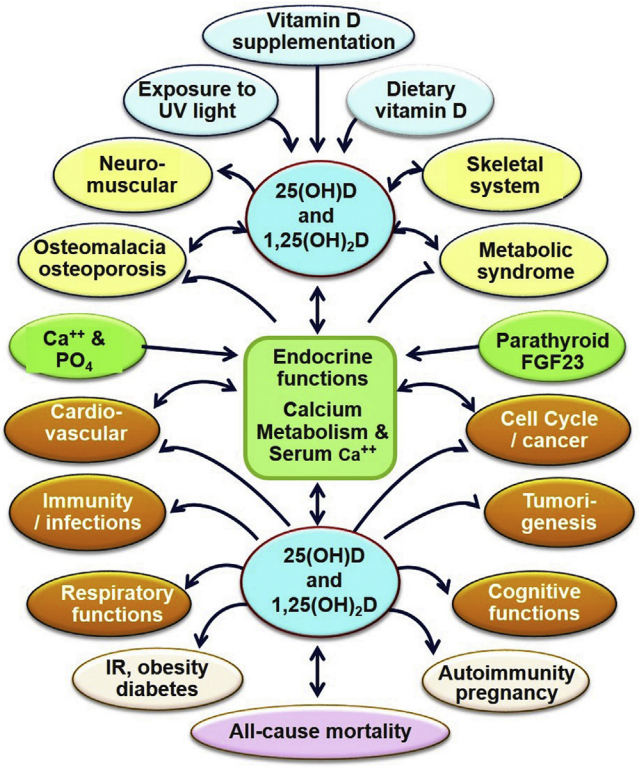

Fig. 5. Vitamin D has broad and diverse beneficial effects in humans.
The complex interactions between supply of vitamin D, 25(OH)D, and $1,25(OH)_2D$ and various organ systems, bodily functions, and disease staAdequate vitamin D could improve, prevent, or decrease the severity of many disorders [modified from Wimalawansa,[1]] (abbreviations used: FGF23: fibroblast growth factor-23; IR; insulin resistance; UV: ultra-violet rays).

effects of vitamin D supplementation on lipids, including a reduction in the apolipoproteins, Apo A1 and B [191].

Intervention: studies have reported significant clinical improvements in patients with heart failure with vitamin D supplementation [187]. Interaction of vitamin D with its receptors on the vasculature and the myocardium seems to be the mechanistic path of action in the reduction of the wall thickness, decreasing the severity of cardiac failure [192]. The cardiovascular protective effects of vitamin D also encompass suppression of matrix metalloproteinases and FGF-23, and remodeling of the myocardium and the vasculature [187,193].

A recent meta-analysis reported that the circulating levels of 25 (OH)D were lower in patients with peripheral artery disease, compared to those who do not have such [194]. Hypovitaminosis D was associated with peripheral artery disease, especially in those patients with critical limb ischemia. Authors concluded that low 25 (OH)D contributes to the development of advanced peripheral vascular disease [194]. Additional cellular level, beneficial effects of vitamin D includes its actions on anti-inflammatory effects, renin-angiotensin system, parathyroid hormone, *etc.* [187,193,195].

Sufficient blood levels of vitamin D may reduce deaths associated with heart disease, all-cause mortality, and strokes secondary to hypertension [176]. Meanwhile, intervention studies have reported clinical improvements in patients with heart failure after vitamin D supplementation [187]. Most of the associations reported between vitamin D deficiency and non-skeletal diseases are based on retrospective analyses, cohort studies, case reports, and epidemiological studies. Evidence from prospective randomized clinical studies would be helpful in reaching conclusions about the reported associations.

3.3. Autoimmune diseases

Autoimmune diseases such as multiple sclerosis, Hashimoto's thyroiditis, and inflammatory bowel disease occur because of an inappropriate immune-mediated destruction of specific body tissue and T-cell development and function; these are at least in part regulated through vitamin D [196]. Both 25(OH)D and 1,25 $(OH)_2D$ are involved in the regulation of the immune system [197].

In the absence of vitamin D and signals delivered through the VDR, actions through autoreactive T-cells manifest, especially in the presence of insufficient $1,25(OH)_2D$ and VDR activity. Once bound to VDR in immune cells, vitamin D acts as a selective immunosuppressant [198] and decreases the severity of autoimmune diseases [199]. When vitamin D is sufficient, T-cell response is restored and autoimmunity minimized. In persons with type 1 diabetes, multiple sclerosis, and thyroid autoimmunity, serum 1,25 $(OH)_2D$ levels are reduced [200].

Low vitamin D levels worsen most autoimmune diseases and increase the susceptibility to autoimmune diseases such as cancer, metabolic syndrome, type 2 diabetes, and infectious diseases [44,54,97,201]. Women with autoimmune diseases who received vitamin D 400 IU/day had a 40% reduction in the risk of multiple sclerosis, chronic fatiguing illnesses, Behcet's disease, and rheumatoid arthritis [202–205]. Research also suggests an association between low serum vitamin D levels and increased prevalence of inflammatory bowel diseases [206–209] and rheumatoid arthritis [210–213]. However, not all studies agree with this conclusion [214].

3.4. Infections

The immune system would not function efficiently in the absence of vitamin D adequacy. This leads to increased susceptibility to bacterial and viral infections, particularly intracellular bacterial infections such as tuberculosis [215]. Adequate vitamin D levels are inversely associated with decreased seasonal infections [216] but also enhance immunity and the ability to overcome bacterial and viral infections [217,218].

Exposure to sunlight is known to enhance recovery from mycobacterial diseases such as mycobacterium tuberculosis [219,220] and leprosy [221,222]. Mycobacterial products increase the activity of the 1α-hydroxylase enzyme within macrophage in granulomatous tissues, thus increasing the intracellular levels of $1,25(OH)_2D_3$ and the expression of the VDR. These together enhance the expression of the gene-encoding, bactericidal protein cathelicidin, which destroys mycobacterium tuberculosis and similar intra-cellular pathogenic organisms. T-cells and macrophages have high concentration of VDRs [223]. VDR activation also increases the synthesis and secretion of the bactericidal peptides cathelicidin and defensins [205,224] while reducing inflammatory cytokines [178,225].

Vitamin D deficiency is strongly associated with pneumonia [226]. Vitamin D adequacy plays an important role in combating bacterial infections, such as tuberculosis, and viral infections, including influenza [22,217,218,227–229]. Hypovitaminosis D is associated with reduced cellular immune function and hyponatremia in patients with H7N9 pneumonia [230]. Nevertheless, some studies do not support this concept [231,232].

A recent publication concluded that due to the heterogeneity of studies, where included studies differed with respect to population, baseline vitamin D levels and study length, and so forth, conclusion is based on vitamin D meta-analysis cannot be relied upon [233]. Future RCTs should be focus on subjects with vitamin D deficient and apply more objective and standardized outcome measurements.

3.5. Role of vitamin D in regulation of blood pressure

Vitamin D has been reported to lower blood pressure *in vivo* in humans by regulating the renin-angiotensin system [234,235]. In addition, some epidemiological and clinical studies have shown that increased dairy consumption and calcium and/or vitamin D supplementation have a beneficial effect on blood pressure [236,237]. Thus, vitamin D therapy has been suggested to be an effective short-term intervention for reducing blood pressure [234,235].

Experimental studies have demonstrated novel actions of vitamin D metabolites on cardiomyocytes and endothelial and vascular smooth muscle cells. Low 25(OH)D levels are associated with left ventricular hypertrophy, vascular dysfunction, and renin-angiotensin system activation [238]. However, despite a large number of smaller experimental, cross-sectional, and prospective studies supporting a key role of suboptimal levels of vitamin D in the pathogenesis of CVDs, a causal relationship remains to be established. Vitamin D reduces vascular stiffness and vascular dysfunction [239]. However, not all studies agree with these findings [240]. Patients with hypertension who had tanning bed exposure nearly doubled their serum 25(OH)D levels and reported a reduction in blood pressure [241,242], but the use of tanning beds is not recommended.

3.6. Type 1 and type 2 diabetes mellitus

Several observational studies have reported the effects of vitamin D in reducing the risk of type 2 diabetes (T2D) [177,243,244]. These cohort studies have reported that persons with serum 25(OH)D levels greater than 29 ng/mL had a 20%–50% reduction in the risk of developing T2D [244]. A few studies indicate that those with serum levels greater than 40 ng/mL had the lowest incidence for T2D [103,235]. Nevertheless, once a person has T2D, vitamin D may not have a measurable effect on the

course of the disease [50,190], except for some reduction in insulin resistance [44,54,97,201].

Release of insulin including secretion in response to glucose from pancreatic β-cells, at least in part seems to be dependent on vitamin D adequacy. Having physiological blood levels of vitamin D reduces the overproduction and tissue-damage caused by free radicals and blocks renin production [245]. This results in decreased islet cell harm from the effects of hyperglycemia and insulin resistance [246,247]. In addition, in persons with T2D, short-term, daily supplementation of vitamin D reduces central obesity and T2D, particularly in the carriers of the AA genotype [248].

Data related to type 1 diabetes (T1D) comes from ecological/epidemiological studies, small supplementation studies and meta-analyses [249]. In addition to the reduction of T1D risks and related autoimmunity, vitamin D deficiency in early life is associated with a higher risk of T1D in adulthood [92,250]. A meta-analysis of data supports that supplementation of vitamin D during early infancy reduces the incidence of T1D [251]. Nevertheless, the available data are conflicting on the cause-effect relationship between of vitamin D and diabetes. Although not studied yet, it is plausible that vitamin D supplementation early in the disease—the prediabetes stage, may prevent β-cell damage.

Among the many possible mechanisms, reduction of inflammation [54,178,252], improved insulin sensitivity, and reduced insulin resistance have been proposed [50,52,53,253,254]. In addition, vitamin D has positive physiological effects on the regulation of plasma calcium levels, which indirectly regulate insulin synthesis and secretion, and also have actions on pancreatic β-cell function [50,255,256]. These complex relationships are described mostly in observational and epidemiological studies and their existence have not been substantiated by RCTs [92].

3.7. Pregnancy

Vitamin D deficiency increases the risks of pre-eclampsia and development of problems in the child in later life [257–259]. Serum 25(OH)D levels are inversely correlated with the incidence of pre-eclampsia. Current evidence supports an immunological etiology for pre-eclampsia and auto-immunity, and vitamin D deficiency as a predisposing factor for the development of pre-eclampsia [260].

Women with recurrent pregnancy losses and low blood vitamin D have an increased prevalence of autoimmune and cellular immune abnormalities and pre-eclampsia compared with women with recurrent pregnancy losses but with normal vitamin D [261]. The aforementioned is particularly noticeable in pregnant women whose vitamin D intake is below 400 IU per day [262]. Vitamin D supplementation during pregnancy increases the circulating 25 (OH)D levels in the women and fetuses, which is associated with increased birth weight and infant height but not with other maternal and neonatal outcomes [263].

Non-breast-fed infants need higher doses of oral vitamin D supplementation [171]. Another study reported a 6-week supplementation of calcium and vitamin D in pregnant women with gestational diabetes mellitus led to several beneficial outcomes, including decreased cesarean section rate and duration of maternal hospitalization, and decreased macrosomia, hyperbilirubinemia and hospitalization in newborns [264].

3.8. Physical functions

Several studies have reported performance improvement of athletes after exposure to artificial UVB. Cross-sectional studies also reported that 25(OH)D improves physical performance in older people [265]. Vitamin D increases the quality and the quantity of type II, fast-twitch skeletal muscle fibers. Studies conducted in older individuals show that vitamin D improves their functional capabilities.

Vitamin D has genomic and non-genomic actions on musculoskeletal tissues [266,267]. The genomic pathway involves activation of the $1,25(OH)_2D$ nuclear receptors, resulting in expression of several messenger RNAs and synthesis of key proteins [265,268]. The non-genomic pathway acts directly through secondary messenger systems in the cell and/or by activating protein kinase C [267,269,270].

These are some of the reasons for the myopathy that is associated with rickets and osteomalacia [271,272]. In the case of milder disease, patients may present with a variety of non-specific features, such as muscle pain and tenderness, arthralgia, and paraesthesia. Those with severe vitamin deficiency will present with the classic signs of proximal limb-girdle myopathy (muscle weakness) [271,272].

3.9. Sarcopenia and muscle weakness

Vitamin D receptors are widely expressed in muscle cells [273]. Serum 25(OH)D levels and the expression of VDR in muscle cells as well as testosterone levels decline with age [274]. Collectively, these contribute to sarcopenia and muscle weakness [275]. VDR are located predominantly on the fast-twitch muscle fibers, which respond first in rapid actions, so it is not surprising that vitamin D adequacy increases muscle strength and coordination, enabling the preventing falls [62,171,276].

Vitamin D deficiency leads to proximal muscle weakness with loss of type II muscle fibers. Consequently, muscular symptoms of vitamin D deficiency include easy fatigability, difficulty in rising from a chair or bed, and inability to climb stairs. These abnormalities reverse after replenishment of vitamin D. An age-associated decrease in muscle fiber content, decreased intracellular calcium transportation and the speed of muscle contraction and relaxation have been reported. Associations have been reported with lower limb and grip strengths and serum vitamin D levels [277,278]. However, not all studies agree with these findings [279]. Nevertheless, data suggest that vitamin D provides a physiological important benefit to muscle function.

3.10. Difficulty in swallowing

Dysphagia is common in the elderly; approximately half of individuals older than 65 years have swallowing difficulties independent of neurological diseases, such as Parkinson's disease, stroke, or CVDs. Recent research showed that even healthy older adults, especially those receiving multiple medications, swallow more slowly and generate lower tongue pressures than do younger adults [280].

Dysphagia in the elderly is multifactorial, including abnormal posture, recurrent infections (mostly oropharyngeal yeast), gastroesophageal reflux disease, and frailty, especially among those with vitamin D deficiency [87,281]. Correction of dysphagia is important because it is known to lead to aspiration pneumonia and a vicious cycle of social withdrawal, depression, malnutrition, and sarcopenia, and premature death [282,283].

3.11. Overactive bladder

Urinary urgency with or without incontinence, increased frequency of urination, and nocturia are common in the elderly [284]. Overactive bladder occurs in 30% to 40% of adults older than 70 years and more than 70% of residents in nursing homes. Suboptimal vitamin D levels affect the severity of overactive bladder in patients with chronic disabilities. Generalized muscle

weakness and poor muscle coordination exacerbate bladder dysfunctions that aggravate control of urination [285].

3.12. Pulmonary function

There is an age-associated decline in the forced expiratory volume and forced vital capacity [286,287]. Serum vitamin 25(OH) D levels are related to peak airflow and the severity of chronic obstructive airway disease and asthma [287]. In addition, pulmonary function worsens in the presence of vitamin D deficiency and, combined with aging, further increases morbidity and mortality. However, whether the decline of respiratory muscle function is attributable to vitamin D deficiency, chronic airway inflammation, or impaired lung tissue remodeling is not known [286,288].

3.13. Age-related macular degeneration

The risk of macular degeneration increases with age, especially in those with vitamin D deficiency [289]. Multivariate models have demonstrated that in women younger than 75 years, increased intake of vitamin D decreased the odds of early age-related macular degeneration [290]. Higher serum 25(OH)D levels are thought to protect against early age-related macular degeneration. Apart from observational studies, no data are available to confirm this. Whether the correction of vitamin D deficiency would decrease the rate of occurrence and/or the severity of macular degeneration is unknown [291].

3.14. Vitamin D and pain relief

The elderly, especially those who live in northern latitudes have a high incidence of hypovitaminosis D, which is a risk factor for enhanced perception of pain. Vitamin D deficiency is an independent risk factor for pain and poor prognosis in persons with diabetic peripheral neuropathy [292]. A systematic review concluded an association of vitamin D deficiency with diabetic peripheral neuropathy [293]. In addition, there are other studies showing plausible associations between vitamin D deficiency and diabetic peripheral neuropathy [292–297]. Based on a number of data sets, a mechanistic link has been established between hypovitaminosis D and diabetic neuropathy as well as certain pain symptoms such as, arthritic pain, rheumatism, and fibromyalgia, in the general population [298].

The content of nerve growth factor (NGF) has been studied in experimental, diabetic models [299]. In patients with diabetic neuropathy, NGF skin keratinocytes immunostaining is correlates with skin axon-reflex vasodilation, a measure of painful small (c) fiber neuropathy [294]. In addition, animal studies have reported a preservation of NGF expression in sciatic nerves of diabetic animals, treated with active vitamin D_3 analogs, which induce NGF production in human epidermal keratinocytes [300].

Vitamin D also has been shown to reduce demyelination in a cuprizone experimental model of demyelination [296] and in a spinal cord compression model, it induced axonal regeneration [297]. Vitamin D deficiency may lead to selective alterations in target innervation, resulting in presumptive nociceptor hyperinnervation of skeletal muscle, which in turn is likely to contribute to hypersensitivity in muscles and exaggerated pain [295]. These data suggest connections between neuropathic issues and nociception with vitamin D status [292,301]. Nevertheless, a causation cannot be inferred from such cross-sectional studies; thus, specifically designed prospective studies are needed to clarify these issues [295,298].

Calcitonin gene-related peptide (CGRP) is the most potent endogenous vasodilator in humans, which is also a neuromodulator and a nociceptive agent [302–304]. CGRP containing sensory neurons have a distinct vitamin D phenotype and hormonal regulation [305]. Vitamin D deficiency results in increased numbers of axons containing CGRP and growth, and neuronal sprouting in culture. This seems to be regulated by VDR-mediated rapid response signaling pathways [295]. In this regard, a recent clinical trial reported a significant decrease in pain (reduction of total McGill pain score from 19 to 6, $p < 0.0001$) following a single intramuscular dose of 600 000 IU of vitamin D that led to an increase in the mean serum 25(OH)D level from 31.7 ± 23 to 46.0 ± 10 ng/mL, in persons with diabetic neuropathy [301].

3.15. Vitamin D deficiency and epilepsy

Many studies have shown a link between vitamin D deficiency and epilepsy [306–311]. Children and adolescents treated with antiepileptic drugs are known to develop skeletal problems such as osteomalacia. Children with epilepsy are at risk for poor bone health, and vitamin D therapy may be beneficial. Vitamin D supplementation is recommended for all children with epilepsy to prevent the development of hypovitaminosis D [308,309,311]. In addition, the long-term use of antiepileptic drugs leads to sustained vitamin D deficiency, and is a significant risk factor for epilepsy, especially in children. Targeted strategies such as, vitamin D supplementation and lifestyle advice regarding healthy sunlight exposure behavior, reduce the prevalence of epilepsy in high-risk children [306].

Regular monitoring of vitamin D levels and supplements is needed, especially in the presence of longer duration of antiepileptic medication use, brain magnetic resonance imaging abnormality, abnormal underlying conditions, and in non-ambulatory status [309]. Vitamin D is also thought to have anticonvulsant properties [310]. Irrespective of where they live, a high proportion of children taking antiepileptic drugs on a long-term basis are at risk for vitamin D deficiency [307]. Considering this, monitoring and supplementation and safe sun exposure are important in the care of children on long-term antiepileptic drug regimens.

3.16. Dementia, cognitive functions, and Alzheimer's disease

Vitamin D influences brain functions; those who live at higher latitudes and have lower blood levels of 25(OH)D are more predisposed to schizophrenia [312–314] and depression [315]. Vitamin D deficiency has been correlated with worsening Alzheimer's disease and memory, both of which can lead to increased falls and fractures [62,316]. Vitamin D- and VDR-associated responsive neurohormonal cascades are abundantly expressed in the central nervous system, particularly in areas that are commonly affected by neurodegenerative disorders, such as in the hippocampus [317]. These suggest that such areas could be therapeutic targets for vitamin D actions.

Low serum 25(OH)D levels are associated with cognitive deterioration with age [318]. The use of metformin in diabetics has been associated with impaired cognitive performance [319,320]. In patients with diabetes, vitamin supplements have been reported to alleviate metformin-induced cognitive deteriorations [321]. Vitamin D supplementation has been shown to stabilize Parkinson's disease for a short period without triggering hypercalcemia [322].

A prospective 30-year follow-up study reported that low 25 (OH)D levels were associated with a 20% increased risk of Alzheimer's disease and vascular dementia [323]. Vitamin D is also an anti-inflammatory and reduces oxidative stress, enhancing immune response, and is thought to protect the central nervous system [316]. Some have suggested vitamin D supplements as an adjutant therapy for dementia and Alzheimer's disease [324].

Table 3
The minimum optimal levels of serum 25(OH)D levels needed to have positive impact of various diseases and disorders.

Disease entity or disorder	Minimal serum 25 (OH)D levels needed	References
Musculoskeletal	20 to 32 ng/mL	
• Sarcopenia and muscle weakness		[266,267,275,277,278]
• General fractures	32 ng/mL	[79,349,350]
• Hip fractures		[79,87,351–355]
• Rickets and osteomalacia	20 ng/mL	[271,272,352–354,356]
• Fall prevention		[62,87,171,276,357]
• Frailty		[87,103,338,339]
• Dysphagia in the elderly		[280–283]
• Urgency and overactive bladder		[284,285]
Cardiovascular (CVD):	30 to 40 ng/mL	
• Blood pressure		[87,176,187,193,195,235–237,241,242,358,359]
• Regulate renin-angiotensin system		[234,238]
• Protective effects on CVD		[178,179,360,361]
• Vascular tone		[180,181,238,239]
• Vascular calcification		[41,177,182,183]
• Smooth muscle cell and endothelial functions		[184–186]
• Decreasing CVD risks; stroke, myocardial infarction, heart failure		[51,176,177,187,193,195]
• Mechanisms of CVD risk-reduction		[192,238]
• Cardiovascular mortality		[172–177]
• Lipids/apo-proteins (Apo A1 and B)		[191,362]
Cancer:	40 ng/mL	
• Cancer		[46,94,108–112,120,130–133,143,149–151,363–365]
• Breast cancer and survival		[108–112,127–129,162,366–368]
• Colorectal cancers		[76,108–112,124,126,152–154,162,342]
• Lymphoma		[156–161]
• VDR polymorphisms		[116–121]
• Relationship to living in higher latitudes		[108,109,113–115,124,144–148]
• Relationship to serum 25(OH)D levels		[46,94,124,127–133,135,154,164–167]
• Mechanisms of cancer reduction		[125,134,135,163]
• UVB/sun exposure and cancer reduction		[44,46–54,108–115,123–125,135]
• Cancer metastasis		[137–140]
Respiratory system:	30 to 40 ng/mL	
• Respiratory infections		[228,369]
• Asthma and chronic obstructive airway diseases		[286–288,364,370,371]
• Cystic fibrosis		[361,364,372,373]
• Forced expiratory volume and vital capacity		[286–288]
Metabolic disorders:	30 to 40 ng/mL	
• Type 1 diabetes mellitus		[249–251]
• Type 2 diabetes mellitus		[44,54,97,177,200,201,235,243,244,248,374,375]
• Insulin resistance		[44,50,52–54,97,201,246,247,253,254,376–379]
• Metabolic syndrome		[246,247,380]

Table 3 (*Continued*)

Disease entity or disorder	Minimal serum 25 (OH)D levels needed	References
• Reduced HbA1c levels		[362,381]
• Obesity and body mass index		[168,382–388]
• Mechanisms		[50,54,178,255,256,389–392].
Immunity and autoimmunity:	40 ng/mL	
• T-cell function and immune regulation		[196,197,202–204]
• General immunity		[200,393]
• Multiple sclerosis		[200,394]
• Rheumatoid arthritis		[210–213,395]
• Inflammatory bowel diseases		[206–209]
• Autoimmune liver disease		[396]
Infections:	40 ng/mL	
• Viral and seasonal infections		[22,216–218,227–229]
• Pneumonia		[226,231,232,397]
• Tuberculosis and leprosy (mycobacterial infections)		[215,219–222,398]
• Hepatitis C		[399,400]
• Anti-bacterial/viral mechanisms		[178,209,224,225]
Neurological system:	30 to 40 ng/mL	
• Cognition and dementia		[318–321,323,401,402]
• Alzheimer's disease		[62,316,323,324]
• Depression		[205,315,325–329]
• Schizophrenia		[312–314]
• Epilepsy		[306–311,403]
Pregnancy-related:	30 ng/mL	
• Pregnancy outcomes		[261,263,264,404–406]
• Fetal developmental problems		[257–259,264]
• Preeclampsia		[257–261,407,408]
Miscellaneous:	30 ng/mL	
• Genomic effects		[103,265,268]
• Non-genomic effects		[266,267,269,270]
• Anti-inflammatory		[50,54,178,179,225,316,390–392].
• Physical performance		[265,271,272,275]
• Oral and dental health		[333–336]
• Dental caries		[331,409]
• Age-related macular degeneration		[289–291]
• All-cause mortality		[172–177,337,340,341,364]

3.17. Vitamin D deficiency and depression

Several reports indicate an inverse relationship between vitamin D deficiency and depression [325,326]. Lower vitamin D levels are associated with depression: increased odds ratio of depression for the lowest *versus* the highest vitamin D categories in cross-sectional studies (OR = 1.31, 95% CI, 1.0–1.71) and a significantly increased hazard ratio of depression for the lowest *versus* the highest vitamin D categories in cohort studies (HR = 2.21, 95% CI, 1.40–3.49) [327].

Vitamin D affects T- and B-lymphocyte activation, as well as quantity, maturation and function of regulatory natural killer T-

cells and their counterparts in the gut. These includes, T-cell receptor-alpha-beta, cluster of differentiation-8-alpha alpha-positive intraepithelial lymphocytes [205]. Consequently, vitamin D deficiency decreases innate and adaptive immunity, leading to persistent infections, chronic inflammation, and fatigue.

Vitamin D deficiency worsens depression and mental health-related quality of life among women [328]. Correction of vitamin D deficiency improves depression, as measured by the Beck Depression Inventory [329]. Vitamin D deficiency, in those with alcohol abuse also showed an inverse relationship with severity of alcohol-use and comorbid major depression [325]. Despite all of these findings, conflicting evidence about the relationship between vitamin D deficiency and depression still exists [327,328,330].

3.18. Oral and dental health

Vitamin D's role in reducing the risk of dental caries has been explored [331]. A placebo-controlled trial reported that vitamin D supplements reduced the incidence of dental caries [332]. A meta-analysis of 24 controlled clinical trials reported significant benefit of vitamin D supplementation on oral health [333]. Other studies have linked vitamin D deficiency to periodontal disease [334] and premature tooth loss [335].

Indirect bactericidal effects of vitamin D may manifest via the induction of cathelicidin in reducing oral infections [336]. Nevertheless, it is more likely that low vitamin D levels could be a surrogate marker for poor oral hygiene malnutrition, and frailty, and reflect a low socio-economic state and less access to care from dentists and oral hygienists.

3.19. All-cause morbidity and mortality

Several studies have reported the beneficial effects of vitamin D in reducing all-cause mortality [174,176,337]. Studies have also demonstrated an inverse relationship between 25(OH)D level and frailty [338,339] and the all-cause mortality rate [340,341]. Meta-analysis shows that an increase in serum 25(OH)D levels from 22 to 42 ng/mL (54 to 105 nmol/L) was associated with a statistically significant 15% reduction in the incidence of CVDs [51,176,177] and a 30% reduction in breast and colorectal cancer incidence [124,342].

Cardiovascular disease, including coronary artery disease and stroke, is the leading cause of mortality in most countries and especially in certain racial groups such as African Americans [343]. Although, vitamin D deficiency causes increased morbidity and mortality, it is also an indicator of poor health and nutrition [41,344]. In cross-sectional analysis of 9579 subjects with vitamin D deficiency, higher odds of a poor self-rated health and frailty was reported but not in longitudinal analyses [345]. Authors suggested that vitamin D deficiency may not cause frailty or poor general health but may be a prognostic marker for mortality, independent of the individual's morbidity.

African American men and women have greater prevalence of vitamin D insufficiency, which may be a factor in their susceptibility to certain cancers. Recommendations for vitamin D should be made for the otherwise "healthy populations in greatest need" of dietary vitamin D due to lack of adequate sun exposure [346]. However, among others, low serum 25(OH)D levels can also be a marker for poor socio-economic status, malnutrition, and general ill-health, and thus may be linked to confounding factors [347,348].

Many cross-sectional studies and RCTs indicate that the minimum optimal serum 25(OH)D concentration is 30 ng/mL or higher. Complementary to Fig. 2, Table 3 illustrates examples from the literature that indicate the minimum levels of serum 25(OH)D needed to have a meaningful effect on reducing the incidences of various disorders and diseases, categorized into systems for easy reference.

Data from multiple studies suggests that the serum 25(OH)D levels that needed to maintain to alleviate different diseases various much. For example, while rickets and osteomalacia could be resolved with serum 25(OH)D levels approximately 20 ng/mL, conditions such as cancer, multiple sclerosis, heart failure, osteoporosis, diabetes metabolic syndrome and so forth, need much higher steady levels of vitamin D in the blood. Summary of such from a large number of studies are illustrated in Fig. 6.

4. Discussion

Vitamin D supplementation is a highly cost-effective, easy to administer, simple solution to alleviating wide-ranging chronic health problems. Many vitamin D studies report a link between low blood 25(OH)D levels and increased risks of dying prematurely to CVDs, cancer, and several other diseases. Adequate vitamin D status is protective against musculoskeletal disorders, infectious diseases, cancer, autoimmune diseases, CVDs, diabetes mellitus, neurocognitive dysfunctions, other disorders and diseases. Vitamin D deficiency is also increases all-cause mortality [417]. Nevertheless, whether vitamin D supplementation leads to longevity is not clear. Clarifying this issue will require more research and longer duration RCTs with adequate doses of vitamin D to increase and maintain the serum 25(OH)D levels of study participants to more than 30 ng/mL.

The use of RCTs with selection bias (*e.g.*, studies that are not designed to assess the efficacy of calcium and vitamin D supplements) has caused some scientists to raise concerns about the safety of calcium supplements, particularly their potential to cause myocardial infarction [418–421]. However, when calcium intake (*i.e.*, diet plus supplements) does not exceed 1.5 g a day and vitamin D supplementation does not exceed 5000 IU per day, no hazard or worsening of any condition, including CVDs, has been documented [422,423]. Introducing investigator bias and selecting inappropriate data sets to test a given hypothesis would generate misleading conclusions from meta-analyses.

Most of the negative clinical studies with vitamin D published to-date, have faulty study designs: they have used too-small dosages (≤800 IU/day) [424]; too high, infrequent dosages (*i.e.*, the

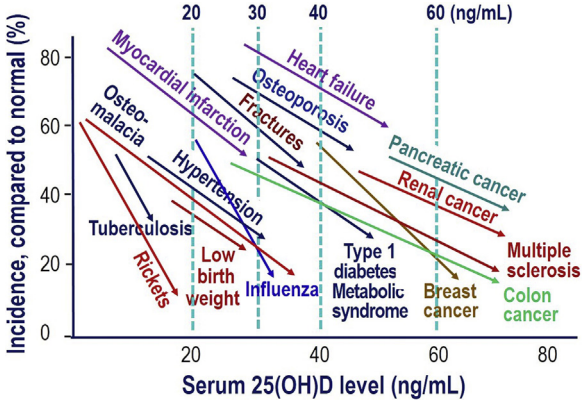

Fig. 6. Higher blood levels of 25(OH)D will decrease the incidence and the severity of a number of diseases.
Skeletal disorders such as rickets and osteomalacia will respond efficiently to the serum 25(OH)D levels close to 20 ng/mL. However, as depicted in the figure, many other conditions and diseases need varied but higher levels of 25(OH)D concentrations in the blood for longer periods. Data presented are redrawn primarily from Garland and Baggerly, 2010; Grassroots Health, 2013 [http://www.vitamindwiki.com/tiki-index.php?page_id=62], and authors personal data, and a number of other publicly available data sets [410–416].

use of supra pharmacological doses, once in 3 months, 6 month or yearly); treated persons with varying blood levels of 25(OH)D (subjects with wide scatter of serum 25(OH)D levels or vitamin D levels have not been tested), provided interventions to those who are not vitamin D deficient; and used too small sample size and short study durations [425,426]. Taking into consideration the half-life of vitamin D, and thus the fluctuation in blood levels, supplements given at intervals of greater than once a month are unphysiological, and thus are unlikely to have health benefits or improve the signs and symptoms of deficiency status [62,425,427,428].

Because of the design failures, the three large RCTs that are currently under way using vitamin D as an intervention, are unlikely to provide answers to the questions related to the public health needs of vitamin D. These studies have inherent biases in design, inclusion of persons who are already taking supplements and/or who are vitamin D sufficient (*i.e.*, vitamin D sufficient persons), and so forth. Nevertheless, when the minimum serum levels of 25(OH)D exceed 30 ng/mL and are maintained over a long period, most studies point to significant protective effects of vitamin D in humans.

Alleviation of various diseases and disorders requires, persons to achieve and sustain serum 25(OH)D levels that are appropriate to the disease being treated (*e.g.*, osteomalacia/rickets, musculo-skeletal system *versus* cancer, diabetes, autoimmune disorders, *etc.*) (Fig. 2 and Table 3). While data are mounting, the current evidence is somewhat inconsistent with reference to blood concentrations of 25(OH)D with risks for certain health conditions. As with other physiological phenomena, the goal should be to achieve the optimal serum 25(OH)D levels to obtain the most protective effects for the person [i.e., maintaining the serum 25 (OH)D levels between 30 and 50 ng/mL] that benefit all body tissues with minimal or no adverse effects.

Conflicts of interest

The author received no funds for this work and has no conflicts of interest.

References

[1] S.J. Wimalawansa, Vitamin D: Everything You Need to Know, Karunaratne & Sons, Homagama, Sri Lanka, 2012978-955-9098-94-2.
[2] D.A. Wahl, C. Cooper, P.R. Ebeling, M. Eggersdorfer, J. Hilger, K. Hoffmann, et al., A global representation of vitamin D status in healthy populations, Arch. Osteoporos. 7 (2012) 155–172.
[3] A.R. Webb, O. Engelsen, Ultraviolet exposure scenarios: risks of erythema from recommendations on cutaneous vitamin D synthesis, Adv. Exp. Med. Biol. 810 (2014) 406–422.
[4] W.B. Grant, R.C. Strange, C.F. Garland, Sunshine is good medicine: the health benefits of ultraviolet-B induced vitamin D production, J. Cosmet. Dermatol. 2 (2) (2003) 86–98.
[5] N.M. van Schoor, P. Lips, Worldwide Vitamin D status, Best Pract. Res. Clin. Endocrinol. Metab. 25 (4) (2011) 671–680.
[6] A.R. Eggemoen, K.V. Knutsen, I. Dalen, A.K. Jenum, Vitamin D status in recently arrived immigrants from Africa and Asia: a cross-sectional study from Norway of children, adolescents and adults, BMJ Open 3 (10) (2013) e003293.
[7] C.F. Garland, E.D. Gorham, S.B. Mohr, F.C. Garland, Vitamin D for cancer prevention: global perspective, Ann. Epidemiol. 19 (7) (2009) 468–483.
[8] A. Mithal, D.A. Wahl, J.P. Bonjour, P. Burckhardt, B. Dawson-Hughes, J.A. Eisman, et al., Global vitamin D status and determinants of hypovitaminosis D, Osteoporos. Int. 20 (11) (2009) 1807–1820.
[9] S.J. Wimalawansa, Vitamin D in the new millennium, Curr. Osteoporos. Rep. 10 (1) (2012) 4–15.
[10] W.B. Grant, S.J. Wimalawansa, M.F. Holick, Vitamin D supplements and reasonable solar UVB should be recommended to prevent escalating incidence of chronic diseases, Br. Med. J. 350 (2015) h321.
[11] M.F. Holick, High prevalence of vitamin D inadequacy and implications for health, Mayo Clin. Proc. 81 (3) (2006) 353–373.
[12] C.K. Colapinto, M. Rossiter, M.K. Khan, S.F. Kirk, P.J. Veugelers, Obesity, lifestyle and socio-economic determinants of vitamin D intake: a population-based study of Canadian children, Can. J. Public Health 105 (6) (2014) e418–24.
[13] M.F. Holick, Vitamin D and bone health, J. Nutr. 126 (4 Suppl) (1996) 1159S–1164S.
[14] Z. Lu, T.C. Chen, A. Zhang, K.S. Persons, N. Kohn, R. Berkowitz, et al., An evaluation of the vitamin D3 content in fish: is the Vitamin D content adequate to satisfy the dietary requirement for Vitamin D? J. Steroid Biochem. Mol. Biol. 103 (3–5) (2007) 642–644.
[15] L. Hedlund, P. Brembeck, H. Olausson, Determinants of vitamin D status in fair-skinned women of childbearing age at northern latitudes, PLoS One 8 (4) (2013) e60864.
[16] Z. Touma, L. Eder, D. Zisman, J. Feld, V. Chandran, C.F. Rosen, et al., Seasonal variation in vitamin D levels in psoriatic arthritis patients from different latitudes and its association with clinical outcomes, Arthritis Care Res. (Hoboken) 63 (10) (2011) 1440–1447.
[17] S.J. Wimalawansa, Vitamin D: biology, physiology, and pathology, J. Diabetes Treat. (2016) (in press).
[18] P. Lips, Worldwide status of vitamin D nutrition, J. Steroid Biochem. Mol. Biol. 121 (1–2) (2010) 297–300.
[19] G. Chaplin, N.G. Jablonski, Vitamin D and the evolution of human depigmentation, Am. J. Phys. Anthropol. 139 (4) (2009) 451–461.
[20] R.A. Durazo-Arvizu, P. Camacho, P. Bovet, T. Forrester, E.V. Lambert, J. Plange-Rhule, et al., 25-Hydroxyvitamin D in African-origin populations at varying latitudes challenges the construct of a physiologic norm, Am. J. Clin. Nutr. 100 (3) (2014) 908–914.
[21] J.E. Rockell, T.J. Green, C.M. Skeaff, S.J. Whiting, R.W. Taylor, S.M. Williams, et al., Season and ethnicity are determinants of serum 25-hydroxyvitamin D concentrations in New Zealand children aged 5–14 y, J. Nutr. 135 (11) (2005) 2602–2608.
[22] L.M. Bodnar, J.M. Catov, H.N. Simhan, M.F. Holick, R.W. Powers, J.M. Roberts, Maternal vitamin D deficiency increases the risk of preeclampsia, J. Clin. Endocrinol. Metab. 92 (9) (2007) 3517–3522.
[23] L.M. Bodnar, J.M. Catov, J.M. Zmuda, M.E. Cooper, M.S. Parrott, J.M. Roberts, et al., Maternal serum 25-hydroxyvitamin D concentrations are associated with small-for-gestational age births in white women, J. Nutr. 140 (5) (2010) 999–1006.
[24] S. Lewis, R.M. Lucas, J. Halliday, A.L. Ponsonby, Vitamin D deficiency and pregnancy: from preconception to birth, Mol. Nutr. Food Res. 54 (8) (2010) 1092–1102.
[25] O.A. Hakim, K. Hart, P. McCabe, J. Berry, R. Francesca, L.E. Rhodes, et al., Vitamin D production in UK Caucasian and South Asian women following UVR exposure, J. Steroid Biochem. Mol. Biol. (2016).
[26] N. Rojansky, A. Brzezinski, J.G. Schenker, Seasonality in human reproduction: an update, Hum. Reprod. 7 (6) (1992) 735–745.
[27] W.B. Grant, C.F. Garland, The vitamin D revolution, Mol. Nutr. Food Res. 54 (8) (2010) 1053.
[28] G. Parikh, M. Varadinova, P. Suwandhi, T. Araki, Z. Rosenwaks, L. Poretsky, et al., Vitamin D regulates steroidogenesis and insulin-like growth factor binding protein-1 (IGFBP-1) production in human ovarian cells, Horm. Metab. Res. 42 (10) (2010) 754–757.
[29] N.M. Al-Daghri, Y. Al-Saleh, N. Khan, S. Sabico, N. Aljohani, H. Alfawaz, et al., Sun exposure, skin color and vitamin D status in Arab children and adults, J. Steroid Biochem. Mol. Biol. (2016).
[30] N. Buyukuslu, K. Esin, H. Hizli, N. Sunal, P. Yigit, M. Garipagaoglu, Clothing preference affects vitamin D status of young women, Nutr. Res. 34 (8) (2014) 688–693.
[31] V. Terushkin, A. Bender, E.L. Psaty, O. Engelsen, S.Q. Wang, A.C. Halpern, Estimated equivalency of vitamin D production from natural sun exposure versus oral vitamin D supplementation across seasons at two US latitudes, J. Am. Acad. Dermatol. 62 (6) (2010) e1–e9 929.
[32] P.T. Alpert, U. Shaikh, The effects of vitamin D deficiency and insufficiency on the endocrine and paracrine systems, Biol. Res. Nurs. 9 (2) (2007) 117–129.
[33] L.C. Breslin, P.J. Magee, J.M. Wallace, E.M. McSorley, An evaluation of vitamin D status in individuals with systemic lupus erythematosus, Proc. Nutr. Soc. (2011) 1–9.
[34] D.E. Godar, S.J. Pope, W.B. Grant, M.F. Holick, U.V. Solar, Doses of young americans and vitamin D3 production, Environ. Health Perspect. (2011).
[35] L.Y. Matsuoka, L. Ide, J. Wortsman, J.A. MacLaughlin, M.F. Holick, Sunscreens suppress cutaneous vitamin D3 synthesis, J. Clin. Endocrinol. Metab. 64 (6) (1987) 1165–1168.
[36] U. Osterwalder, B. Herzog, Sun protection factors: world wide confusion, Br. J. Dermatol. 161 (Suppl 3) (2009) 13–24.
[37] S.A. Stechschulte, R.S. Kirsner, D.G. Federman, Sunscreens for non-dermatologists: what you should know when counseling patients, Postgrad. Med. 123 (4) (2011) 160–167.
[38] M.F. Holick, Sunlight, UV-radiation, vitamin D and skin cancer: how much sunlight do we need, Adv. Exp. Med. Biol. 624 (2008) 1–15.
[39] E. Harju, E. Sotaniemi, J. Puranen, R. Lahti, High incidence of low serum vitamin D concentration in patients with hip fracture, Arch. Orthop. Trauma Surg. 103 (6) (1985) 408–416.
[40] B.W. Hollis, C.L. Wagner, Clinical review: the role of the parent compound vitamin D with respect to metabolism and function: why clinical dose intervals can affect clinical outcomes, J. Clin. Endocrinol. Metab. 98 (12) (2013) 4619–4628.

[41] S.J. Wimalawansa, Vitamin D deficiency is a surrogate marker for visceral fat content, metabolic syndrome, type 2 diabetes, and future metabolic complications, J. Diabetes Metab. Disord. Control 3 (1) (2016) 1–10.
[42] R.P. Heaney, M.S. Dowell, C.A. Hale, A. Bendich, Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D, J. Am. Coll. Nutr. 22 (2) (2003) 142–146.
[43] L. Steingrimsdottir, O. Gunnarsson, O.S. Indridason, L. Franzson, G. Sigurdsson, Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake, JAMA 294 (18) (2005) 2336–2341.
[44] H. Khan, S. Kunutsor, O.H. Franco, R. Chowdhury, Vitamin D type 2 diabetes and other metabolic outcomes: a systematic review and meta-analysis of prospective studies, Proc. Nutr. Soc. 72 (1) (2013) 89–97.
[45] J.M. Lappe, R.P. Heaney, Why randomized controlled trials of calcium and vitamin D sometimes fail, Dermatoendocrinology 4 (2) (2012) 95–100.
[46] C.F. Garland, F.C. Garland, E.D. Gorham, M. Lipkin, H. Newmark, S.B. Mohr, et al., The role of vitamin D in cancer prevention, Am. J. Public Health 96 (2) (2006) 252–261.
[47] E. Giovannucci, Y. Liu, W.C. Willett, Cancer incidence and mortality and vitamin D in black and white male health professionals, Cancer Epidemiol. Biomarkers Prev. 15 (12) (2006) 2467–2472.
[48] M.D. Gross, Vitamin D and calcium in the prevention of prostate and colon cancer: new approaches for the identification of needs, J. Nutr. 135 (2) (2005) 326–331.
[49] R. Vieth, Why the optimal requirement for Vitamin D3 is probably much higher than what is officially recommended for adults, J. Steroid Biochem. Mol. Biol. 89–90 (1–5) (2004) 575–579.
[50] P.S. George, E.R. Pearson, M.D. Witham, Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis, Diabet. Med. 29 (8) (2012) e142–50.
[51] A. Manousopoulou, N.M. Al-Daghri, S.D. Garbis, G.P. Chrousos, Vitamin D and cardiovascular risk among adults with obesity: a systematic review and meta-analysis, Eur. J. Clin. Invest. 45 (10) (2015) 1113–1126.
[52] S. Pilz, K. Kienreich, F. Rutters, R. de Jongh, A.J. van Ballegooijen, M. Grubler, et al., Role of vitamin D in the development of insulin resistance and type 2 diabetes, Curr. Diab. Rep. 13 (2) (2013) 261–270.
[53] C.C. Sung, M.T. Liao, K.C. Lu, C.C. Wu, Role of vitamin D in insulin resistance, J. Biomed. Biotechnol. 2012 (2012) 634195.
[54] T. Takiishi, C. Gysemans, R. Bouillon, C. Mathieu, Vitamin D and diabetes, Rheum. Dis. Clin. North Am. 38 (1) (2012) 179–206.
[55] M.F. Luxwolda, R.S. Kuipers, I.P. Kema, E. van der Veer, D.A.J. Dijck-Brouwer, F. A.J. Muskiet, Vitamin D status indicators in indigenous populations in East Africa, Eur. J. Nutr. 52 (3) (2013) 1115–1125.
[56] T. Weishaar, J.M. Vergili, Vitamin D status is a biological determinant of health disparities, J. Acad. Nutr. Diet 113 (5) (2013) 643–651.
[57] A.A. Ginde, M.C. Liu, C.A. Camargo Jr., Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004, Arch. Intern. Med. 169 (6) (2009) 626–632.
[58] M.L. Melamed, E.D. Michos, W. Post, B. Astor, 25-hydroxyvitamin D levels and the risk of mortality in the general population, Arch. Intern. Med. 168 (15) (2008) 1629–1637.
[59] N.E. Adler, T. Boyce, M.A. Chesney, S. Cohen, S. Folkman, R.L. Kahn, et al., Socioeconomic status and health: the challenge of the gradient, Am. Psychol. 49 (1) (1994) 15–24.
[60] T. Weishaar, J.M. Vergili, Vitamin D status is a biological determinant of health disparities, J Acad. Nutr. Diet. 113 (5) (2013) 643–651.
[61] C. Meier, H.W. Woitge, K. Witte, B. Lemmer, M.J. Seibel, Supplementation with oral vitamin D3 and calcium during winter prevents seasonal bone loss: a randomized controlled open-label prospective trial, J. Bone Miner. Res. 19 (8) (2004) 1221–1230.
[62] T. Suzuki, J. Kwon, H. Kim, H. Shimada, Y. Yoshida, H. Iwasa, et al., Low serum 25-hydroxyvitamin D levels associated with falls among Japanese community-dwelling elderly, J. Bone Miner. Res. 23 (8) (2008) 1309–1317.
[63] H.S. Choi, K.A. Kim, C.Y. Lim, S.Y. Rhee, Y.C. Hwang, K.M. Kim, et al., Low serum vitamin D is associated with high risk of diabetes in Korean adults, J. Nutr. 141 (8) (2011) 1524–1528.
[64] A.K. Gupta, M.M. Brashear, W.D. Johnson, Prediabetes and prehypertension in healthy adults are associated with low vitamin D levels, Diabetes Care 34 (3) (2011) 658–660.
[65] K.L. Munger, S.M. Zhang, E. O'Reilly, M.A. Hernan, M.J. Olek, W.C. Willett, D. et al. Vitamin, intake and incidence of multiple sclerosis, Neurology 62 (1) (2004) 60–65.
[66] L.A. Merlino, J. Curtis, T.R. Mikuls, J.R. Cerhan, L.A. Criswell, K.G. Saag, D. Vitamin, intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study, Arthritis Rheum. 50 (1) (2004) 72–77.
[67] M.L. McCullough, A.S. Robertson, C. Rodriguez, E.J. Jacobs, A. Chao, J. Carolyn, et al., Calcium, vitamin D, dairy products, and risk of colorectal cancer in the cancer prevention study II nutrition cohort (United States), Cancer Causes Control 14 (1) (2003) 1–12.
[68] L.N. Cosenso-Martin, J.F. Vilela-Martin, Is there an association between vitamin D and hypertension? Recent Pat. Cardiovasc. Drug Discov. 6 (2) (2011) 140–147.
[69] B. Altieri, W.B. Grant, S.D. Casa, F. Orio, A. Pontecorvi, A. Colao, et al., Vitamin D and pancreas: the role of sunshine vitamin in the pathogenesis of diabetes mellitus and pancreatic cancer, Crit. Rev. Food Sci. Nutr. (2016) 0.
[70] B.L. Mark, J.A. Carson, Vitamin D and autoimmune disease–implications for practice from the multiple sclerosis literature, J. Am. Diet. Assoc. 106 (3) (2006) 418–424.
[71] A.L. Ponsonby, R.M. Lucas, I.A. van der Mei, UVR, vitamin D and three autoimmune diseases-multiple sclerosis, type 1 diabetes, rheumatoid arthritis, Photochem. Photobiol. 81 (6) (2005) 1267–1275.
[72] K.C. Chiu, A. Chu, V.L. Go, M.F. Saad, Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction, Am. J. Clin. Nutr. 79 (5) (2004) 820–825.
[73] E.A. Hamed, N.H. Abu Faddan, H.A. Adb Elhafeez, D. Sayed, Parathormone – 25 (OH)-vitamin D axis and bone status in children and adolescents with type 1 diabetes mellitus, Pediatr. Diabetes 12 (6) (2011) 536–546.
[74] D. Feskanich, W.C. Willett, G.A. Colditz, Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women, Am J. Clin. Nutr. 77 (2) (2003) 504–511.
[75] D.A. Lieberman, S. Prindiville, D.G. Weiss, W. Willett, Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals, JAMA 290 (22) (2003) 2959–2967.
[76] M.L. Slattery, S.L. Neuhausen, M. Hoffman, B. Caan, K. Curtin, K.N. Ma, et al., Dietary calcium, vitamin D, VDR genotypes and colorectal cancer, Int. J. Cancer 111 (5) (2004) 750–756.
[77] K. Rummens, S.J. van Cromphaut, G. Carmeliet, E. van Herck, R. van Bree, I. Stockmans, et al., Pregnancy in mice lacking the vitamin D receptor: normal maternal skeletal response, but fetal hypomineralization rescued by maternal calcium supplementation, Pediatr. Res. 54 (4) (2003) 466–473.
[78] W.W. Koo, R. Tsang, Bone mineralization in infants, Prog. Food Nutr. Sci. 8 (3–4) (1984) 229–302.
[79] N. Khazai, S.E. Judd, V. Tangpricha, Calcium and vitamin D: skeletal and extraskeletal health, Curr. Rheumatol. Rep. 10 (2) (2008) 110–117.
[80] I. Elmadfa, A.L. Meyer, Vitamins for the first 1000 days: preparing for life, Int. J. Vitam. Nutr. Res. 82 (5) (2012) 342–347.
[81] S.J. Genuis, Maternal and pediatric health outcomes: in relation to gestational Vitamin D sufficiency, Obstet. Gynecol. Int. 2015 (2015) 501829.
[82] C.S. Kovacs, Vitamin D in pregnancy and lactation: maternal, fetal, and neonatal outcomes from human and animal studies, Am. J. Clin. Nutr. 88 (2) (2008) 520S–528S.
[83] C.K. Kramer, C. Ye, B. Swaminathan, A.J. Hanley, P.W. Connelly, M. Sermer, et al., The persistence of maternal vitamin D deficiency and insufficiency during pregnancy and lactation irrespective of season and supplementation, Clin. Endocrinol. (Oxf.) 84 (5) (2016) 680–686.
[84] M. Strom, T.I. Halldorsson, S. Hansen, C. Granstrom, E. Maslova, S.B. Petersen, et al., Vitamin D measured in maternal serum and offspring neurodevelopmental outcomes: a prospective study with long-term follow-up, Ann. Nutr. Metab. 64 (3–4) (2014) 254–261.
[85] M. Pfeifer, B. Begerow, H.W. Minne, Vitamin D and muscle function, Osteoporos. Int. 13 (3) (2002) 187–194.
[86] N. Boudville, C. Inderjeeth, G.J. Elder, P. Glendenning, Association between 25-hydroxyvitamin D, somatic muscle weakness and falls risk in end stage renal failure, Clin. Endocrinol. (Oxf.) (2010).
[87] L. Mosekilde, Vitamin D and the elderly, Clin. Endocrinol. (Oxf.) 62 (3) (2005) 265–281.
[88] M. Nashimoto, K. Nakamura, S. Matsuyama, M. Hatakeyama, M. Yamamoto, Hypovitaminosis D and hyperparathyroidism in physically inactive elderly Japanese living in nursing homes: relationship with age, sunlight exposure and activities of daily living, Aging Clin. Exp. Res. 14 (1) (2002) 5–12.
[89] S. Vanlint, M. Nugent, S. Durvasula, Vitamin D and people with intellectual disability, Aust. Fam. Phys. 37 (5) (2008) 348–351.
[90] D.A. Jolliffe, Y. Hanifa, K.D. Witt, T.R. Venton, M. Rowe, P.M. Timms, et al., Environmental and genetic determinants of vitamin D status among older adults in London, UK, J. Steroid Biochem. Mol. Biol. (2016).
[91] K.Y. Ng, M.T. Ma, K.K. Leung, P.S. Leung, Vitamin D and vitamin A receptor expression and the proliferative effects of ligand activation of these receptors on the development of pancreatic progenitor cells derived from human fetal pancreas, Stem Cell Rev. 7 (1) (2011) 53–63.
[92] M.A. Moyad, The potential benefits of dietary and/or supplemental calcium and vitamin D, Urol. Oncol. 21 (5) (2003) 384–391.
[93] P. Kilpinen-Loisa, H. Nenonen, H. Pihko, O. Makitie, High-dose vitamin D supplementation in children with cerebral palsy or neuromuscular disorder, Neuropediatrics 38 (4) (2007) 167–172.
[94] N. Binkley, Is vitamin D the fountain of youth? Endocr. Pract. 15 (6) (2009) 590–596.
[95] A.W. Norman, R. Bouillon, S.J. Whiting, R. Vieth, P. Lips, 13th Workshop consensus for vitamin D nutritional guidelines, J. Steroid Biochem. Mol. Biol. 103 (3–5) (2007) 204–205.
[96] N. Binkley, Does low vitamin D status contribute to age-related morbidity? J. Bone Miner. Res. 22 (Suppl 2) (2007) V55–V58.
[97] M.F. Holick, Vitamin D: a D-lightful health perspective, Nutr. Rev. 66 (10 Suppl 2) (2008) S182–S194.
[98] H.A. Bischoff-Ferrari, T. Dietrich, E.J. Orav, F.B. Hu, Y. Zhang, E.W. Karlson, et al., Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or = 60 y, Am. J. Clin. Nutr. 80 (3) (2004) 752–758.
[99] D.G. Bruce, A. St John, F. Nicklason, P.R. Goldswain, Secondary hyperparathyroidism in patients from Western Australia with hip fracture: relationship to type of hip fracture, renal function, and vitamin D deficiency, J. Am. Geriatr. Soc. 47 (3) (1999) 354–359.

[100] H.A. Bischoff-Ferrari, Optimal serum 25-hydroxyvitamin D levels for multiple health outcomes, Adv. Exp. Med. Biol. 624 (2008) 55–71.
[101] M.B. Snijder, N.M. van Schoor, S.M. Pluijm, R.M. van Dam, M. Visser, P. Lips, Vitamin D status in relation to one-year risk of recurrent falling in older men and women, J. Clin. Endocrinol. Metab. 91 (8) (2006) 2980–2985.
[102] Institute of Medicine, 2010. Pages. Accessed at Food and Nutrition Board at http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx.
[103] F.R. Perez-Lopez, Vitamin D and its implications for musculoskeletal health in women: an update, Maturitas 58 (2) (2007) 117–137.
[104] S.J. Whiting, M.S. Calvo, Dietary recommendations for vitamin D: a critical need for functional end points to establish an estimated average requirement, J. Nutr. 135 (2) (2005) 304–309.
[105] P.G. Weyland, W.B. Grant, J. Howie-Esquivel, Does sufficient evidence exist to support a causal association between vitamin D status and cardiovascular disease risk? An assessment using Hill's criteria for causality, Nutrients 6 (9) (2014) 3403–3430.
[106] J. Hisatake, J. O'Kelly, M.R. Uskokovic, S. Tomoyasu, H.P. Koeffler, Novel vitamin D(3) analog, 21-(3-methyl-3-hydroxy-butyl)-19-nor D(3), that modulates cell growth, differentiation, apoptosis, cell cycle, and induction of PTEN in leukemic cells, Blood 97 (8) (2001) 2427–2433.
[107] V. Morales-Tirado, D.G. Wichlan, T.E. Leimig, S.E. Street, K.A. Kasow, J.M. Riberdy, 1alpha,25-dihydroxyvitamin D3 (vitamin D3) catalyzes suppressive activity on human natural regulatory T cells, uniquely modulates cell cycle progression, and augments FOXP3, Clin. Immunol. 138 (2) (2011) 212–221.
[108] A.C. Porojnicu, A. Dahlback, J. Moan, Sun exposure and cancer survival in Norway: changes in the risk of death with season of diagnosis and latitude, Adv. Exp. Med. Biol. 624 (2008) 43–54.
[109] A.C. Porojnicu, Z. Lagunova, T.E. Robsahm, J.P. Berg, A. Dahlback, J. Moan, Changes in risk of death from breast cancer with season and latitude: sun exposure and breast cancer survival in Norway, Breast Cancer Res. Treat. 102 (3) (2007) 323–328.
[110] C.F. Garland, F.C. Garland, E.D. Gorham, Calcium and vitamin D. Their potential roles in colon and breast cancer prevention, Ann. N. Y. Acad. Sci. 889 (1999) 107–119.
[111] O. Health Quality, Clinical utility of vitamin d testing: an evidence-based analysis, Ont. Health Technol. Assess. Ser. 10 (2) (2010) 1–93.
[112] Z. Lagunova, A.C. Porojnicu, A. Dahlback, J.P. Berg, T.M. Beer, J. Moan, Prostate cancer survival is dependent on season of diagnosis, Prostate 67 (12) (2007) 1362–1370.
[113] R.A. Petersen, C.T. Damsgaard, S.M. Dalskov, L.B. Sorensen, M.F. Hjorth, C. Ritz, et al., Vitamin D status and its determinants during autumn in children at northern latitudes: a cross-sectional analysis from the optimal well-being, development and health for Danish children through a healthy New Nordic Diet (OPUS) School Meal Study, Br. J. Nutr. 115 (2) (2016) 239–250.
[114] A. Huotari, K.H. Herzig, Vitamin D and living in northern latitudes-an endemic risk area for vitamin D deficiency, Int. J. Circumpolar Health 67 (2–3) (2008) 164–178.
[115] M.G. Kimlin, N.J. Downs, A.V. Parisi, Comparison of human facial UV exposure at high and low latitudes and the potential impact on dermal vitamin D production, Photochem. Photobiol. Sci. 2 (4) (2003) 370–375.
[116] P.J. Malloy, D. Feldman, Genetic disorders and defects in vitamin D action, Rheum. Dis. Clin. North Am. 38 (1) (2012) 93–106.
[117] J.W. Pike, M.B. Meyer, The vitamin D receptor: new paradigms for the regulation of gene expression by 1,25-dihydroxyvitamin D3, Rheum. Dis. Clin. North Am. 38 (1) (2012) 13–27.
[118] J.R. Muindi, A.A. Adjei, Z.R. Wu, I. Olson, H. Huang, A. Groman, et al., Serum vitamin d metabolites in colorectal cancer patients receiving cholecalciferol supplementation: correlation with polymorphisms in the Vitamin D genes, Horm. Cancer (2013).
[119] B.J. Fuhrman, D.M. Freedman, P. Bhatti, M.M. Doody, Y.P. Fu, S.C. Chang, et al., Sunlight, polymorphisms of Vitamin D-related genes and risk of Breast cancer, Anticancer Res. 33 (2) (2013) 543–551.
[120] E. Giovannucci, Epidemiology of vitamin d and colorectal cancer, Anticancer Agents Med. Chem. 13 (1) (2013) 11–19.
[121] M. Pande, P.A. Thompson, K.A. Do, A.A. Sahin, C.I. Amos, M.L. Frazier, et al., Genetic variants in the vitamin D pathway and breast cancer disease-free surviv al, Carcinogenesis 34 (3) (2013) 587–594.
[122] N. Binkley, R. Ramamurthy, D. Krueger, Low vitamin D status: definition, prevalence, consequences, and correction, Rheum. Dis. Clin. North Am. 38 (1) (2012) 45–59.
[123] W.B. Grant, 25-hydroxyvitamin D and breast cancer, colorectal cancer, and colorectal adenomas: case-control versus nested case-control studies, Anticancer Res. 35 (2) (2015) 1153–1160.
[124] J.M. Lappe, D. Travers-Gustafson, K.M. Davies, R.R. Recker, R.P. Heaney, Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial, Am. J. Clin. Nutr. 85 (6) (2007) 1586–1591.
[125] M. Moukayed, W.B. Grant, Molecular link between vitamin D and cancer prevention, Nutrients 5 (10) (2013) 3993–4021.
[126] M.J. Ferronato, E.N. Alonso, N.A. Gandini, M.E. Fermento, M.E. Villegas, M.A. Quevedo, et al., The UVB1 Vitamin D analogue inhibits colorectal carcinoma progression, J. Steroid Biochem. Mol. Biol. 163 (2016) 193–205.
[127] K. Edvardsen, M.B. Veierod, M. Brustad, T. Braaten, O. Engelsen, E. Lund, Vitamin D-effective solar UV radiation, dietary vitamin D and breast cancer risk, Int. J. Cancer 128 (6) (2011) 1425–1433.
[128] P. Engel, G. Fagherazzi, S. Mesrine, M.C. Boutron-Ruault, F. Clavel-Chapelon, Joint effects of dietary vitamin D and sun exposure on breast cancer risk: results from the French E3N Cohort, Cancer Epidemiol. Biomarkers Prev. 20 (1) (2011) 187–198.
[129] W.B. Grant, A. Juzeniene, Z. Lagunova, A.C. Porojnicu, J.E. Moan, Vitamin D levels in Norway may be inadequate to reduce risk of breast cancer, Int. J. Cancer 128 (9) (2011) 2249–2250.
[130] W.B. Grant, C.F. Garland, Evidence supporting the role of vitamin D in reducing the risk of cancer, J. Intern. Med. 252 (2) (2002) 178–179 (author reply 9–80).
[131] W.B. Grant, An estimate of premature cancer mortality in the U.S due to inadequate doses of solar ultraviolet-B radiation, Cancer 94 (6) (2002) 1867–1875.
[132] J.A. Baron, M. Beach, J.S. Mandel, R.U. van Stolk, R.W. Haile, R.S. Sandler, et al., Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group, N. Engl. J. Med. 340 (2) (1999) 101–107.
[133] E. Giovannucci, Y. Liu, E.B. Rimm, B.W. Hollis, C.S. Fuchs, M.J. Stampfer, et al., Prospective study of predictors of vitamin D status and cancer incidence and mortality in men, J. Natl. Cancer Inst. 98 (7) (2006) 451–459.
[134] M. Lazzeroni, D. Serrano, S. Pilz, S. Gandini, Vitamin D supplementation and cancer: review of randomized controlled trials, Anticancer Agents Med. Chem. 13 (1) (2013) 118–125.
[135] S. Pilz, Editorial: vitamin d and cancer: current evidence and future perspective, Anticancer Agents Med. Chem. 13 (1) (2013) 2–3.
[136] D.M. Freedman, A.C. Looker, S.C. Chang, B.I. Graubard, Prospective study of serum vitamin D and cancer mortality in the United States, J. Natl. Cancer Inst. 99 (21) (2007) 1594–1602.
[137] W.B. Grant, Weighing the evidence linking UVB irradiance, vitamin D, and cancer risk, Mayo Clin. Proc. 86 (4) (2011) 362–363 (author reply 3).
[138] S. Veldhuis, F. Wolbers, O. Brouckaert, I. Vermes, H.R. Franke, Cancer prevalence in osteoporotic women with low serum vitamin D levels, Menopause 18 (3) (2011) 319–322.
[139] W.B. Grant, The Institute of Medicine did not find the vitamin D-cancer link because it ignored UV-B dose studies, Public Health Nutr. 14 (4) (2011) 745–746.
[140] C.D. Davis, J.A. Milner, Nutrigenomics, vitamin D and cancer prevention, J Nutrigenet. Nutrigenom. 4 (1) (2011) 1–11.
[141] W.B. Grant, Sun exposure, vitamin D and cancer risk reduction (Letter to the Editor), Eur. J. Cancer 49 (2013) 2073 207–5.
[142] T. Bergren, R. Heuberger, Vitamin D and breast cancer prevention: practical guidelines for clinicians, Nurs. Womens Health 14 (5) (2010) 368–375.
[143] K.K. Deeb, D.L. Trump, C.S. Johnson, Vitamin D signalling pathways in cancer: potential for anticancer therapeutics, Nat. Rev. Cancer 7 (9) (2007) 684–700.
[144] X. Zhang, E. Giovannucci, Calcium, vitamin D and colorectal cancer chemoprevention, Best Pract. Res. Clin. Gastroenterol. 25 (4–5) (2011) 485–494.
[145] T. Shao, P. Klein, M.L. Grossbard, Vitamin D and breast cancer, Oncologist 17 (1) (2012) 36–45.
[146] K.D. Crew, M.D. Gammon, S.E. Steck, D.L. Hershman, S. Cremers, E. Dworakowski, et al., Association between plasma 25-hydroxyvitamin D and breast cancer risk, Cancer Prev. Res. (Phila.) 2 (6) (2009) 598–604.
[147] K.J. Helzlsouer, Overview of the cohort consortium Vitamin D pooling project of rarer cancers, Am. J. Epidemiol. 172 (1) (2010) 4–9.
[148] J. Welsh, Cellular and molecular effects of vitamin D on carcinogenesis, Arch. Biochem. Biophys. (2011).
[149] J.A. Cauley, R.T. Chlebowski, J. Wactawski-Wende, J.A. Robbins, R.J. Rodabough, Z. Chen, et al., Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative, J. Womens Health (Larchmt.) 22 (11) (2013) 915–929.
[150] F. Sperati, P. Vici, M. Maugeri-Sacca, S. Stranges, N. Santesso, L. Mariani, et al., Vitamin D supplementation and breast cancer prevention: a systematic review and meta-analysis of randomized clinical trials, PLoS One 8 (7) (2013) e69269.
[151] A.M. Lindsey, G. Gross, J. Twiss, N. Waltman, C. Ott, T.E. Moore, Postmenopausal survivors of breast cancer at risk for osteoporosis: nutritional intake and body size, Cancer Nurs. 25 (1) (2002) 50–56.
[152] K. Cooper, H. Squires, C. Carroll, D. Papaioannou, A. Booth, R.F. Logan, et al., Chemoprevention of colorectal cancer: systematic review and economic evaluation, Health Technol. Assess. 14 (32) (2010) 1–206.
[153] M. Huncharek, J. Muscat, B. Kupelnick, Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: a meta-analysis of 26,335 cases from 60 observational studies, Nutr. Cancer 61 (1) (2009) 47–69.
[154] W.B. Grant, Roles of solar UVB and Vitamin D in reducing cancer risk and increasing survival, Anticancer Res. 36 (3) (2016) 1357–1370.
[155] M. Waterhouse, H.A. Risch, C. Bosetti, K.E. Anderson, G.M. Petersen, W.R. Bamlet, et al., Vitamin D and pancreatic cancer: a pooled analysis from the pancreatic cancer case-control consortium, Ann. Oncol. 26 (8) (2015) 1776–1783.
[156] W.B. Grant, How strong is the evidence that solar ultraviolet B and vitamin D reduce the risk of cancer? An examination using Hill's criteria for causality, Dermatoendocrinology 1 (1) (2009) 17–24.
[157] A. Alkhenizan, K. Hafez, The role of vitamin E in the prevention of cancer: a meta-analysis of randomized controlled trials, Ann. Saudi Med. 27 (6) (2007) 409–414.

[158] W.B. Grant, An ecologic study of cancer mortality rates in Spain with respect to indices of solar UVB irradiance and smoking, Int. J. Cancer 120 (5) (2007) 1123–1128.
[159] M.T. van Leeuwen, J.J. Turner, M.O. Falster, N.S. Meagher, D.J. Joske, A.E. Grulich, et al., Latitude gradients for lymphoid neoplasm subtypes in Australia support an association with ultraviolet radiation exposure, Int. J. Cancer 133 (4) (2013) 944–951.
[160] K.A. Bertrand, E.T. Chang, G.A. Abel, S.M. Zhang, D. Spiegelman, A.A. Qureshi, et al., Sunlight exposure, vitamin D, and risk of non-Hodgkin lymphoma in the Nurses' Health Study, Cancer Causes Control 22 (12) (2011) 1731–1741.
[161] L. Gallicchio, K.J. Helzlsouer, W.H. Chow, D.M. Freedman, S.E. Hankinson, P. Hartge, et al., Circulating 25-hydroxyvitamin D and the risk of rarer cancers: design and methods of the cohort consortium Vitamin D pooling project of rarer cancers, Am. J. Epidemiol. 172 (1) (2010) 10–20.
[162] M.J. Bolland, A. Grey, G.D. Gamble, I.R. Reid, Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set, Am. J. Clin. Nutr. 94 (4) (2011) 1144–1149.
[163] J.C. Fleet, M. DeSmet, R. Johnson, Y. Li, Vitamin D and cancer: a review of molecular mechanisms, Biochem. J 441 (1) (2012) 61–76.
[164] P.G. Vashi, K. Trukova, C.A. Lammersfeld, D.P. Braun, D. Gupta, Impact of oral vitamin D supplementation on serum 25-hydroxyvitamin D levels in oncology, Nutr. J. 9 (2010) 60.
[165] M. Aguirre, N. Manzano, Y. Salas, M. Angel, F.A. Diaz-Couselo, M. Zylberman, Vitamin D deficiency in patients admitted to the general ward with breast, lung, and colorectal cancer in Buenos Aires, Argentina, Arch. Osteoporos. 11 (2016) 4.
[166] P.G. Vashi, C.A. Lammersfeld, D.P. Braun, D. Gupta, Serum 25-hydroxyvitamin D is inversely associated with body mass index in cancer, Nutr. J. 10 (2011) 51.
[167] M.F. Holick, Vitamin D and sunlight: strategies for cancer prevention and other health benefits, Clin. J. Am. Soc. Nephrol. 3 (5) (2008) 1548–1554.
[168] L.K. Pourshahidi, Vitamin D and obesity: current perspectives and future directions, Proc. Nutr. Soc. 74 (2) (2015) 115–124.
[169] R. Siegel, E. Ward, O. Brawley, A. Jemal, Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths, CA. Cancer J. Clin. 61 (4) (2011) 212–236.
[170] D.P. Trivedi, R. Doll, K.T. Khaw, Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial, BMJ 326 (7387) (2003) 469.
[171] M.F. Holick, N.C. Binkley, H.A. Bischoff-Ferrari, C.M. Gordon, D.A. Hanley, R.P. Heaney, et al., Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline, J. Clin. Endocrinol. Metab. 96 (7) (2011) 1911–1930.
[172] R.D. Semba, D.K. Houston, S. Bandinelli, K. Sun, A. Cherubini, A.R. Cappola, et al., Relationship of 25-hydroxyvitamin D with all-cause and cardiovascular disease mortality in older community-dwelling adults, Eur. J. Clin. Nutr. 64 (2) (2010) 203–209.
[173] A.A. Ginde, R. Scragg, R.S. Schwartz, C.A. Camargo Jr., Prospective study of serum 25-hydroxyvitamin D level, cardiovascular disease mortality, and all-cause mortality in older U.S. adults, J. Am. Geriatr. Soc. 57 (9) (2009) 1595–1603.
[174] H. Dobnig, S. Pilz, H. Scharnagl, W. Renner, U. Seelhorst, B. Wellnitz, et al., Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality, Arch. Intern. Med. 168 (12) (2008) 1340–1349.
[175] G. Bjelakovic, L.L. Gluud, D. Nikolova, K. Whitfield, J. Wetterslev, R.G. Simonetti, et al., Vitamin D supplementation for prevention of mortality in adults, Cochrane Database Syst. Rev. 7 (2011) CD007470.
[176] W.B. Grant, An estimate of the global reduction in mortality rates through doubling vitamin D levels, Eur. J. Clin. Nutr. 65 (9) (2011) 1016–1026.
[177] J.H.O. Parker, D. Dutton, A. Mavrodaris, S. Stranges, N.B. Kandala, A. Clarke, O. H. Franco, Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis, Maturitas 65 (2010) 225–236.
[178] Y. Chen, J. Kong, T. Sun, G. Li, F.L. Szeto, W. Liu, et al., 1,25-Dihydroxyvitamin D (3) suppresses inflammation-induced expression of plasminogen activator inhibitor-1 by blocking nuclear factor-kappaB activation, Arch. Biochem. Biophys. 507 (2) (2011) 241–247.
[179] B. Venkatesh, P. Nair, Hypovitaminosis D and morbidity in critical illness: is there proof beyond reasonable doubt? Crit. Care 18 (3) (2014) 138.
[180] P.M. Timms, N. Mannan, G.A. Hitman, K. Noonan, P.G. Mills, D. Syndercombe-Court, et al., Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? QJM 95 (12) (2002) 787–796.
[181] Y.C. Li, J. Kong, M. Wei, Z.F. Chen, S.Q. Liu, L.P. Cao, 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system, J. Clin. Invest. 110 (2) (2002) 229–238.
[182] T.R. Braun, L.F. Been, P.R. Blackett, D.K. Sanghera, Vitamin D deficiency and cardio-metabolic risk in a north indian community with highly prevalent type 2 diabetes, J. Diabetes Metab. (2012) 3.
[183] J.L. Anderson, H.T. May, B.D. Horne, T.L. Bair, N.L. Hall, J.F. Carlquist, D.L. Lappé, J.B. Muhlestein, Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population, Am. J. Cardiol. 106 (2010) 963–968.
[184] D. Somjen, Y. Weisman, F. Kohen, B. Gayer, R. Limor, O. Sharon, et al., 25-hydroxyvitamin D3-1alpha-hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds, Circulation 111 (13) (2005) 1666–1671.
[185] K.L. Margolis, R.M. Ray, L. Van Horn, J.E. Manson, M.A. Allison, H.R. Black, et al., Effect of calcium and vitamin D supplementation on blood pressure: the women's health initiative randomized trial, Hypertension 52 (5) (2008) 847–855.
[186] J. Parker, O. Hashmi, D. Dutton, A. Mavrodaris, S. Stranges, N.B. Kandala, et al., Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis, Maturitas 65 (3) (2010) 225–236.
[187] S. Pilz, K. Kienreich, A. Tomaschitz, E. Ritz, E. Lerchbaum, B. Obermayer-Pietsch, et al., Vitamin d and cancer mortality: systematic review of prospective epidemiological studies, Anticancer Agents Med. Chem. 13 (1) (2013) 107–117.
[188] M.F. McCarty, Poor vitamin D status may contribute to high risk for insulin resistance, obesity, and cardiovascular disease in Asian Indians, Med. Hypotheses 72 (6) (2009) 647–651.
[189] R. Kelishadi, Z. Farajzadegan, M. Bahreynian, Association between vitamin D status and lipid profile in children and adolescents: a systematic review and meta-analysis, Int. J. Food Sci. Nutr. 65 (4) (2014) 404–410.
[190] K. Lach, K. Krajewski-Siuda, Vitamin D3 in prevention of diseases in adults-a systematic review, Wiad. Lek. 63 (4) (2010) 316–330.
[191] S. Heravifard, T.R. Neyestani, B. Nikooyeh, H. Alavi-Majd, A. Houshiarrad, A. Kalayi, et al., Regular consumption of both vitamin D- and calcium- and vitamin D-fortified yogurt drink is equally accompanied by lowered blood lipoprotein (a) and elevated apoprotein A1 in subjects with type 2 diabetes: a randomized clinical trial, J. Am. Coll. Nutr. 32 (1) (2013) 26–30.
[192] O. Yilmaz, H. Olgun, M. Ciftel, O. Kilic, I. Kartal, N.Y. Iskenderoglu, et al., Dilated cardiomyopathy secondary to rickets-related hypocalcaemia: eight case reports and a review of the literature, Cardiol. Young 25 (2) (2015) 261–266.
[193] X.F. Wang, X.L. Deng, N.P. Wang, Roles of vitamin D in cardiovascular diseases, Sheng Li Ke Xue Jin Zhan 44 (3) (2013) 223–226.
[194] V. Nsengiyumva, M.E. Fernando, J.V. Moxon, S.M. Krishna, J. Pinchbeck, S.M. Omer, et al., The association of circulating 25-hydroxyvitamin D concentration with peripheral arterial disease: a meta-analysis of observational studies, Atherosclerosis 243 (2) (2015) 645–651.
[195] T.J. Wang, F. Zhang, J.B. Richards, B. Kestenbaum, J.B. van Meurs, D. Berry, et al., Common genetic determinants of vitamin D insufficiency: a genome-wide association study, Lancet 376 (9736) (2010) 180–188.
[196] M.T. Cantorna, Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease, Prog. Biophys. Mol. Biol. 92 (1) (2006) 60–64.
[197] M. Thomasset, Vitamin D and the immune system, Pathol. Biol. (Paris) 42 (2) (1994) 163–172.
[198] D.D. Bikle, Vitamin D and the immune system: role in protection against bacterial infection, Curr. Opin. Nephrol. Hypertens. 17 (4) (2008) 348–352.
[199] R. Lin, J.H. White, The pleiotropic actions of vitamin D, Bioessays 26 (1) (2004) 21–28.
[200] M.A. Pani, K. Regulla, M. Segni, M. Krause, S. Hofmann, M. Hufner, et al., Vitamin D 1alpha-hydroxylase (CYP1alpha) polymorphism in Graves' disease, Hashimoto's thyroiditis and type 1 diabetes mellitus, Eur. J. Endocrinol. 146 (6) (2002) 777–781.
[201] A.Z. LaCroix, J. Kotchen, G. Anderson, R. Brzyski, J.A. Cauley, S.R. Cummings, et al., Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial, J. Gerontol. A. Biol. Sci. Med. Sci. 64 (5) (2009) 559–567.
[202] D.F. Horrobin, M.S. Manku, M. Oka, R.O. Morgan, S.C. Cunnane, A.I. Ally, et al., The nutritional regulation of T lymphocyte function, Med. Hypotheses 5 (9) (1979) 969–985.
[203] M.F. McCarty, Upregulation of lymphocyte apoptosis as a strategy for preventing and treating autoimmune disorders: a role for whole-food vegan diets, fish oil and dopamine agonists, Med. Hypotheses 57 (2) (2001) 258–275.
[204] K. Hamzaoui, I. Ben Dhifallah, E. Karray, F.H. Sassi, A. Hamzaoui, Vitamin D modulates peripheral immunity in patients with Behcet's disease, Clin. Exp. Rheumatol. 28 (4 Suppl 60) (2010) S50–S57.
[205] A.D. Hock, Review: Vitamin D3 deficiency results in dysfunctions of immunity with severe fatigue and depression in a variety of diseases, In Vivo 28 (1) (2014) 133–145.
[206] L. Mascitelli, F. Pezzetta, M.R. Goldstein, Inflammatory bowel disease and the vitamin D endocrine system, Intern. Med. J. 41 (4) (2011) 369–370.
[207] M. Raman, A.N. Milestone, J.R. Walters, A.L. Hart, S. Ghosh, Vitamin D and gastrointestinal diseases: inflammatory bowel disease and colorectal cancer, Ther. Adv. Gastroenterol. 4 (1) (2011) 49–62.
[208] S. Ardizzone, A. Cassinotti, M. Bevilacqua, M. Clerici, G.B. Porro, Vitamin D and inflammatory bowel disease, Vitam. Horm. 86 (2011) 367–377.
[209] A.D. Levin, V. Wadhera, S.T. Leach, H.J. Woodhead, D.A. Lemberg, A. Czarina Mendoza-Cruz, et al., Vitamin D deficiency in children with inflammatory bowel disease, Dig. Dis. Sci. (2011).
[210] S.M. Attar, Vitamin D deficiency in rheumatoid arthritis Prevalence and association with disease activity in Western Saudi Arabia, Saudi Med. J. 33 (5) (2012) 520–525.
[211] T. Furuya, T. Hosoi, E. Tanaka, A. Nakajima, A. Taniguchi, S. Momohara, et al., Prevalence of and factors associated with vitamin D deficiency in 4,793 Japanese patients with rheumatoid arthritis, Clin. Rheumatol. 32 (7) (2013) 1081–1087.

[212] L.L. Ishikawa, P.M. Colavite, T.F. Fraga-Silva, L.A. Mimura, T.G. Franca, S.F. Zorzella-Pezavento, et al., Vitamin D deficiency and rheumatoid arthritis, Clin. Rev. Allergy Immunol. (2016).

[213] M. Struglia, C.A. Stamerra, P. Di Giosia, P. Giorgini, C. Capanna, D. Grassi, D. et al. Vitamin, Deficiency and endothelial dysfunction in rheumatoid arthritis patients, J. Hypertens. 33 (Suppl 1) (2015) e84.

[214] M. Rossini, S. Maddali Bongi, G. La Montagna, G. Minisola, N. Malavolta, L. Bernini, et al., Vitamin D deficiency in rheumatoid arthritis: prevalence, determinants and associations with disease activity and disability, Arthritis Res. Ther. 12 (6) (2010) R216.

[215] N. Liu, A.T. Kaplan, J. Low, L. Nguyen, G.Y. Liu, O. Equils, et al., Vitamin D induces innate antibacterial responses in human trophoblasts via an intracrine pathway, Biol. Reprod. 80 (3) (2009) 398–406.

[216] D.J. Berry, K. Hesketh, C. Power, E. Hypponen, Vitamin D status has a linear association with seasonal infections and lung function in British adults, Br. J. Nutr. 106 (9) (2011) 1433–1440.

[217] R. Anty, Q.M. Anstee, P. Gual, A. Tran, Prophylaxis of bacterial infections in cirrhosis: is an optimal 25-OH vitamin D level required? J. Hepatol. 61 (4) (2014) 965–966.

[218] W.B. Grant, M. Goldstein, L. Mascitelli, Ample evidence exists from human studies that vitamin D reduces the risk of selected bacterial and viral infections, Exp Biol Med (Maywood) 235 (12) (2010) 1395–1396 discussion 7.

[219] P. Selvaraj, Vitamin D, vitamin D receptor, and cathelicidin in the treatment of tuberculosis, Vitam. Horm. 86 (2011) 307–325.

[220] A.V. Yamshchikov, E.V. Kurbatova, M. Kumari, H.M. Blumberg, T.R. Ziegler, S. M. Ray, D. Vitamin, et al., status and antimicrobial peptide cathelicidin (LL-37) concentrations in patients with active pulmonary tuberculosis, Am. J. Clin. Nutr. 92 (3) (2010) 603–611.

[221] P.T. Liu, M. Wheelwright, R. Teles, E. Komisopoulou, K. Edfeldt, B. Ferguson, et al., MicroRNA-21 targets the vitamin D-dependent antimicrobial pathway in leprosy, Nat. Med. 18 (2) (2012) 267–273.

[222] M. Matzner, A.R. Al Samie, H.M. Winkler, J. Nemeth, A. Grasnek, A. Indra, et al., Low serum levels of cathelicidin LL-37 in leprosy, Acta Trop. 117 (1) (2011) 56–59.

[223] H.F. DeLuca, M.T. Cantorna, Vitamin D: its role and uses in immunology, FASEB J. 15 (14) (2001) 2579–2585.

[224] A.F. Gombart, The vitamin D-antimicrobial peptide pathway and its role in protection against infection, Future Microbiol. 4 (9) (2009) 1151–1165.

[225] L.E. Jeffery, A.M. Wood, O.S. Qureshi, T.Z. Hou, D. Gardner, Z. Briggs, et al., Availability of 25-hydroxyvitamin D(3) to APCs controls the balance between regulatory and inflammatory T cell responses, J. Immunol. 189 (11) (2012) 5155–5164.

[226] S.M. Banajeh, Nutritional rickets and vitamin D deficiency–association with the outcomes of childhood very severe pneumonia: a prospective cohort study, Pediatr. Pulmonol. 44 (12) (2009) 1207–1215.

[227] K.E. Nnoaham, A. Clarke, Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis, Int. J. Epidemiol. 37 (1) (2008) 113–139.

[228] A.A. Ginde, J.M. Mansbach, C.A. Camargo Jr., Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey, Arch. Intern. Med. 169 (4) (2009) 384–390.

[229] R.W. Chesney, Vitamin D and The Magic Mountain: the anti-infectious role of the vitamin, J. Pediatr. 156 (5) (2010) 698–703.

[230] L. Lin, J. Yao, G. Chen, C. Lin, A severe H7N9 pneumonia with syndrome of inappropriate antidiuresis and vitamin D deficiency, Respir. Med. Case Rep. 12 (2014) 37–38.

[231] J. Niederstrasser, C. Herr, L. Wolf, C.M. Lehr, C. Beisswenger, R. Bals, Vitamin D deficiency does not result in a breach of host defense in murine models of pneumonia, Infect. Immun. (2016).

[232] M.W. Pletz, C. Terkamp, U. Schumacher, G. Rohde, H. Schutte, T. Welte, et al., Vitamin D deficiency in community-acquired pneumonia: low levels of 1,25 (OH)2 D are associated with disease severity, Respir. Res. 15 (2014) 53.

[233] D. Vuichard Gysin, D. Dao, C.M. Gysin, L. Lytvyn, M. Loeb, Effect of vitamin D3 supplementation on respiratory tract infections in healthy individuals: a systematic review and meta-analysis of randomized controlled trials, PLoS One 11 (9) (2016) e0162996.

[234] S.E. Judd, S.N. Raiser, M. Kumari, V. Tangpricha, 1,25-dihydroxyvitamin D3 reduces systolic blood pressure in hypertensive adults: a pilot feasibility study, J. Steroid Biochem. Mol. Biol. 121 (1–2) (2010) 445–447.

[235] H. Nasri, S. Behradmanesh, A. Ahmadi, M. Rafieian-Kopaei, Impact of oral vitamin D (cholecalciferol) replacement therapy on blood pressure in type 2 diabetes patients; a randomized, double-blind, placebo controlled clinical trial, J. Nephropathol. 3 (1) (2014) 29–33.

[236] R.M. Daly, C.A. Nowson, Long-term effect of calcium-vitamin D(3) fortified milk on blood pressure and serum lipid concentrations in healthy older men, Eur. J. Clin. Nutr. 63 (8) (2009) 993–1000.

[237] S.J. Wimalawansa, Antihypertensive effects of oral calcium supplementation may be mediated through the potent vasodilator CGRP, Am. J. Hypertens. 6 (12) (1993) 996–1002.

[238] I. Al Mheid, R.S. Patel, V. Tangpricha, A.A. Quyyumi, Vitamin D and cardiovacular disease: is the evidence solid? Eur. Heart J. 34 (483) (2013) 691–698.

[239] I.A. Mheid e.a, Vitamin D status is associated with arterial stiffness and vascular dysfunction in healthy humans, J. Am. Coll. Cardiol. 58 (2) (2011) 186–192.

[240] A.D. Gepner, R. Ramamurthy, D.C. Krueger, C.E. Korcarz, N. Binkley, J.H. Stein, A prospective randomized controlled trial of the effects of vitamin D supplementation on cardiovascular disease risk, PLoS One 7 (5) (2012) e36617.

[241] T.M. Halliday, N.J. Peterson, J.J. Thomas, K. Kleppinger, B.W. Hollis, D.E. Larson-Meyer, Vitamin D status relative to diet, lifestyle, injury, and illness in college athletes, Med. Sci. Sports Exerc. 43 (2) (2011) 335–343.

[242] V. Tangpricha, A. Turner, C. Spina, S. Decastro, T.C. Chen, M.F. Holick, Tanning is associated with optimal vitamin D status (serum 25-hydroxyvitamin D concentration) and higher bone mineral density, Am. J. Clin. Nutr. 80 (6) (2004) 1645–1649.

[243] S. Afzal, S.E. Bojesen, B.G. Nordestgaard, Low 25-hydroxyvitamin D and risk of type 2 diabetes: a prospective cohort study and metaanalysis, Clin. Chem. 59 (2) (2013) 381–391.

[244] J. Mitri, M.D. Muraru, A.G. Pittas, Vitamin D and type 2 diabetes: a systematic review, Eur. J. Clin. Nutr. 65 (9) (2011) 1005–1015.

[245] D.M. Lee, A. Tajar, S.R. Pye, S. Boonen, D. Vanderschueren, R. Bouillon, et al., Association of hypogonadism with vitamin d status: the european male ageing study, Eur. J. Endocrinol. 166 (1) (2012) 77–85.

[246] S. Tepper, D.R. Shahar, D. Geva, S. Ish-Shalom, Differences in homeostatic model assessment (HOMA) values and insulin levels after vitamin D supplementation in healthy men: a double-blind randomized controlled trial, Diabetes Obes. Metab. 18 (6) (2016) 633–637.

[247] Q. Cheng, B.J. Boucher, P.S. Leung, Modulation of hypovitaminosis D-induced islet dysfunction and insulin resistance through direct suppression of the pancreatic islet renin-angiotensin system in mice, Diabetologia 56 (3) (2013) 553–562.

[248] S. Shab-Bidar, T.R. Neyestani, A. Djazayery, Vitamin D receptor Cdx-2-dependent response of central obesity to vitamin D intake in the subjects with type 2 diabetes: a randomised clinical trial, Br. J. Nutr. 114 (9) (2015) 1375–1384.

[249] C. Mathieu, Vitamin D and diabetes: where do we stand? Diabetes Res. Clin. Pract. 108 (2) (2015) 201–209.

[250] T.L. Van Belle, C. Gysemans, C. Mathieu, Vitamin D and diabetes: the odd couple, Trends Endocrinol. Metab. 24 (11) (2013) 561–568.

[251] C. Zipitis, A.K. Akobeng, Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis, Arch. Dis. Child. 93 (6) (2008) 512–517.

[252] J.J. Cannell, W.B. Grant, M.F. Holick, Vitamin D and inflammation, Dermatoendocrinology 6 (1) (2014) e983401.

[253] I. Gonzalez-Molero, G. Rojo-Martinez, S. Morcillo, C. Gutierrez-Repiso, E. Rubio-Martin, M.C. Almaraz, et al., Vitamin D and incidence of diabetes: a prospective cohort study, Clin. Nutr. 31 (4) (2012) 571–573.

[254] A.M.T.A. Belenchia, L.S. Hillman, C.A. Peterson, Correcting vitamin D insufficiency improves insulin sensitivity in obese adolescents: a randomized controlled trial, Am. J. Clin. Nutr. 97 (2013) 774–781.

[255] J. Mitri, B. Dawson-Hughes, F.B. Hu, A.G. Pittas, Effects of vitamin D and calcium supplementation on pancreatic beta cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial, Am. J. Clin. Nutr. 94 (2) (2011) 486–494.

[256] X. Palomer, J.M. Gonzalez-Clemente, F. Blanco-Vaca, D. Mauricio, Role of vitamin D in the pathogenesis of type 2 diabetes mellitus, Diabetes Obes. Metab. 10 (3) (2008) 185–197.

[257] G. Amaliev, E. Uchikova, B. Pehlivanov, N. Parahuleva, I. Amaliev, The vitamin D deficiency-an independent risk factor for developing preeclampsia, Akush. Ginekol. (Sofiia) 53 (8) (2014) 15–17.

[258] R. Singla, P. Gurung, N. Aggarwal, U. Dutta, R. Kochhar, Relationship between preeclampsia and vitamin D deficiency: a case control study, Arch. Gynecol. Obstet. 291 (6) (2015) 1247–1251.

[259] I.V. Reeves, Z.D. Bamji, G.B. Rosario, K.M. Lewis, M.A. Young, K.N. Washington, Vitamin D deficiency in pregnant women of ethnic minority: a potential contributor to preeclampsia, J. Perinatol. 34 (10) (2014) 767–773.

[260] G.F. Behrouz, G.S. Farzaneh, J. Leila, Z. Jaleh, K.S. Eskandar, Presence of auto-antibody against two placental proteins, annexin A1 and vitamin D binding protein, in sera of women with pre-eclampsia, J. Reprod. Immunol. 99 (1–2) (2013) 10–16.

[261] K. Ota, S. Dambaeva, A.R. Han, K. Beaman, A. Gilman-Sachs, J. Kwak-Kim, Vitamin D deficiency may be a risk factor for recurrent pregnancy losses by increasing cellular immunity and autoimmunity, Hum. Reprod. 29 (2) (2014) 208–219.

[262] P. Abedi, Z. Mohaghegh, P. Afshary, M. Latifi, The relationship of serum vitamin D with pre-eclampsia in the Iranian women, Matern. Child Nutr. 10 (2) (2014) 206–212.

[263] F.R. Perez-Lopez, V. Pasupuleti, E. Mezones-Holguin, V.A. Benites-Zapata, P. Thota, A. Deshpande, et al., Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials, Fertil. Steril. 103 (5) (2015) 1278–1288 e4.

[264] M. Karamali, Z. Asemi, M. Ahmadi-Dastjerdi, A. Esmaillzadeh, Calcium plus vitamin D supplementation affects pregnancy outcomes in gestational diabetes: randomized, double-blind, placebo-controlled trial, Public Health Nutr. 19 (1) (2016) 156–163.

[265] J.J. Cannell, B.W. Hollis, M.B. Sorenson, T.N. Taft, J.J. Anderson, Athletic performance and vitamin D, Med. Sci. Sports Exerc. 41 (5) (2009) 1102–1110.

[266] D.T. Dahlquist, B.P. Dieter, M.S. Koehle, Plausible ergogenic effects of vitamin D on athletic performance and recovery, J. Int. Soc. Sports Nutr. 12 (2015) 33.
[267] H. Gerster, The role of vitamin C in athletic performance, J. Am. Coll. Nutr. 8 (6) (1989) 636–643.
[268] B. Hamilton, Vitamin D and athletic performance: the potential role of muscle, Asian J. Sports Med. 2 (4) (2011) 211–219.
[269] S. Neal, J. Sykes, M. Rigby, B. Hess, A review and clinical summary of vitamin D in regard to bone health and athletic performance, Phys. Sportsmed. 43 (2) (2015) 161–168.
[270] I.M. Sharman, M.G. Down, N.G. Norgan, The effects of vitamin E on physiological function and athletic performance of trained swimmers, J. Sports Med. Phys. Fitness 16 (3) (1976) 215–225.
[271] H. Bischoff-Ferrari, Vitamin D – from essentiality to functionality, Int. J. Vitam. Nutr. Res. 82 (5) (2012) 321–326.
[272] L. Mosekilde, Vitamin D requirement and setting recommendation levels: long-term perspectives, Nutr. Rev. 66 (10 Suppl 2) (2008) S170–S177.
[273] H.A. Bischoff, M. Borchers, F. Gudat, U. Duermueller, R. Theiler, H.B. Stahelin, et al., In situ detection of 1,25-dihydroxyvitamin D3 receptor in human skeletal muscle tissue, Histochem. J. 33 (1) (2001) 19–24.
[274] H.A. Bischoff-Ferrari, M. Borchers, F. Gudat, U. Durmuller, H.B. Stahelin, W. Dick, Vitamin D receptor expression in human muscle tissue decreases with age, J. Bone Miner. Res. 19 (2) (2004) 265–269.
[275] P. Lips, N. Binkley, M. Pfeifer, R. Recker, S. Samanta, D.A. Cohn, et al., Once-weekly dose of 8400 IU vitamin D(3) compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency, Am. J. Clin. Nutr. 91 (4) (2010) 985–991.
[276] M.F. Holick, Evidence-based D-bate on health benefits of vitamin D revisited, Dermato-Endocrinology 4 (2) (2012) 183–190.
[277] H. Blain, A. Jaussent, E. Thomas, J.P. Micallef, A.M. Dupuy, P.L. Bernard, et al., Appendicular skeletal muscle mass is the strongest independent factor associated with femoral neck bone mineral density in adult and older men, Exp. Gerontol. 45 (9) (2010) 679–684.
[278] J. Okuno, S. Tomura, H. Yanagi, M.J. Kim, T. Okura, K. Tanaka, Evaluation of the association between impaired renal function and physical function among community-dwelling Japanese frail elderly based on the estimated glomerular filtration rate (eGFR), Nihon Ronen Igakkai Zasshi 46 (1) (2009) 63–70.
[279] N. Nigil Haroon, A. Anton, J. John, M. Mittal, Effect of vitamin D supplementation on glycemic control in patients with type 2 diabetes: a systematic review of interventional studies, J. Diabetes Metab. Disord. 14 (2015) 3.
[280] M.R. Bird, M.C. Woodward, E.M. Gibson, D.J. Phyland, D. Fonda, Asymptomatic swallowing disorders in elderly patients with Parkinson's disease: a description of findings on clinical examination and videofluoroscopy in sixteen patients, Age Ageing 23 (3) (1994) 251–254.
[281] J.J. Heidelbaugh, Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications, Ther. Adv. Drug Saf. 4 (3) (2013) 125–133.
[282] E. Chidlovskii, A. Tahar, G. Deschasse, P. Couturier, Wernicke's encephalopathy associated with pellagra encephalopathy: rare and unusual complication in an elderly woman hospitalized for aspiration pneumonia, Rev. Med. Interne 33 (8) (2012) 453–456.
[283] T.J. Marrie, Pneumonia in the elderly, Curr. Opin. Pulm. Med. 2 (3) (1996) 192–197.
[284] H.M. Dallosso, C.W. McGrother, R.J. Matthews, M.M. Donaldson, M.R.C.I.S.G. Leicestershire, Nutrient composition of the diet and the development of overactive bladder: a longitudinal study in women, Neurourol. Urodyn. 23 (3) (2004) 204–210.
[285] R.A. Appell, P.K. Sand, Nocturia: etiology, diagnosis, and treatment, Neurourol. Urodyn. 27 (1) (2008) 34–39.
[286] S. Afzal, P. Lange, S.E. Bojesen, J.J. Freiberg, B.G. Nordestgaard, Plasma 25-hydroxyvitamin D, lung function and risk of chronic obstructive pulmonary disease, Thorax 69 (1) (2014) 24–31.
[287] J. Zaragoza Buxo, L. Perez, R. Bredy, Relation between serum vitamin D level and asthma, Bol. Asoc. Med P. R. 104 (2) (2012) 12–16.
[288] I.K. Sundar, I. Rahman, Vitamin D and susceptibility of chronic lung diseases: role of epigenetics, Front. Pharmacol. 2 (2011) 50.
[289] J.E. Morley, A.D. Mooradian, A.J. Silver, D. Heber, R.B. Alfin-Slater, Nutrition in the elderly, Ann. Intern. Med. 109 (11) (1988) 890–904.
[290] A.E. Millen, R. Voland, S.A. Sondel, N. Parekh, R.L. Horst, R.B. Wallace, et al., Vitamin D status and early age-related macular degeneration in postmenopausal women, Arch. Ophthalmol. 129 (4) (2011) 481–489.
[291] J.M. Seddon, Multivitamin-multimineral supplements and eye disease: age-related macular degeneration and cataract, Am. J. Clin. Nutr. 85 (1) (2007) 304S–3077S.
[292] D. Shehab, K. Al-Jarallah, O.A. Mojiminiyi, H. Al Mohamedy, N.A. Abdella, Does Vitamin D deficiency play a role in peripheral neuropathy in Type 2 diabetes? Diabet. Med. 29 (1) (2012) 43–49.
[293] W.S. Lv, W.J. Zhao, S.L. Gong, D.D. Fang, B. Wang, Z.J. Fu, et al., Serum 25-hydroxyvitamin D levels and peripheral neuropathy in patients with type 2 diabetes: a systematic review and meta-analysis, J. Endocrinol. Invest. 38 (5) (2015) 513–518.
[294] P. Anand, G. Terenghi, G. Warner, P. Kopelman, R.E. Williams-Chestnut, D.V. Sinicropi, The role of endogenous nerve growth factor in human diabetic neuropathy, Nat. Med. 2 (6) (1996) 703–707.
[295] S.E. Tague, G.L. Clarke, M.K. Winter, K.E. McCarson, D.E. Wright, P.G. Smith, Vitamin D deficiency promotes skeletal muscle hypersensitivity and sensory hyperinnervation, J. Neurosci. 31 (39) (2011) 13728–13738.
[296] S. Wergeland, O. Torkildsen, K.M. Myhr, L. Aksnes, S.J. Mork, L. Bo, Dietary vitamin D3 supplements reduce demyelination in the cuprizone model, PLoS One 6 (10) (2011) e26262.
[297] J. Bianco, Y. Gueye, T. Marqueste, O. Alluin, J.J. Risso, S. Garcia, et al., Vitamin D (3) improves respiratory adjustment to fatigue and H-reflex responses in paraplegic adult rats, Neuroscience 188 (2011) 182–192.
[298] V. Hirani, Vitamin D status and pain: analysis from the Health Survey for England among English adults aged 65 years and over, Br. J. Nutr. 107 (7) (2012) 1080–1084.
[299] R. Hellweg, M. Wohrle, H.D. Hartung, H. Stracke, C. Hock, K. Federlin, Diabetes mellitus-associated decrease in nerve growth factor levels is reversed by allogeneic pancreatic islet transplantation, Neurosci. Lett. 125 (1) (1991) 1–4.
[300] M. Fukuoka, K. Sakurai, T. Ohta, M. Kiyoki, I. Katayama, Tacalcitol, an active vitamin D3, induces nerve growth factor production in human epidermal keratinocytes, Skin Pharmacol. Appl. Skin Physiol. 14 (4) (2001) 226–233.
[301] A. Basit, K.A. Basit, A. Fawwad, F. Shaheen, N. Fatima, I.N. Petropoulos, et al., Vitamin D for the treatment of painful diabetic neuropathy, BMJ Open Diabetes Res. Care 4 (1) (2016) e000148.
[302] S.J. Wimalawansa, Calcitonin gene-related peptide and its receptors: molecular genetics, physiology, pathophysiology, and therapeutic potentials, Endocr. Rev. 17 (5) (1996) 533–585.
[303] V. Vandevska-Radunovic, I. Fristad, S.J. Wimalawansa, I.H. Kvinnsland, CGRP1 and NK1 receptors in postnatal, developing rat dental tissues, Eur. J. Oral Sci. 111 (6) (2003) 497–502.
[304] S.J. Wimalawansa, Amylin calcitonin gene-related peptide, calcitonin, and adrenomedullin: a peptide superfamily, Crit. Rev. Neurobiol. 11 (2–3) (1997) 167–239.
[305] S. Tague, P.G. Smith, Vitamin D receptor and enzyme expression in dorsal root ganglia of adult female rats: modulation by ovarian hormones, J. Chem. Neuroanat. 41 (2011) 1–12.
[306] C.Y. Fong, A.N. Kong, B.K. Poh, A.R. Mohamed, T.B. Khoo, R.L. Ng, et al., Vitamin D deficiency and its risk factors in Malaysian children with epilepsy, Epilepsia 57 (8) (2016) 1271–1279.
[307] C.Y. Fong, C.J. Riney, Vitamin D deficiency among children with epilepsy in South Queensland, J. Child Neurol. 29 (3) (2014) 368–373.
[308] P. Harijan, A. Khan, N. Hussain, Vitamin D deficiency in children with epilepsy: do we need to detect and treat it? J. Pediatr. Neurosci. 8 (1) (2013) 5–10.
[309] S.H. Lee, J. Yu, Risk factors of vitamin D deficiency in children with epilepsy taking anticonvulsants at initial and during follow-up, Ann. Pediatr. Endocrinol. Metab. 20 (4) (2015) 198–205.
[310] F.A. Scorza, M. Albuquerque, R.M. Arida, V.C. Terra, H.R. Machado, E.A. Cavalheiro, Benefits of sunlight: vitamin D deficiency might increase the risk of sudden unexpected death in epilepsy, Med. Hypotheses 74 (1) (2010) 158–161.
[311] F.M. Sonmez, A. Donmez, M. Namuslu, M. Canbal, E. Orun, D. Vitamin, Deficiency in children with newly diagnosed idiopathic epilepsy, J. Child Neurol. 30 (11) (2015) 1428–1432.
[312] D.M. Zhu, Y. Liu, A.G. Zhang, Z.X. Chu, Q. Wu, H. Li, et al., High levels of vitamin D in relation to reduced risk of schizophrenia with elevated C-reactive protein, Psychiatry Res. 228 (3) (2015) 565–570.
[313] S. Sullivan, A. Wills, D. Lawlor, J. McGrath, S. Zammit, Prenatal vitamin D status and risk of psychotic experiences at age 18years-a longitudinal birth cohort, Schizophr. Res. 148 (1–3) (2013) 87–92.
[314] D. Itzhaky, D. Amital, K. Gorden, A. Bogomolni, Y. Arnson, H. Amital, Low serum vitamin D concentrations in patients with schizophrenia, Isr. Med. Assoc. J. 14 (2) (2012) 88–92.
[315] C.M. Imai, T.I. Halldorsson, G. Eiriksdottir, M.F. Cotch, L. Steingrimsdottir, I. Thorsdottir, et al., Depression and serum 25-hydroxyvitamin D in older adults living at northern latitudes – AGES-Reykjavik Study, J Nutr Sci. 4 (2015) e37.
[316] D. Gezen-Ak, S. Yilmazer, E. Dursun, Why vitamin d in alzheimer's disease? the hypothesis, J. Alzheimers Dis. 40 (2) (2014) 257–269.
[317] D. Gezen-Ak, E. Dursun, S. Yilmazer, Vitamin D inquiry in hippocampal neurons: consequences of vitamin D-VDR pathway disruption on calcium channel and the vitamin D requirement, Neurol. Sci. 34 (8) (2013) 1453–1458.
[318] X. Cui, N.J. Groves, T.H. Burne, D.W. Eyles, J.J. McGrath, Low vitamin D concentration exacerbates adult brain dysfunction, Am J. Clin. Nutr. 97 (5) (2013) 907–908.
[319] Y. Zhou, R. Fang, L.H. Liu, S.D. Chen, H.D. Tang, Clinical characteristics for the relationship between type-2 diabetes mellitus and cognitive impairment: a cross-sectional study, Aging Dis. 6 (4) (2015) 236–244.
[320] J.E. Morley, H.M. Perry 3rd, The management of diabetes mellitus in older individuals, Drugs 41 (4) (1991) 548–565.
[321] E.M. Moore, A.G. Mander, D. Ames, M.A. Kotowicz, R.P. Carne, H. Brodaty, et al., Increased risk of cognitive impairment in patients with diabetes is associated with metformin, Diabetes Care 36 (10) (2013) 2981–2987.
[322] M. Suzuki, M. Yoshioka, M. Hashimoto, M. Murakami, M. Noya, D. Takahashi, et al., Randomized, double-blind, placebo-controlled trial of vitamin D supplementation in Parkinson disease, Am. J. Clin. Nutr. 97 (5) (2013) 1004–1013.

[323] S. Afzal, S.E. Bojesen, B.G. Nordestgaard, Reduced 25-hydroxyvitamin D and risk of Alzheimer's disease and vascular dementia, Alzheimers Dement. 10 (3) (2014) 296–302.

[324] C. Annweiler, S.N. Karras, P. Anagnostis, O. Beauchet, Vitamin Dsupplements: a novel therapeutic approach for Alzheimer patients, Front. Pharmacol. 5 (2014) 6.

[325] S.P. Neupane, L. Lien, T. Hilberg, J.G. Bramness, Vitamin D deficiency in alcohol-use disorders and its relationship to comorbid major depression: a cross-sectional study of inpatients in Nepal, Drug Alcohol Depend. 133 (2) (2013) 480–485.

[326] R. Rastmanesh, O. Beauchet, C. Annweiler, Vitamin D deficiency and depression: causal relationship or artifact? Biofactors 38 (5) (2012) 317–319.

[327] R.E. Anglin, Z. Samaan, S.D. Walter, S.D. McDonald, Vitamin D deficiency and depression in adults: systematic review and meta-analysis, Br. J. Psychiatry 202 (2013) 100–107.

[328] F.M. Moy, V.C. Hoe, N.N. Hairi, S.R. Vethakkan, A. Bulgiba, Vitamin D deficiency and depression among women from an urban community in a tropical country, Public Health Nutr. (2016) 1–7.

[329] H. Mozaffari-Khosravi, L. Nabizade, S.M. Yassini-Ardakani, H. Hadinedoushan, K. Barzegar, The effect of 2 different single injections of high dose of vitamin D on improving the depression in depressed patients with vitamin D deficiency: a randomized clinical trial, J. Clin. Psychopharmacol. 33 (3) (2013) 378–385.

[330] S.C. Stalpers-Konijnenburg, R.M. Marijnissen, A.B. Gaasbeek, R.C. Oude Voshaar, Can I have some sunshine to cheer me up? vitamin D deficiency and depression in the elderly, Tijdschr Psychiatr. 53 (6) (2011) 365–370.

[331] M. Mellanby, C.L. Pattison, The action of Vitamin D in preventing the spread and promoting the arrest of caries in children, Br. Med. J. 2 (3545) (1928) 1079–1082.

[332] E.C. McBeath, Vitamin D studies, 1933–1934, Am. J. Public Health Nations Health 24 (10) (1934) 1028–1030.

[333] P.P. Hujoel, Vitamin D and dental caries in controlled clinical trials: systematic review and meta-analysis, Nutr. Rev. 71 (2) (2013) 88–97.

[334] E.N. Alshouibi, E.K. Kaye, H.J. Cabral, C.W. Leone, R.I. Garcia, Vitamin D and periodontal health in older men, J. Dent. Res. 92 (8) (2013) 689–693.

[335] E.A. Krall, C. Wehler, R.I. Garcia, S.S. Harris, B. Dawson-Hughes, Calcium and vitamin D supplements reduce tooth loss in the elderly, Am. J. Med. 111 (6) (2001) 452–456.

[336] W.B. Grant, A review of the role of solar ultraviolet-B irradiance and vitamin D in reducing risk of dental caries, Dermatoendocrinology 3 (3) (2011) 193–198.

[337] A. Avenell, G.S. MacLennan, D.J. Jenkinson, G.C. McPherson, A.M. McDonald, P. R. Pant, et al., Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial), J. Clin. Endocrinol. Metab. 97 (2) (2012) 614–622.

[338] K.E. Ensrud, T.L. Blackwell, J.A. Cauley, S.R. Cummings, E. Barrett-Connor, T.T. Dam, et al., Circulating 25-hydroxyvitamin D levels and frailty in older men: the osteoporotic fractures in men study, J. Am. Geriatr. Soc. 59 (1) (2011) 101–106.

[339] K.E. Ensrud, S.K. Ewing, L. Fredman, M.C. Hochberg, J.A. Cauley, T.A. Hillier, et al., Circulating 25-hydroxyvitamin D levels and frailty status in older women, J. Clin. Endocrinol. Metab. 95 (12) (2010) 5266–5273.

[340] A. Zittermann, S. Iodice, S. Pilz, W.B. Grant, V. Bagnardi, S. Gandini, Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies, Am. J. Clin. Nutr. 95 (1) (2012) 91–100.

[341] Y. Dror, S.M. Giveon, M. Hoshen, I. Feldhamer, R.D. Balicer, B.S. Feldman, Vitamin D levels for preventing acute coronary syndrome and mortality: evidence of a nonlinear association, J. Clin. Endocrinol. Metab. 98 (5) (2013) 2160–2167.

[342] W.B. Grant, Relation between prediagnostic serum 25-hydroxyvitamin D level and incidence of breast, colorectal, and other cancers, J. Photochem. Photobiol. B 101 (2) (2010) 130–136.

[343] J.N. Artaza, S. Contreras, L.A. Garcia, R. Mehrotra, G. Gibbons, R. Shohet, et al., Vitamin D and cardiovascular disease: potential role in health disparities, J. Health Care Poor Underserved 22 (4 Suppl) (2011) 23–38.

[344] W.B. Grant, S.J. Wimalawansa, M.F. Holick, J.J. Cannell, P. Pludowski, J.M. Lappe, et al., Emphasizing the health benefits of vitamin D for those with neurodevelopmental disorders and intellectual disabilities, Nutrients 7 (3) (2015) 1538–1564.

[345] B. Schottker, K.U. Saum, L. Perna, J.M. Ordonez-Mena, B. Holleczek, H. Brenner, Is vitamin D deficiency a cause of increased morbidity and mortality at older age or simply an indicator of poor health? Eur. J. Epidemiol. 29 (3) (2014) 199–210.

[346] S.J. Whiting, M.S. Calvo, Dietary recommendations to meet both endocrine and autocrine needs of Vitamin D, J. Steroid Biochem. Mol. Biol. 97 (1–2) (2005) 7–12.

[347] J.E. Manson, S.T. Mayne, S.K. Clinton, Vitamin D and prevention of cancer–ready for prime time? N. Engl. J. Med. 364 (15) (2011) 1385–1387.

[348] A.C. Ross, J.E. Manson, S.A. Abrams, J.F. Aloia, P.M. Brannon, S.K. Clinton, et al., The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know, J. Clin. Endocrinol. Metab. 96 (1) (2011) 53–58.

[349] A.S. Carmel, A. Shieh, H. Bang, R.S. Bockman, The 25(OH)D level needed to maintain a favorable bisphosphonate response is 33 ng/ml, Osteoporos. Int. 23 (10) (2012) 2479–2487.

[350] B. Dawson-Hughes, What is the optimal dietary intake of vitamin D for reducing fracture risk? Calcif. Tissue Int. 92 (2) (2013) 184–190.

[351] L. de Koning, D. Henne, B.R. Hemmelgarn, P. Woods, C. Naugler, Non-linear relationship between serum 25-hydroxyvitamin D concentration and subsequent hip fracture, Osteoporos. Int. 24 (7) (2013) 2061–2065.

[352] R. Okazaki, Updates on rickets and osteomalacia: vitamin D deficiency: its pathophysiology and treatment, Clin. Calcium 23 (10) (2013) 1483–1489.

[353] D. Ray, R. Goswami, N. Gupta, N. Tomar, N. Singh, V. Sreenivas, Predisposition to vitamin D deficiency osteomalacia and rickets in females is linked to their 25(OH)D and calcium intake rather than vitamin D receptor gene polymorphism, Clin. Endocrinol. (Oxf.) 71 (3) (2009) 334–340.

[354] S.W. Stanbury, P. Torkington, G.A. Lumb, P.H. Adams, P. de Silva, C.M. Taylor, Asian rickets and osteomalacia: patterns of parathyroid response in vitamin D deficiency, Proc. Nutr. Soc. 34 (2) (1975) 111–117.

[355] I. Nurmi, J.P. Kaukonen, P. Luthje, H. Naboulsi, S. Tanninen, M. Kataja, et al., Half of the patients with an acute hip fracture suffer from hypovitaminosis D: a prospective study in southeastern Finland, Osteoporos. Int. 16 (12) (2005) 2018–2024.

[356] E.B. Mawer, M. Davies, D. Vitamin, deficiency, rickets and osteomalacia, a returning problem worldwide, in: A.W. Norman, R. Bouillon, M. Thomasset (Eds.), Vitamin D. Chemistry, Biology and Clinical Applications of the Steroid Hormone, University of California, California, 1997, pp. 899–906.

[357] AGS WG. American Geriatrics Society Workgroup on Vitamin D Supplementation for older adults. Recommendations bbstracted from the American Geriatrics Society Consensus Statement on Vitamin D for prevention of falls and their consequences. J. Am. Geriatr. Soc. (2013).

[358] T. Larsen, F.H. Mose, J.N. Bech, A.B. Hansen, E.B. Pedersen, Effect of cholecalciferol supplementation during winter months in patients with hypertension: a randomized, placebo-controlled trial, Am. J. Hypertens. 25 (11) (2012) 1215–1222.

[359] M. Tabesh, L. Azadbakht, E. Faghihimani, M. Tabesh, A. Esmaillzadeh, Effects of calcium plus vitamin D supplementation on anthropometric measurements and blood pressure in Vitamin D insufficient people with type 2 diabetes: a randomized controlled clinical trial, J. Am. Coll. Nutr. 34 (4) (2015) 281–289.

[360] J.L. Anderson, H.T. May, B.D. Horne, T.L. Bair, N.L. Hall, J.F. Carlquist, et al., Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population, Am. J. Cardiol. 106 (7) (2010) 963–968.

[361] L. Perna, B. Schottker, B. Holleczek, H. Brenner, Serum 25-hydroxyvitamin D and incidence of fatal and nonfatal cardiovascular events: a prospective study with repeated measurements, J. Clin. Endocrinol. Metab. 98 (12) (2013) 4908–4915.

[362] M. Tabesh, L. Azadbakht, E. Faghihimani, M. Tabesh, A. Esmaillzadeh, Effects of calcium-vitamin D co-supplementation on metabolic profiles in vitamin D insufficient people with type 2 diabetes: a randomised controlled clinical trial, Diabetologia 57 (10) (2014) 2038–2047.

[363] L. Yin, J.M. Ordonez-Mena, T. Chen, B. Schottker, V. Arndt, H. Brenner, Circulating 25-hydroxyvitamin D serum concentration and total cancer incidence and mortality: a systematic review and meta-analysis, Prev. Med. 57 (6) (2013) 753–764.

[364] B.H.U. Schöttker, L. Schomburg, J. Köhrle, L. Perna, H. Müller, B. Holleczek, H. Brenner, Strong associations of 25-hydroxyvitamin D concentrations with all-cause, cardiovascular, cancer, and respiratory disease mortality in a large cohort study, Am. J. Clin. Nutr. 97 (4) (2013) 782–793.

[365] A.C. Porojnicu, T.E. Robsahm, A. Dahlback, J.P. Berg, D. Christiani, O.S. Bruland, et al., Seasonal and geographical variations in lung cancer prognosis in Norway. Does Vitamin D from the sun play a role? Lung Cancer 55 (3) (2007) 263–270.

[366] S. Tretli, G.G. Schwartz, P.A. Torjesen, T.E. Robsahm, Serum levels of 25-hydroxyvitamin D and survival in Norwegian patients with cancer of breast, colon, lung, and lymphoma: a population-based study, Cancer Causes Control 23 (2) (2012) 363–370.

[367] S.R. Bauer, S.E. Hankinson, E.R. Bertone-Johnson, E.L. Ding, Plasma vitamin D levels, menopause, and risk of breast cancer: dose-response meta-analysis of prospective studies, Medicine (Baltimore) 92 (3) (2013) 123–131.

[368] S.B. Mohr, C.F. Garland, E.D. Gorham, W.B. Grant, F.C. Garland, Relationship between low ultraviolet B irradiance and higher breast cancer risk in 107 countries, Breast J. 14 (3) (2008) 255–260.

[369] M. Science, J.L. Maguire, M.L. Russell, M. Smieja, S.D. Walter, M. Loeb, Low serum 25-hydroxyvitamin D level and risk of upper respiratory tract infection in children and adolescents, Clin. Infect. Dis. 57 (3) (2013) 392–397.

[370] S. Korn, M. Hubner, M. Jung, M. Blettner, R. Buhl, Severe and uncontrolled adult asthma is associated with vitamin D insufficiency and deficiency, Respir. Res. 14 (2013) 25.

[371] W. Checkley, C.L. Robinson, L.M. Baumann, N.N. Hansel, K.M. Romero, S.L. Pollard, et al., 25-hydroxy vitamin D levels are associated with childhood asthma in a population-based study in Peru, Clin. Exp. Allergy 45 (1) (2015) 273–282.

[372] V. Tangpricha, A. Kelly, A. Stephenson, K. Maguiness, J. Enders, K.A. Robinson, et al., An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: evidence-based recommendations from the cystic fibrosis foundation, J. Clin. Endocrinol. Metab. 97 (4) (2012) 1082–1093.

[373] L. Wang, Y. Song, J.E. Manson, S. Pilz, W. Marz, K. Michaelsson, et al., Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies, Circ. Cardiovasc. Qual. Outcomes 5 (6) (2012) 819–829.
[374] A.G. Pittas, J. Nelson, J. Mitri, W. Hillmann, C. Garganta, D.M. Nathan, et al., Plasma 25-hydroxyvitamin D and progression to diabetes in patients at risk for diabetes: an ancillary analysis in the Diabetes Prevention Program, Diabetes Care 35 (3) (2012) 565–573.
[375] A. Tsur, B.S. Feldman, I. Feldhammer, M.B. Hoshen, G. Leibowitz, R.D. Balicer, Decreased serum concentrations of 25-hydroxycholecalciferol are associated with increased risk of progression to impaired fasting glucose and diabetes, Diabetes Care 36 (5) (2013) 1361–1367.
[376] R. Khadgawat, T. Thomas, M. Gahlot, N. Tandon, V. Tangpricha, D. Khandelwal, et al., The effect of puberty on interaction between Vitamin D status and insulin resistance in obese asian-Indian children, Int. J. Endocrinol. 2012 (2012) 173581.
[377] C.L. Roth, C. Elfers, M. Kratz, A.N. Hoofnagle, Vitamin D deficiency in obese children and its relationship to insulin resistance and adipokines, J. Obes. 2011 (2011) 495101.
[378] R.P. Heaney, Health is better at serum 25(OH)D above 30 ng/mL, J. Steroid Biochem. Mol. Biol. 136 (2013) 224–228.
[379] P.R. von Hurst, W. Stonehouse, J. Coad, Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient – a randomised, placebo-controlled trial, Br. J. Nutr. 103 (4) (2010) 549–555.
[380] L. Pacifico, C. Anania, J.F. Osborn, F. Ferraro, E. Bonci, E. Olivero, et al., Low 25 (OH)D3 levels are associated with total adiposity, metabolic syndrome, and hypertension in Caucasian children and adolescents, Eur. J. Endocrinol. 165 (4) (2011) 603–611.
[381] S. Sabherwal, V. Bravis, D. Devendra, Effect of oral vitamin D and calcium replacement on glycaemic control in South Asian patients with type 2 diabetes, Int. J. Clin. Pract. 64 (8) (2010) 1084–1089.
[382] H.D. Aridi, R.S. Alami, T. Fouani, G. Shamseddine, H. Tamim, B. Safadi, Prevalence of vitamin D deficiency in adults presenting for bariatric surgery in Lebanon, Surg. Obes. Relat. Dis. 12 (2) (2016) 405–411.
[383] M. Censani, E.M. Stein, E. Shane, S.E. Oberfield, D.J. McMahon, S. Lerner, D. et al. Vitamin, Deficiency is prevalent in morbidly obese adolescents prior to bariatric surgery, ISRN Obes. (2013) 2013.
[384] R. Ducloux, C. Janin, H. Ducloux, J.J. Altman, High vitamin D deficiency rate in metabolic inpatients: is bariatric surgery planning found guilty? Obes. Surg. 24 (11) (2014) 1947–1953.
[385] K. Gemmel, H.P. Santry, V.N. Prachand, J.C. Alverdy, Vitamin D deficiency in preoperative bariatric surgery patients, Surg. Obes. Relat. Dis. 5 (1) (2009) 54–59.
[386] L.A. Peterson, L.J. Cheskin, M.A. Schweitzer, T.H. Magnuson, K.E. Steele, Treatment: for Vitamin D deficiency prior to bariatric surgery: a prospective cohort study, Obes. Surg. 26 (5) (2016) 1146–1149.
[387] M.M. Rothkopf, Reversible neurologic dysfunction caused by severe vitamin deficiency after malabsorptive bariatric surgery, Surg. Obes. Relat. Dis. 2 (6) (2006) 656–660.
[388] G.H. Slater, C.J. Ren, N. Siegel, T. Williams, D. Barr, B. Wolfe, et al., Serum fat-soluble vitamin deficiency and abnormal calcium metabolism after malabsorptive bariatric surgery, J. Gastrointest. Surg. 8 (1) (2004) 48–55 discussion 4–5.
[389] U. Zeitz, K. Weber, D.W. Soegiarto, E. Wolf, R. Balling, R.G. Erben, Impaired insulin secretory capacity in mice lacking a functional vitamin D receptor, FASEB J. 17 (3) (2003) 509–511.
[390] T.R. Neyestani, B. Nikooyeh, H. Alavi-Majd, N. Shariatzadeh, A. Kalayi, N. Tayebinejad, et al., Improvement of Vitamin D status via daily intake of fortified yogurt drink either with or without extra calcium ameliorates systemic inflammatory biomarkers, including adipokines, in the subjects with type 2 diabetes, J. Clin. Endocrinol. Metab. (2012).
[391] C.E. Chagas, M.C. Borges, L.A. Martini, M.M. Rogero, Focus on vitamin D, inflammation and type 2 diabetes, Nutrients 4 (1) (2012) 52–67.
[392] N. Poolsup, N. Suksomboon, N. Plordplong, Effect of vitamin D supplementation on insulin resistance and glycaemic control in prediabetes: a systematic review and meta-analysis, Diabet. Med. 33 (3) (2016) 290–299.
[393] B.M. Dixon, T. Barker, T. McKinnon, J. Cuomo, B. Frei, N. Borregaard, et al., Positive correlation between circulating cathelicidin antimicrobial peptide (hCAP18/LL-37) and 25-hydroxyvitamin D levels in healthy adults, BMC Res. Notes 5 (2012) 575.
[394] T. Holmoy, M.T. Kampman, J. Smolders, Vitamin D in multiple sclerosis: implications for assessment and treatment, Expert Rev. Neurother. 12 (9) (2012) 1101–1112.
[395] M.K. Quraishi, H. Badsha, Rheumatoid arthritis disease activity and vitamin D deficiency in an Asian resident population, Int. J. Rheum. Dis. (2013).
[396] D.S. Smyk, T. Orfanidou, P. Invernizzi, D.P. Bogdanos, M. Lenzi, Vitamin D in autoimmune liver disease, Clin. Res. Hepatol. Gastroenterol. 37 (5) (2013) 535–545.
[397] S.A. Quraishi, A.A. Litonjua, T. Moromizato, F.K. Gibbons, C.A. Camargo Jr., E. Giovannucci, et al., Association between prehospital vitamin D status and hospital-acquired bloodstream infections, Am. J. Clin. Nutr. 98 (4) (2013) 952–959.
[398] K.E. Nnoaham, A. Clarke, Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis, Int. J. Epidemiol. 200837 (1) (2016) 113–119.
[399] L.M. Villar, J.A. Del Campo, I. Ranchal, E. Lampe, M. Romero-Gomez, Association between vitamin D and hepatitis C virus infection: a meta-analysis, World J. Gastroenterol. 19 (35) (2013) 5917–5924.
[400] B. Cacopardo, C. Camma, S. Petta, M.R. Pinzone, A. Cappellani, A. Zanghi, et al., Diagnostic and therapeutical role of vitamin D in chronic hepatitis C virus infection, Front. Biosci. (Elite Ed.) 4 (2012) 1276–1286.
[401] Y. Slinin, M. Paudel, B.C. Taylor, A. Ishani, R. Rossom, K. Yaffe, et al., Association between serum 25(OH) vitamin D and the risk of cognitive decline in older women, J. Gerontol. A. Biol. Sci. Med. Sci. 67 (10) (2012) 1092–1098.
[402] M. Soni, K. Kos, I.A. Lang, K. Jones, D. Melzer, D.J. Llewellyn, Vitamin D and cognitive function, Scand. J. Clin. Lab. Invest. Suppl. 243 (2012) 79–82.
[403] A.C.Z. Holló, A. Kamondi, P. Lakatos, A. Szűcs, Correction of vitamin D deficiency improves seizure control in epilepsy: a pilot study, Epilepsy Behav. 202 (24 (1)) (2016) 131–133.
[404] N. Principi, S. Bianchini, E. Baggi, S. Esposito, Implications of maternal vitamin D deficiency for the fetus, the neonate and the young infant, Eur. J. Nutr. 52 (3) (2013) 859–867.
[405] L.M. Bodnar, G. Tang, R.B. Ness, G. Harger, J.M. Roberts, Periconceptional multivitamin use reduces the risk of preeclampsia, Am. J. Epidemiol. 164 (5) (2006) 470–477.
[406] A.J.H.B. Whitehouse, M. Serralha, P.G. Holt, M.M. Kusel, P.H. Hart, Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development, Pediatrics 129 (3) (2012) 485–493.
[407] A.D. Gernand, H.N. Simhan, S. Caritis, L.M. Bodnar, Maternal vitamin D status and small-for-gestational-age offspring in women at high risk for preeclampsia, Obstet. Gynecol. 123 (1) (2014) 40–48.
[408] L.M. Bodnar, H.N. Simhan, J.M. Catov, J.M. Roberts, R.W. Platt, J.C. Diesel, et al., Maternal vitamin D status and the risk of mild and severe preeclampsia, Epidemiology 25 (2) (2014) 207–214.
[409] R.J. Schroth, N.S. Jeal, E. Kliewer, E.A. Sellers, The relationship between vitamin D and severe early childhood caries: a pilot study, Int. J. Vitam. Nutr. Res. 82 (1) (2012) 53–62.
[410] S.B. Mohr, F.C. Garland, C.F. Garland, E.D. Gorham, C. Ricordi, Is there a role of vitamin D deficiency in type 1 diabetes of children? Am. J. Prev. Med. 39 (2) (2010) 189–190.
[411] S.B. Mohr, C.F. Garland, E.D. Gorham, W.B. Grant, F.C. Garland, Ultraviolet B irradiance and vitamin D status are inversely associated with incidence rates of pancreatic cancer worldwide, Pancreas 39 (5) (2010) 669–764.
[412] H. Li, M.J. Stampfer, J.B. Hollis, L.A. Mucci, J.M. Gaziano, D. Hunter, et al., A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer, PLoS Med. 4 (3) (2007) e103.
[413] C.F. Garland, E.D. Gorham, S.B. Mohr, W.B. Grant, E.L. Giovannucci, M. Lipkin, et al., Vitamin D and prevention of breast cancer: pooled analysis, J. Steroid Biochem. Mol. Biol. 103 (3–5) (2007) 708–711.
[414] E.D. Gorham, C.F. Garland, F.C. Garland, W.B. Grant, S.B. Mohr, M. Lipkin, et al., Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis, Am. J. Prev. Med. 32 (3) (2007) 210–216.
[415] W.B. Grant, C.F. Garland, E.D. Gorham, An estimate of cancer mortality rate reductions in Europe and the US with 1,000 IU of oral vitamin D per day, Recent Results: Cancer Res. 174 (2007) 225–234.
[416] C.F. Garland, E.D. Gorham, C.A. Baggerly, F.C. Garland, Re: prospective study of vitamin D and cancer mortality in the United States, J. Natl. Cancer Inst. 100 (11) (2008) 826–827.
[417] P. Pludowski, M.F. Holick, S. Pilz, C.L. Wagner, B.W. Hollis, W.B. Grant, et al., Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence, Autoimmun. Rev. 12 (10) (2013) 976–989.
[418] S. Singh, C.D. Furberg, Calcium supplements increase risk of myocardial infarction, Evid. Based Med. 15 (6) (2010) 181.
[419] I.R. Reid, M.J. Bolland, A. Grey, Calcium supplements and risk of myocardial infarction: an hypothesis twice tested, Am. J. Med. 125 (4) (2012) e15 author reply e7.
[420] M.J. Bolland, A. Avenell, J.A. Baron, A. Grey, G.S. MacLennan, G.D. Gamble, et al., Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis, BMJ 341 (2010) c3691.
[421] A.G. Pittas, S.S. Harris, P.C. Stark, B. Dawson-Hughes, The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults, Diabetes Care 30 (4) (2007) 980–986.
[422] C.H. Hennekens, E.J. Barice, Calcium supplements and risk of myocardial infarction: a hypothesis formulated but not yet adequately tested, Am. J. Med. 124 (12) (2011) 1097–1098.
[423] R.L. Prentice, R.D. Jackson, J.E. Rossouw, Calcium supplements and cardiovascular risk in the Women's Health Initiative: response to Bolland et al, Osteoporos. Int. 24 (8) (2013) 2373–2374.
[424] D. Group, Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe, BMJ 340 (2010) b5463.
[425] K.M. Sanders, A.L. Stuart, E.J. Williamson, J.A. Simpson, M.A. Kotowicz, D. Young, et al., Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial, JAMA 303 (18) (2010) 1815–1822.
[426] K.M. Sanders, A.L. Stuart, E.J. Williamson, F.N. Jacka, S. Dodd, G. Nicholson, et al., Annual high-dose vitamin D3 and mental well-being: randomised controlled trial, Br. J. Psychiatry 198 (5) (2011) 357–364.

[427] R.A. Lyons, A. Johansen, S. Brophy, R.G. Newcombe, C.J. Phillips, B. Lervy, et al., Preventing fractures among older people living in institutional care: a pragmatic randomised double blind placebo controlled trial of vitamin D supplementation, Osteoporos. Int. 18 (6) (2007) 811–818.

[428] M. Law, H. Withers, J. Morris, F. Anderson, Vitamin D supplementation and the prevention of fractures and falls: results of a randomised trial in elderly people in residential accommodation, Age Ageing 35 (5) (2006) 482–486.