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Review Article

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Vitamin D: Genetics, Environment & Health

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Abstract

Vitamin D, the "sunshine vitamin" was once thought to be a micronutrient that was solely important for development, growth, and the maintenance of a healthy skeleton. Today, the risk and consequences of vitamin D deficiency extend well beyond the original recognition of its contribution to diseases such as rickets in children and osteomalacia in adults. Consideration now has its focus on the wide distribution of the vitamin D receptor in cells and tissues, along with the plethora of diverse biologic actions reported for calcitriol, the active form of the vitamin. This renaissance of interest in this micronutrient may explain how the vitamin D related phenomena can modify risk for such a great variety of diseases. Australia, a continent with an average sunshine quota of 3000 hours/year, and the highest skin cancer rates in the world, has been reported to have an increasing incidence of vitamin D deficiency across all ages of the population. This had led to confusion regarding vitamin D recommendations, particularly dietary requirements and the relative merits of sun exposure versus protection in the context of skin cancer risk. This review examines health benefits of vitamin D from a molecular, environmental, evolutionary and health perspective. Current vitamin D fortification trends and the vitamins overall importance across the human lifecycle in respect of various clinical phenotypes are discussed.

Keywords: Vitamin D; VDR; Ultraviolet radiation; Lifecycle; Diet; Degenerative disorders

Abbreviations: $1,25(OH)_2D$: Calcitriol; 25(OH)D: Calcidiol; BCC: Basal Cell Carcinoma; BMD: Bone Mineral Density; BMI: Body Mass Index; CYP24A1: Calcidiol 24-hydroxylase; CYP27B1: Calcidiol 1-hydroxylase; CYP2R1: Calciol 25-hydroxylase; CRC: Colorectal Cancer; CVD: Cardiovascular Disease; DBP: Vitamin D Binding Protein; HELENA: Healthy Lifestyle in Europe by Nutrition in Adolescence; IVF: *In Vitro Fertilization;* MM: Malignant Melanoma; MC1R: Melanocortin 1 Receptor; MS: Multiple Sclerosis; PCOS: Polycystic Ovary Syndrome; PTH: Parathyroid Hormone; RFLP: Restriction Fragment Length Polymorphism; RXR: Retinoid X Receptor; SCC: Squamous Cell Carcinoma; SNP: Single Nucleotide Polymorphism; SPF: Sun Protection Factor; T1DM:Type1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; UVA: Ultraviolet-A; UVB: Ultraviolet-B; UVMED: UV Minimum-Erythemal Dose; UVR: Ultraviolet Radiation; VDR: Vitamin D Receptor; VDRE: Vitamin D Response Element

Introduction

Vitamin D, once seen as a micronutrient with actions primarily in bone, is now known for its spectrum of activity throughout the body. The multiple roles of vitamin D in the body has stimulated an appreciation that many cells have receptors for the active form of the vitamin, calcitriol [$1,25(OH)_2D$]. This soluble receptor protein is termed the vitamin D receptor (VDR). The VDR binds $1,25(OH)_2D$ with high affinity and high selectivity. In the target cell, this interaction initiates a cascade of molecular events, causing alterations in the transcription of specific genes.

VDR distribution embraces all organs, tissues and every major body function, indicating how important its role is in a variety of stages through the human lifecycle. Adequate calcidiol (25(OH)D) levels in the blood (effectively the storage form of the vitamin) are imperative in regulating several physiologic functions particularly those related to calcium homeostasis [1]. However, recent evidence suggests that besides its effect on bone health, a lack of vitamin D may be associated with numerous negative health outcomes. These include cardiovascular disease (CVD) [2-4], cancer, including prostate, colon, oesophageal, and pancreatic [5-7], skin disorders [8-10], adiposity [11-13] problems with the reproductive system [14-16], the renal system – effecting the distal tubular reabsorption of calcium and phosphorus [17-19], crohn's disease and inflammatory bowel disease [20-22], cognition [23-25], multiple sclerosis (MS) [26-28], other endocrine and immune disorders [29-31] and inflammatory responses [32-34].

Vitamin D nomenclature: Vitamin D exists in numerous forms making it necessary to clarify the major vitamins (Table 1). Cholecalciferol/calciol (vitamin D_3) is synthesised by ultraviolet radiation (UVR) from 7-dehydrocholesterol in the skin of vertebrates, whilst ergocalciferol/ercalciol (vitamin D_2) is synthesised by UVR from ergosterol in plants, and occurs naturally in some mushrooms. 25(OH)D represents the primary circulatory form of vitamin D, whilst $1,25(OH)_2D$ also known as calcitriol, is the most physiologically active form in the human body. Both are synthesised by the subsequent hydroxylation of cholecalciferol [35].

Environmental Origins of Vitamin D

Strictly speaking, vitamin D is not a vitamin, i.e. it is not an essential dietary factor, but rather a prohormone synthesized photochemically in the skin from 7-dehydrocholesterol, primarily driven by exposure of the skin to solar UVR [36]. Incipient UVR varies according to the season, particularly so at higher latitudes compared to at the equator. The total amount of ultraviolet-B (UVB) radiation available depends on the angle at which UVR strikes the Earth's atmosphere, but the critical wavelength range is 280-320 nm with maximal dermal synthesis occurring at 295 nm [37].

Australia receives an average of 3000 hours of sunshine annually, with some regions in Central and Western Australia receiving up to 3500 hours each year. It has been estimated that Australians receive almost all (90-95%) of their vitamin D from solar UVR [38]. Due to Australia's extreme UVR exposure pattern, it was previously thought that problems relating to vitamin D insufficiency were only relevant to the elderly population [39], who may be housebound and have diminished capacity to synthesise cholecalciferol/calciol in the skin. However, recent studies show that deficiency rates are far more widespread than originally believed [40], as reflected by the increased testing and supplementation both in Australia and worldwide.

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Vitamin D name	Comments
Cholecalciferol/Calciol/Vitamin D_3	Produced in the skin by action of UVB irradiation on 7-dehydrocholesterol Occurs in some oily fish More bioavailable than ergocalciferol. Often used in supplements and as a fortificant
Ergocalciferol/Ercalciol/Vitamin D_2	Produced by UVB irradiation of ergosterol Found naturally in some mushrooms and other fungi and yeast Less bioavailable than cholecalciferol Used less in supplements and as a fortificant
25-hydroxyvitamin D/ Calcidiol/25(OH)D	Synthesised by hydroxylation of cholecalciferol in the liver Most accurate metabolite to determine vitamin D status
1,25-dihydroxyvitamin D/ Calcitriol/1,25$(OH)_2$D	Form of vitamin D produced by hydroxylation of 25-hydroxyvitamin D

Table 1: The nomenclature of vitamin D.

Indeed, between 2000-2010 the number of vitamin D tests increased 100-fold, an annual cost to Medicare Australia of approximately $96 million [41].

De novo vitamin D synthesis: The two major forms of dietary vitamin D are vitamin D_2, commonly known as ergocalciferol and vitamin D_3, commonly known as cholecalciferol. However, while vitamin D_3 is a dietary component, it also arises from the irradiation of 7-dehydrocholesterol, a sterol naturally present in the skin. Provitamin D structures have a four-membered steroid ring structure with two conjugated double bonds in the B ring at C_5 and C_7. The side chain identifies whether the form of provitamin D is ergosterol (provitamin D_2) or 7-dehydrocholesterol (provitamin D_3).

Vitamin D synthesis is initiated with 7-dehydrocholesterol absorbing UVB in the 290-315nm range. The sterol absorbs a quantum of energy, transforming it from a ground to excited state. Following this, the sterol ring opens at C9-C10, and yields the 6,7-cis-hexatriene derivative, previtamin D. A slower thermal-dependant isomerisation then shifts the double bonds and the resulting rotation of the single C6-C7 bond leads to a thermodynamically stable 5,6-cis isomer form of vitamin D.

Previtamin D can then undergo a reversible photoconversion involving either a ring closure to its parent provitamin D, or ring closure to form the inactive stereoisomer metabolite, lumisterol, or isomerisation to form the inactive 6,7-trans isomer, tachysterol [42]. As previously mentioned, the photolysis of provitamin D to form previtamin D, and subsequent isomerisation to vitamin D_3 in the bilayer of the plasma membrane, is a temperature-dependent process [43,44]. At body temperature (37°C), 50% conversion of vitamin D occurs after 28 hours, and takes four days to reach equilibrium, with 80% of previtamin D converted into vitamin D_3. Once formed, vitamin D_3 is translocated away from the skin, and drawn into the capillary bed by vitamin D binding protein (DBP) [43-46]. Vitamin D_3 in the form of calcidiol represents the main circulating and storage form of the vitamin.

Photobiology of vitamin D: Elucidation of the two steps involved in activation of the hormone form of vitamin D, 1,25$(OH)_2$D was a critically significant development in molecular nutrition. The unique action of vitamin D synthesis is initiated on dermal exposure to UVR.

The efficiency of vitamin D_3 synthesis in the keratinocytes of the epidermis and fibroblasts of the skin is reliant on the absorption of UVB photons. Most humans are able to maintain vitamin D synthesis through casual sunlight exposure. However, as skin type is genetically determined, the level of melanin in the skin can determine the amount of sunlight exposure required to enable maximum synthesis of vitamin D. Those with lightly pigmented skin and higher 25(OH) D levels produce larger amounts of previtamin D_3, whereas darkly pigmented skin only produces moderate rates of previtamin D_3 following UVB exposure. As a result, deeply melanised skin becomes non-adaptive in circumstances where the melanin concentration is too high to allow enough vitamin D_3 to be synthesized under conditions of available UVR.

The influence of altitude, latitude, time of day, and weather conditions can all affect previtamin D_3 production. First observed in 1897, the incidence of rickets was increased during the winter months compared with the summer months [47]. This may be due to the increase in the zenith angle of the sun during winter; during shorter days, the amount of UVB radiation reaching the earth's surface is considerably reduced due to the fact that it is absorbed by the ozone layer and has more atmosphere to traverse. Therefore, the level of solar UVB radiation which reaches the Earth's surface is a function of the solar zenith angle, a function of latitude, season and time of day. A study in Boston, USA (42°N) found formation of previtamin D_3 to clearly be season and time-dependent [48].

If sunlight exposure is insufficient to permit the vitamin D_3 precursor to be synthesised, a deficiency in vitamin D becomes increasingly likely [49]. Melanin concentration, along with the use of sunscreen can markedly hinder efficient absorption of UVB photons for the production of vitamin $D_3$by more than 90% [50,51]. By contrast, excess vitamin D_3 produced in the skin cannot cause intoxication, as all surplus is destroyed by sun exposure [52].

Geo-evolutionary perspective

Life on earth evolved as a direct consequence of a close synergy between biological processes and solar energy [1,53]. By harnessing the suns energy, photosynthesis has provided the energy-rich structural molecules responsible for what most life on earth depends. This UVR requirement is not limited to plants, higher organisms also rely on solar energy to drive physiological processes [54].

Human skin obtains the majority of its pigmentation from melanin which is found in two forms, eumelanin and phaeomelanin [55]. High eumelanin levels are exhibited in those with darker, tanned skin, whilst phaeomelanin is found in all individuals at varied concentrations, although significant amounts are found in northern Europeans, east Asians and native Americans [55,56].

Skin colouration is highly adaptive and has evolved to accommodate the physiological requirements of humans who receive variable annual ultraviolet (UV) exposure in their dispersed regions around the world [57]. This varying exposure expressed as the annual UV minimum-erythemal dose (UVMED) is defined as the quantity of UVR needed to generate a slight reddening of lightly-pigmented skin [57]. The prevailing theory put forward by Jablonski et al. [57] was established by UVR data collection testing the distribution of skin colour of indigenous people with highly melanised skin. Findings indicated that the degree of melanin pigmentation was an adaptation for regulating the penetration of UVR into the epidermis.

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The critical element being that a slight decrease in vitamin D synthesis (a result of decreased annual UVR exposure) can trigger a deficiency in vitamin D in moderate to darkly pigmented humans. This supported previous findings [49,51], which found that those exhibiting darker pigmented skin require up to six times the UVR than those with lighter skin to obtain the equivalent in vitamin D synthesis, and are at a higher risk of deficiency due to changes in UVR regime. Therefore, humans in contemporary populations with darker pigmented skin are chromatically tuned for vitamin D synthesis within the specific UVR regimes under which they evolved, and this can be disrupted by migration/locality and lifestyle [57].

Recent ideas on vitamin D and the origin of human skin pigmentation: Recent work by Jablonski and Chaplin [57-59], has led to an adaptation to their original hypothesis on the evolution of human skin pigmentation alluded to earlier. They suggest the degree of melanin pigmentation in the skin evolved to regulate UVR penetration, a critical factor in the potential photolysis of photo-labile compounds while allowing the photosynthesis of others [59]. Their hypothesis argues that protection against photolysis of the important B-vitamin, folic acid, was the driving force in the evolution of deeply pigmented skin within high UV regimes [57-59]. In the tissues near the skin surface, folate is sensitive to ultraviolet-A (UVA) radiation, a major environmental stressor. UVA light near 312nm can significantly degrade plasma/cellular 5-methyltetrahydrofolate, resulting in irreversible loss of vitamin activity [60]. Within the cell, folate coenzymes are required for DNA-thymidylate biosynthesis. DNA fragility exists when folate levels are depleted, due to the misincorporation of uracil in place of thymine into the primary base sequence. Subsequently, cell division is affected, possibly impacting reproductive success. A recent Australian study supports this proposition [61].

Vitamin D synthesis occurs via UVB light exposure, and a deficiency of this vitamin can similarly affect reproductive success through disruption of calcium homeostasis. In effect, it has been proposed that natural selection supports two opposing phenotypic clines of skin pigmentation. The first relates to vitamin D_3 photosynthesis and involves a gradient shift of high to low pigmentation, from the equator to the poles. The second is a cline relating to the prevention of the C9-C10 bond scission of 5-methyltetrahydrofolate. This evolved gradient of photo protection runs from deeply pigmented skin at the Equator, to lightly pigmented skin near the Poles. Between UV exposure extremes, the ability for optional (facultative) pigmentation/tanning has evolved according to seasonal changes in UVR levels [58,59]. This theory is widely cited, and has been termed the folate-vitamin D-sunlight hypothesis, and is an important paradigm within the overall evolutionary model of skin pigmentation.

Growing evidence suggests that the relationship between skin pigmentation and photo protection is complex, with over 120 genes now shown to regulate skin pigmentation in mammals. To date, studies have determined that one of the major loci of pigment phenotype is the melanocortin 1 receptor (MC1R). The MC1R protein is a G-protein coupled receptor that is expressed on the melanocyte, and has a role in the regulation of melanin synthesis. Genetic variations within this gene are key contributors to the diversity in human skin pigmentation [62,63]. Other genes which affect melanocyte function through numerous mutations include P-gene and members of the *TYRP, SILV, OCA2, DCT, KITLG, DRD, PPARD* and *EGFR* families [64].

Metabolism and molecular biology of vitamin D

After entering the circulation, via absorption by the gut or production in the skin, vitamin D_2 and vitamin D_3 are incorporated into chylomicrons and transported by the lymphatic system into the venous circulation [45]. Vitamin D (from now "D" represents D_2 or D_3) can be stored and released from fat cells. Vitamin D is then subsequently carried in the blood, bound to DBP and metabolised to yield the metabolically active hormone form $1,25(OH)_2D$.

To undertake metabolism, vitamin D must be activated by two sequential hydroxylations. In the liver, vitamin D is hydroxylated into 25(OH)D assisted by calciol 25-hydroxylase (CYP2R1), while subsequently in the kidney, 25(OH)D is metabolised to $1,25(OH)_2D$ by calcidiol 1-hydroxylase (CYP27B1) (Figure 1).

$1,25(OH)_2D$ is the most biologically active vitamer, and is responsible for stimulating calcium absorption and mobilisation from the gut [65]. 25(OH)D is the metabolite used clinically to determine a subject's vitamin D status [35,66].

Calcium homeostasis is closely linked to the metabolism of 25(OH)D bound to DBP. The onward hydroxylation by CYP27B1 in the kidneys to form the secosteroid preserves calcium homeostasis, a process enhanced by parathyroid hormone (PTH). Circulating $1,25(OH)_2D$ bound to DBP subsequently reaches the target cell where it enters and binds to a nuclear VDR in the cytoplasm. Upon entering the nucleus, $1,25(OH)_2D$ heterodimerizes with the retinoid X receptor (RXR), facilitating binding to the vitamin D response element (VDRE) (Figure 2).

This action enhances transcription of vitamin D-dependant genes which are important in the metabolism of calcium and maintenance of bone mineral [35,65,66]. Up to 2000 genes are either directly or indirectly controlled or influenced by the VDRE, whilst almost all cells and tissues contain a VDR, and hence a target for $1,25(OH)_2D$ [45,67,68]. A recent study found serum 25(OH)D status altered the expression of a number of genes 1.5-fold following vitamin D supplementation.

Intricate inhibitory feedback mechanisms exist; $1,25(OH)_2D$ has the ability to stimulate its own destruction in the kidneys through enhancing the expression of the calcidiol 24-hydroxylase enzyme (CYP24A1). This pathway leads to inactive forms of the vitamins, which are subsequently excreted in the bile [66].

Role of vitamin D in calcium & phosphorus homeostasis: The major physiological role of vitamin D is to maintain serum calcium and phosphorus levels required for functions such as skeletal mineralisation. This regulatory role on calcium can occur in the small intestine, kidneys and bone. In the small intestine, $1,25(OH)_2D$ interacts with the VDR to stimulate active transport of calcium and phosphate in the blood. The resulting increase in calcium binding protein increases the efficiency of calcium absorption from 10% to 15% up to 30% to 40%, and phosphorus from around 60% to 80% [45]. In the presence of PTH, $1,25(OH)_2D$ acts on distal nephrons to enhance calcium reabsorption and escalate bone resorption; the process by which osteoclasts break down bone and release calcium and phosphorus providing an additional source of mineral for maintaining blood calcium and phosphorus levels [45,66,67,69].

The Deficiency Syndrome – Rickets/Osteomalacia

Vitamin D deficiency can exert deleterious effects on the body throughout life. The established deficiency disease of vitamin D is

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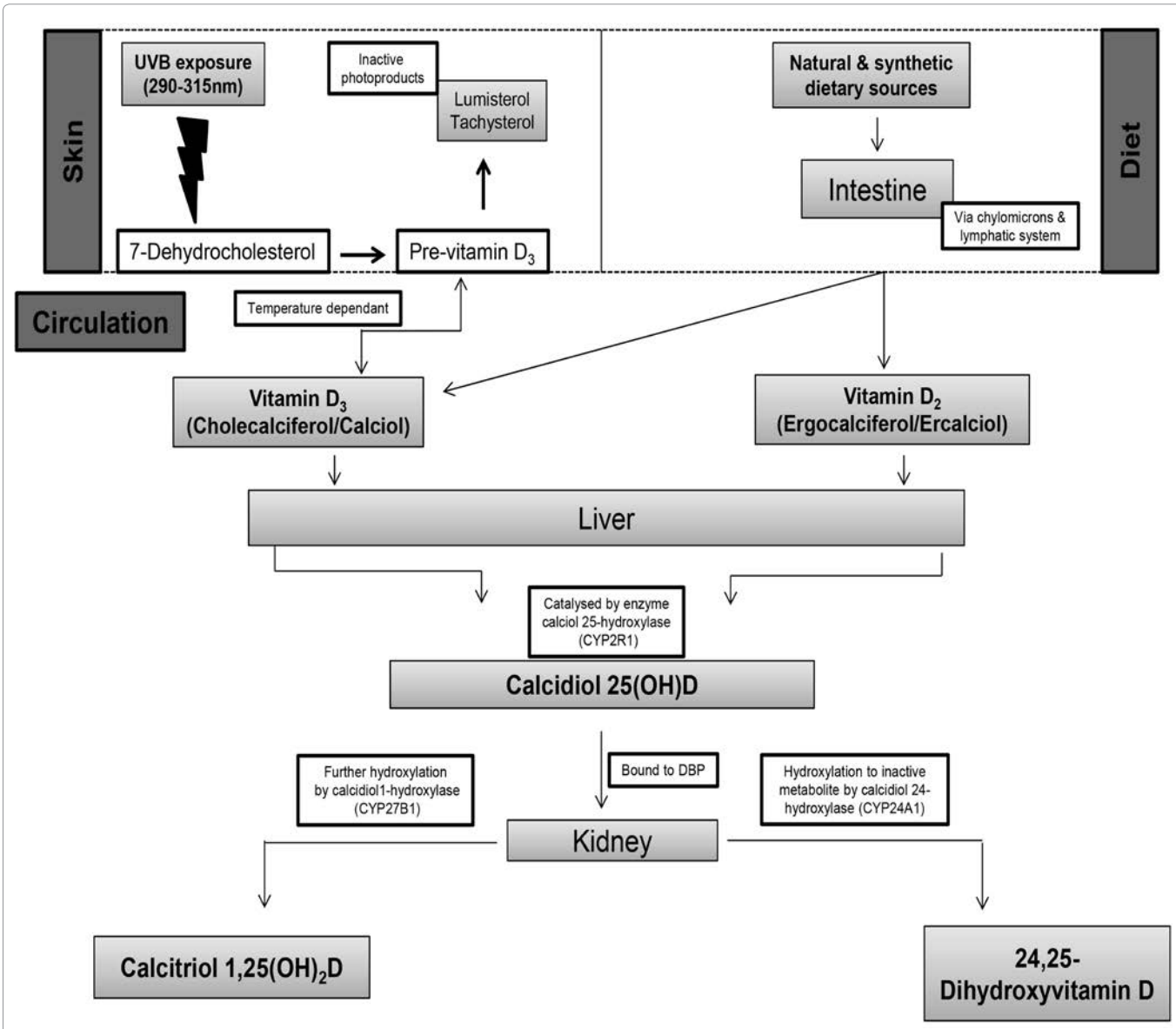

Figure 1: Schematic representation of the initial synthesis and beginning of the metabolism of vitamin D for skeletal and non-skeletal function. The figure shows the pathway for vitamin D synthesis from UVB exposure and the diet, which then continues into the circulation.

rickets, which causes a failure of mineralisation in the cartilaginous matrix of developing tissues as a result of calcium and phosphate malabsorption. Rickets is characterized by a widening at the ends of the long bones due to disorganization in the hypertrophy and maturation of chondrocytes. The lack of calcium in the bone causes the classic rachitic deformities – knock-knees or bowed legs [70]. It was in the mid-17th century that rickets was first recognized as a distinct endemic disease that arose as a consequence of the urbanization of England's population. Urban atmospheric pollution in the form of smoke and smog hindered seasonal vitamin D synthesis from the sun at northerly latitudes, increasing the rate of rickets [71].

Into the 20th century, further expansion in industrialization and migration in western Europe and the United States saw the spread of big-city slums and over-crowded impoverished living areas, causing UVR deprivation and nutrient deficits as a direct consequence. A high prevalence of rickets developed amongst infants subjected to this vitamin D inhibited environment. Atmospheric pollution absorbs essential UVB photons, and this compromises vitamin D production [72,73]. Early studies into rickets led to the discovery of the curative properties of cod liver oil and UVR therapy. In 1919, clinicians found that exposing infants to radiation from mercury vapour lamps for one hour, three times a week cured rickets via an increase in mineralization of the infant's skeleton [71]. Work by Hess and Unger in 1921 supported this finding, demonstrating that varied periods of exposure to sunlight showed increased calcification, a phenomenon that proved curative for rickets [74]. Vitamin D deficiency in adults causes a decrease in intestinal calcium absorption from 30-40% to 10-15%. This results in the softening of the bone matrix, and leads to osteomalacia, a condition which is similar to rickets in children, but is caused by demineralization rather than failure to mineralize bone in the first place [66]. In pregnant women, a deficiency results in hypocalcaemia and subsequently rickets in their child [75,76].

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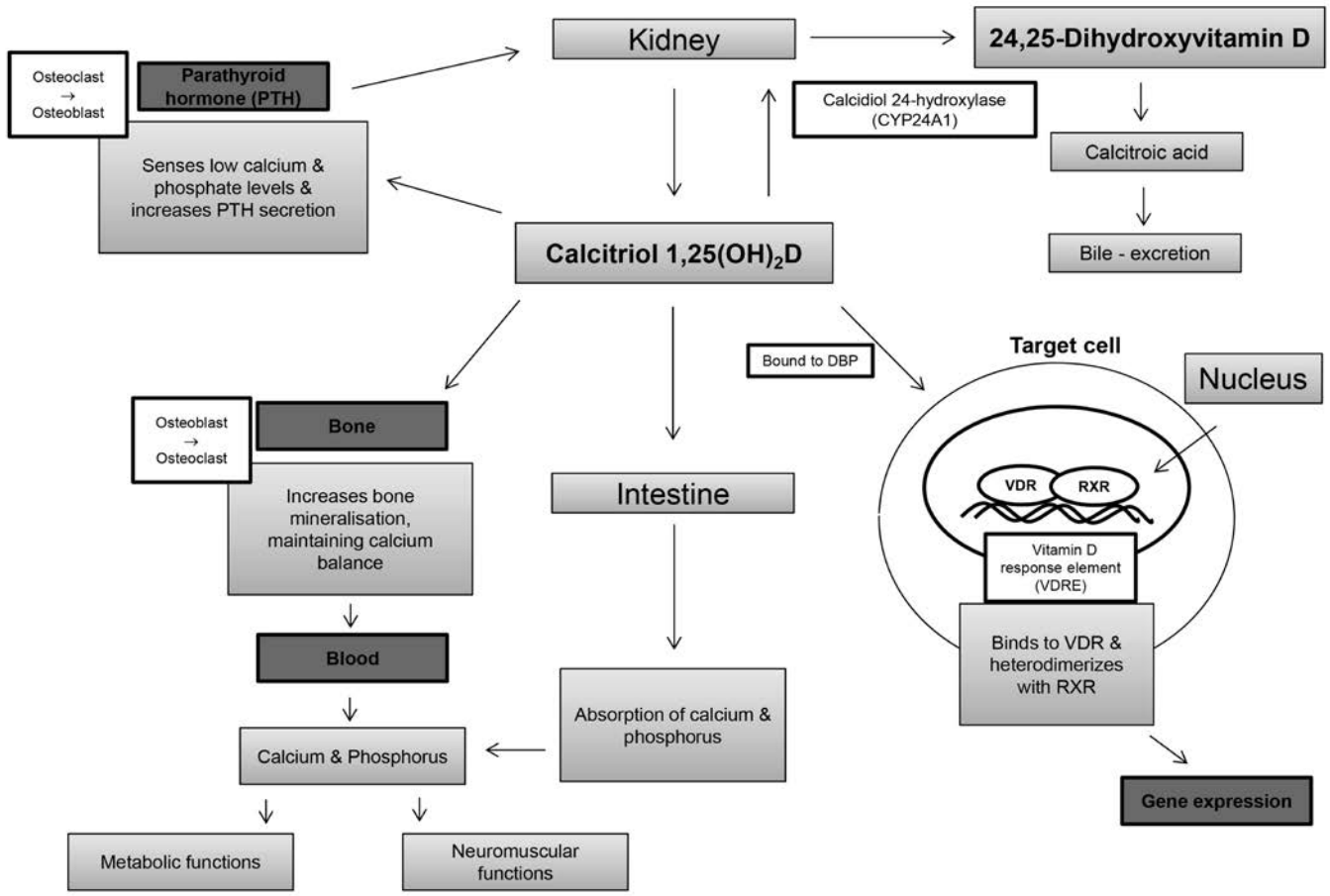

Figure 2: Schematic representation of the synthesis and metabolism of vitamin D from the kidney onwards. The figure illustrates the skeletal and non-skeletal functions of vitamin D, including those related to bone, calcium and phosphorus homeostasis, PTH regulation, inactivation of 24,25-dihydroxyvitamin D and activation of the VDR with RXR for gene expression.

Global Vitamin D Deficiency Rate

It has been estimated that 20-80% of European, United States and Canadian adults are deficient in vitamin D. Between 2001–2006, two-thirds of the United States population had sufficient vitamin D, defined by the Institute of Medicine as a serum 25(OH) D value of 50–125 nmol/l, while one-quarter were at risk of vitamin D insufficiency (serum 25(OH)D levels of 30–49 nmol/l), and 8% of vitamin D deficiency (serum 25(OH)D less than 30 nmol/l) [80]. The most widely recognised role for vitamin D is in relation to bone homeostasis. However, in 2011 Moreno et al. [81] reviewed the health effects of low vitamin D status and the extraskeletal effects of vitamin D. Of the major findings, it was found that low vitamin D concentrations were associated with all-cause mortality. This was observed following an examination of 18 independent vitamin D supplementation random controlled trials where the summary relative risk of mortality was 0.93 (95% CI 0.87-0.99) [81].

In the "Healthy Lifestyle in Europe by Nutrition in Adolescence" (HELENA) study; approximately 80% of the subjects were below the optimal 75 nmol/l level for adults. When analysed by gender, 22·2% of females had an adequate 25(OH)D concentration compared to 15·1% of males, while deficiency rates (25(OH)D <27·5 nmol/l), were of equal proportion in both genders (15%) [79]. More recently, 1006 adolescent participants within the HELENA study were assessed for body composition, biochemical markers, socioeconomic status, dietary intake, physical activity, fitness, sleep time, and a VDR genetic polymorphism. Results showed that season, latitude, fitness, adiposity, sleep time, and micronutrient supplementation were significantly associated with 25(OH)D concentrations. Of these findings, seasonal differences were the strongest predictor of the varying vitamin D status, with the highest concentrations observed in autumn following exposure over the summer period. Conversely winter was negatively associated with low vitamin D status [82].

Previous studies suggest the variation in European vitamin D status is a result of latitude, season and skin pigmentation [83]. Serum 25(OH)D levels are higher in those living in southern Europe than in northern Europe and higher in eastern Europe than in western Europe. In Norway and Sweden, high serum 25(OH)D levels are most likely due to high dietary intake of fatty fish and cod liver oil. While the opposing low serum 25(OH)D levels in Greece, Spain and Italy are due to the impact of skin pigmentation and behavioral effects of sunshine avoidance [83].

Interestingly, in far northern Europe, notably within the Arctic Circle/Lapland, people exhibit skin pigmentation darker than would be predicted on the basis of the UVMED in their habitats [57]. The UVR regime of these latitudes is comprised almost exclusively of UVA throughout the year, with virtually no UVB apart from small

doses during summer. Therefore, habitation within this latitude without reliance on a highly vitamin D rich diet of marine mammals and fish would be impossible. Much of the dietary vitamin D_3 is stored in body fat [84], denoting a possible evolutionary connection between the development of generous subcutaneous fat stores and vitamin D_3 storage in these populations. Therefore, selection pressure for depigmentation is relaxed because of their high vitamin D diet, with darker skin enabling protection from high levels of UVA as a result of direct solar irradiation and reflection from snow and ice [59].

A high variation in serum 25(OH)D levels also exists in Middle Eastern populations. In a study of 1210 Iranians, mean serum 25(OH) D concentrations were 20.6 nmol/l [85]. Lowest concentrations have been observed in elderly Saudi Arabians (mean concentration 9 nmol/l) [86], whilst studies of Turkish and Jordanian women have shown a strong relationship with decreased serum 25(OH)D levels and traditional clothing [87,88]. In Mongolia, very low levels were observed in children (7 nmol/l) and pregnant women (26 nmol/l) [89], while a study in China showed very low levels of serum 25(OH) D in young females in winter (12–13 nmol/l). In Malaysia and Japan, vitamin D status is closer to the recommended level [90,91].

Vitamin D Deficiency Rates in Australia

Although vitamin D deficiency is recognized as a global public health problem, its prevalence has recently been studied specifically in Australia, mainly because of Australia's high level of annual sun exposure. However, because of Australia's geographical size, large latitudinal range, and variable ozone layer, previous studies have shown that the prevalence of vitamin D deficiency varies throughout the states. In 2012, a sample of Australian adults (n=11,247) showed a serum concentration of 25(OH)D of 63 nmol/l (95% CI:59–67 nmol/l), with prevalence of deficiency (<50 nmol/l) in 31% of the population (22% men; 39% women). Deficiency was more common during winter and in subjects living in southern Australia (latitude >35°S) [92]. A similar study of 644 elderly subjects living in the eastern states of Australia (60-84 years), found a mean serum 25(OH) D concentration of 42 nmol/I, with 75% presenting a level of <50 nmol/l and 10% with <25 nmol/l [39]. A small study of Western Australian children found 4.4% were considered vitamin D-deficient (<50 nmol/l) and 36.3% insufficient in vitamin D (50–75 nmol/l) [93].

Little is known about the vitamin D status of the Australian Aborigines, although it is possible that the varying levels of skin pigmentation may influence vitamin D status. Studies regarding the vitamin D status of other highly-pigmented groups including African Americans [94-97], Indigenous Canadians [98]. Pacific Islanders and Maori's [99] have found them all to exhibit lower 25(OH)D levels compared to lightly-pigmented populations. Recently, a study in a South Australian Aboriginal population suggested vitamin D insufficiency (serum 25(OH)D level ≤60 nmol/l) was prevalent [100].

The biggest influence affecting vitamin D synthesis amongst the Australia population is the awareness of excessive sun exposure which can lead to sun damage and increased risk of skin cancer. In Australia, major public health messages have enforced strong sun protection measures including the use of sun protective factor (SPF) cream and protective clothing. This has created a dilemma whereby individuals avoiding UV exposure to reduce their risk of skin cancer, are also increasing their risk of vitamin D insufficiency and deficiency. The current recommendations relating to safe levels of sun exposure are discussed later in this review.

Lifestyle and lifecycle-related factors that can influence Vitamin D status

It has been suggested that elderly individuals exhibit lower circulating levels of 25(OH)D compared with young adults [101]. During the ageing process, the skin becomes less capable of synthesising vitamin D for a given quantum of UVB exposure which correlates with age-dependant decreases in epidermal concentrations of 7-dehydrocholesterol [102,103]. This has been reported in studies which simulated whole-body exposure to sunlight and compared circulating vitamin D concentrations in various aged participants [104]. Conversely, other studies suggest elderly individuals are just as efficient in maintaining 25(OH)D, but require more vitamin D to produce the increased 25(OH)D concentrations required to overcome the hyperparathyroidism associated with their decreased kidney function [105]. As we age, our kidneys become less able to produce the active metabolite $1,25(OH)_2D$, and the intestine becomes less capable of absorbing $1,25(OH)_2D$ to regulate calcium [105]. Lifestyle factors of the elderly such as the type of accommodation, mobility problems, and wearing covered clothing when outside have also been suggested to play a role in vitamin D deficiency [38,106]. Recently, studies have looked at clothing styles which conceal skin from UVR as contributors to vitamin D deficiency, especially in veiled female minorities in high latitudes [107,108]. Studies in Australia have demonstrated that veiled women especially those with dark skin pigmentation are at high risk of vitamin D deficiency due to their cultural practices as their clothing blocks UVB and increased melanin pigmentation reduces the cutaneous production of vitamin D. This is also evident in veiled pregnant women and their unborn children [38,109].

Another lifestyle-related factor which has been examined is veganism and vitamin D status.

A vegan diet involves only consuming plant-based foods and avoiding all animal derived products. By restricting animal product consumption, vitamin D_3 biosynthesis via sun exposure becomes the body's primary source. This can create problems for vegans living at high latitudes where the number of hours of available UVB is limited. Evidence indicates there may be a link between reduced vitamin D and calcium levels in the body and low bone mineral density (BMD), a major risk factor for osteoporosis. Therefore there may also be a connection between a vegan diet, low BMD and increased risk of osteoporosis, which have been discussed recently [110-111]. Considerable evidence shows vitamin D synthesis, metabolism and storage is influenced by adiposity, and that obesity is associated with a low circulating 25(OH)D level in the body [112-114]. Explanations and directions to causality, however, remain somewhat controversial. Several possible theories exist; since vitamin D is a fat-soluble vitamin and stored in adipose tissue, there is a larger storage capacity for vitamin D in obese individuals, creating lower circulating 25(OH) D concentrations [13]; metabolic clearance and uptake of vitamin D is enhanced by adipose tissue [115]; production of $1,25(OH)_2D$ is enhanced in obese individuals and therefore higher concentrations exert negative feedback on the synthesis of 25(OH)D [116]. The identification of the VDR in a number of tissue types including muscle tissue, has led to an increased number of studies involving the examination of vitamin D status with body composition, muscular strength and cardiorespiratory fitness. Previous evidence has suggested that a vitamin D deficiency is linked with muscle weakness, hypotonia, and prolonged time to peak muscle contraction, along with prolonged time to peak muscle relaxation [117]. One study

aimed to determine how body composition and physical fitness are related to 25(OH)D levels in European adolescents. Their results found that for males, maximum oxygen consumption (VO_2max) and body mass index (BMI) were independently associated with 25(OH) D concentrations ($p < 0.01$ and $p < 0.05$, respectively). In the case of females, a significant association was found between handgrip strength and 25(OH)D concentrations ($p<0.01$). Interestingly, adolescents exhibiting a lower BMI (<18.5) and a high fitness score (previously described in [118,119]) presented significantly higher 25(OH)D levels than those at lower fitness score in the other BMI groups ($p<0.05$) [117].

In 2012, 100 Spanish adolescents were examined to evaluate the influence of 25(OH)D on bone mineral content, taking into account the influence of body composition, sex, age, Tanner stage, season, calcium and vitamin D intake, physical fitness and physical activity. Compared with the physically inactive group, the physically active group exhibited 25(OH)D concentrations which independently influenced total and leg bone mineral content after controlling for multifactorial phenotypes ($p < 0.05$, and $p < 0.05$, respectively) [120].

From this it seems plausible to suggest that a low serum 25(OH) D status may be associated with adverse consequences relating to the human musculoskeletal, innate immune, and cardiovascular systems. Previous evidence has shown that cardiovascular and muscular fitness are significant markers of health status [12]. Furthermore, evidence of this during childhood and adolescence, along with a healthier body composition are associated with a healthier cardiovascular profile later in life and with a reduced mortality risk [117]. It is for these reasons that further studies relating to vitamin D concentrations and physical fitness, physical activity, and body composition are important, providing a more thorough understanding of vitamin D and long-term health outcomes.

UV radiation, vitamin D and health – Finding the right balance

The health consequences of both excessive and inadequate solar UVR exposure are the subject of much debate. This is largely because of its role in promoting skin cancer risk as well as a beneficial role in vitamin D synthesis. This represents an interesting challenge to health professionals and policy makers. Solar UVR is a recognised carcinogen and known risk factor for various skin cancers, and although sun-safety campaigns have had some impact, 2-3 million non-melanoma skin cancers and 132,000 malignant melanoma (MM) skin cancers occur globally each year [122]. Skin cancer rates in Australia are alarming; two in three Australians will be diagnosed with skin cancer by the time they reach the age of 70. Trends in incidence rates along the eastern side of Australia have shown a south-north gradient (Victoria lowest incidence, Queensland highest incidence) [123].

The typical skin cancers associated with UVR exposure are basal cell carcinoma (BCC) squamous cell carcinoma (SCC) and MM. BCC and SCC, are more common and account for 70-85% of all skin cancers, usually in chronically sun-exposed areas of the skin, including backs of the hands, face or ears. Australia has amongst the highest incidence of MM (the most dangerous form of skin cancer) in the world [123], and excluding BCC & SCC, MM is the most common cancer in Australia in those aged 15-44 years [124]. Overall the median age of occurrence is 52 years, much earlier than most solid tumours [125]. Survival following metastatic spread is approximately 6-9 months, with a 5-year survival rate less than 5% [125].

All humans, especially those lightly pigmented or whose occupation or lifestyle exposes them to excessive amounts of sunlight, are potentially susceptible to its deleterious effects. But whilst there are numerous deleterious effects and consequences to the human body from chronic exposure to UVR, such as cellular damage/ageing skin or skin cancer, the obligatory requirement for vitamin D synthesis cannot be ignored. Public health officials and dermatologists advise the use of protective clothing and SPF sunscreen. However, sunscreen can prevent the photo-conversion of 7-dehydrocholesterol to pre-vitamin D3, a phenomenon established in a number of studies. Matsuoka et al demonstrated on several occasions that application of the common ingredient in sunscreen, para-amino benzoic acid, inhibits vitamin D production, both in vivo and in vitro [50,126,127]. Despite this, sunscreen use has also been associated with increased serum 25(OH)D) levels [128], while a small South Australian study found no difference in serum 25(OH)D levels between sunscreen users and placebos [129]. Broad spectrum sunscreens protect the skin against UVA (320–400 nm) and UVB (290–320 nm) radiation. Radiation in the UVB range is responsible for skin carcinogenesis as well as conversion of 7-dehydrocholesterol into previtamin D_3. In a further study, the application of sun protection factor SPF 8 has been reported to reduce the amount of vitamin D synthesised from a given dose of UV by more than 95% [127] also confirmed in another study [130]. It is thus not surprising that concerns have been raised regarding use of sunscreens for skin cancer prevention with respect to the unwanted side effect of vitamin D deficiency.

Interestingly, the finding that an increase in serum 25(OH) D levels occurs with sunscreen use[128], may stem from altered behavioral patterns. That is to say sunscreen use may lead to more frequent and longer exposure time to UVR [131].

A conflict therefore arises from the use of sunscreen; achieving the correct balance between vitamin D synthesis and minimizing DNA damage leading to cancer is the key balance that needs to be achieved. Furthermore, there are other influences which can modify the level of vitamin D synthesis according to a given quantum of UV exposure. These include obesity, age, season, and latitude.

Early lifecycle factors related to vitamin D and health

Human response to geophysical cycles: The activity of life on earth is strongly dominated by geophysical cycles, and although humans have the ability to procreate all year round, studies have shown a significant variation in conception/birth rate over the year. The mechanisms driving this seasonal variation in conception/birth rate remains a matter of debate, but suggestions involving environmental factors such as temperature and photoperiod have been proposed [132]. A strong latitudinal cline in the timing of human reproduction from the poles to the equator exists, and may be related to temperature, i.e. highest annual temperatures generally correlate with highest reproduction rates [132]. Photoperiod (day length) may also be an underlying factor, with seasonality in human reproduction weaker during the post-industrialization era, which may have caused increased sheltering from the sun, and hence, vitamin D synthesis [132,133]. Similarly, like the seasonal variation in conception/birth rate, the predisposition to certain disease or phenotypes, follows a seasonal pattern, some of which may have links with vitamin D deficiency. For example, a recognized correlation between the incidence of MS and dietary vitamin D intake/exposure to UVR [27]. Other disorders associated with vitamin D that are known to have seasonality linked within the aetiology include asthma [134,135], crohn's disease [21], autism [136], neural tube defects

[137], schizophrenia [138], Alzheimer's [139], narcolepsy [140] and Parkinson's disease [141].

Infertility including in vitro fertilization and vitamin D: Evidence suggests that vitamin D also modulates reproductive processes in women, as the VDR is distributed and expressed across various reproductive tissues including in ovarian cells, the placenta, the pituitary gland and the endometrium [14]. Major causes of female infertility include polycystic ovarian syndrome (PCOS) and endometriosis, both of which have been previously linked with lower 25(OH)D levels and deficiency [142-144].

With respect to males, the VDR and vitamin D metabolizing enzymes are expressed in spermatids, vesicles within the caput epididymis, and glandular epithelium of cauda epididymis, seminal vesicle, and prostate [145]. Studies have shown that male infertility can also affect reproductive success by up to 30-40% [146], with overall semen quality decreasing, possibly due to exposomal factors [147]. Evidence has also suggested that male ageing resulting in reduced testosterone levels may be associated with androgen and vitamin D metabolism [148,149]. Studies looking at the relationship between vitamin D status and *in vitro fertilization* (IVF) outcome have been widely investigated but have produced inconsistent results [14,150]. For example, one study found sufficient stores of vitamin D translate into improved reproductive success following IVF, notably in follicular fluid [151]. In contrast, another study found no associations with vitamin D levels and IVF outcome [152].

A small number of studies have observed similar seasonal variations in IVF success rates with that of natural conception rates. Possible theories to explain this phenomenon include exposomal and/or endogenous factors. One study in particular found a significant seasonal variability in the fertilization rate and embryo quality, with highest rates observed during spring and lowest during autumn [153,154].

Pregnancy, lactation and vitamin D: Throughout the lifecycle, essential nutrients are required for specific functions. Vitamins in particular, are considered essential nutrients as they are vital for human growth, development and functioning [155].

The elaboration of the developing embryo and foetus during gestation, and later changes during early infancy involve numerous cellular processes. Maternal vitamin D status is integral to normal foetal development, as all vitamin D received by the foetus is provided by the mother. The ability of maternal 25(OH)D to readily cross the placenta, and to be metabolised to 1,25(OH)D by the foetal kidneys, subsequently enables neonatal serum 25(OH)D status to be approximately 50-70% of the overall maternal serum 25(OH)D concentration at birth [156-159]. During pregnancy, a woman needs to support not only her own vitamin D requirement, but also that of the developing foetus and placenta. Furthermore, changes to calcium homeostasis due to the requirements of the foetal skeleton and overall growth, demonstrate the importance of vitamin D at this critical phase of the human lifecycle. Following parturition, placental supply of all nutrients including vitamin D ceases. Mother's milk then takes over delivery of all necessary nutrients. Breast milk is considered the ideal infant nutrient source. Numerous studies have examined the influence of breast-feeding on aspects of growth, mental development, immune-related effects, and non-communicable diseases. Despite this, the concentration of vitamin D in human breast milk has actually been found inadequate for the infant's needs. Therefore, after birth, the adequacy of vitamin D for an exclusively breastfeeding infant is dependent upon its exposure to sunlight. In fact, vitamin D levels are usually considered insufficient to prevent the deficiency disease rickets in exclusively breast-fed infants if sunlight exposure is limited [160]. Studies surrounding optimal supplementation levels for mothers and infants have found 500-1000 IU/day provides no significant improvement in vitamin D levels of lactating mothers, but high-dose vitamin D supplementation (4000 IU/d and 6400 IU/d) increases vitamin D milk concentration providing adequate levels to their offspring [161,162].

Vitamin D adequacy throughout childhood and adolescence is important with implications for lifelong health. Risk factors which may predispose children and adolescents to vitamin D deficiency, including rickets, are geographical location [163], highly melanised skin [164,165], lack of dietary supplementation, or low intake of fortified foods [166,177], female gender [168], and diseases associated with malabsorption [169,170].

Late Lifecycle Factors Related to Vitamin D and Health

At the later stages of the human lifecycle, vitamin D plays an important role in the functioning, regulation and maintenance of numerous biological mechanisms in the body. The elderly population is particularly at risk for a number of degenerative disorders related to low serum 25(OH)D levels. With increasing age, UVR exposure usually decreases due to changes in lifestyle and less outdoor activity. Diet can also become less varied, and low in vitamin D content. Most significant, however, is a decrease in the ability to synthesise cutaneous vitamin D after UVR exposure due to atrophic changes in the skin and a reduced amount of 7-dehydrocholesterol [103]. It has been suggested that the level of previtamin D_3 produced in the skin in an 8-18 year old is more than 2-fold the capacity of a 77-88 year old [103]. Furthermore, it has been found that skin thickness also decreases linearly with age after the age of 20 years [171]. Most adults between 19-50 years were originally able to obtain adequate vitamin D from casual UVR exposure daily from the sun. However, this age group is now at equal risk of vitamin D deficiency due to reduced levels of time spent outdoors and aggressive sun protection measures. Ages 71 years and older are at an even higher risk of vitamin D deficiency due to the reasons alluded to above [66].

Significant evidence supports an inverse association between low serum 25(OH)D levels and increased risk to skeletal and non-skeletal related degenerative disorders, such as confirmation of vitamin D in the pathogenesis of CVD and hypertension [172-176]. Vitamin D elicits various effects on endothelial cells and vascular smooth muscle cells of vessel walls, all of which express the VDR. Increased activation of the renin-angiotensin-aldosterone system, which is the main regulator of electrolyte and volume homoeostasis, contributes to the development of arterial hypertension. It has been established that $1,25(OH)_2D$ exerts a vasculoprotective effect by decreasing endothelial adhesion molecules, by increasing the activity of nitric oxide synthase, and through its anti-inflammatory properties [45-172]. Serum 25(OH)D levels less than 75nmol/l have been associated with significant increases in the prevalence of hyperlipidemia, peripheral vascular disease, coronary artery disease, myocardial infarction, heart failure, stroke and diabetes [177].

The relationship between vitamin D deficiency and type 1 diabetes mellitus (T1DM) has been extensively examined [178,179], with studies showing that vitamin D treatment can improve and even prevent T1DM [180,181]. These effects have been mainly attributed

to the immunomodulatory actions of vitamin D [178]. However, less is known on the association between vitamin D and type 2 diabetes mellitus (T2DM). Vitamin D deficiency causes decreased insulin secretion, while adequate levels improve β-cell function and glucose tolerance [182]. Genetic variations in the VDR and DBP have also been associated with glucose tolerance and insulin secretion [183,184], and risk for T2DM [185,186]. Since vitamin D controls insulin receptor gene expression and insulin secretion, it may be an exposomal factor for the pathogenesis and development of T2DM [184]. Colorectal cancer (CRC) is one of the most common cancers worldwide, although it has been reported that CRC morbidity is greater in northern latitudes, possibly due to lower sun exposure. Epidemiological studies have suggested that dermal vitamin D synthesis mediated by sunlight may protect against CRC, with several reports finding a decreased risk of disease with higher serum levels of vitamin D or increased dietary vitamin D intake [187-191]. The evidence supports a role for vitamin D in the development and progression of cancer and selected studies are provided in (Table 2).

Vitamin D and health – Osteoporosis, bone health, falls: Osteoporosis is a severe condition which causes a gradual loss of bone density, resulting in rarefied bone tissue and is associated with

Disorder	Study Format	Influence/ effect of vitamin D	Reference
Hypertension	1,484 women (32-52 yrs) without hypertension at baseline, were analyzed for any associations between plasma levels of 25(OH)D and risk of hypertension.	Positive: Lowest quartile (15.5-52.4 nmol/l) compared to highest (80.6-223.4 nmol/l) of 25(OH)D had an odds ratio for hypertension of 2.21 (95% CI, 1.57-3.12; p<0.001).	[173]
	1,055 women and 405 men (40-74 yrs) were examined for plasma 25(OH)D levels in association with blood pressure.	Positive: Inverse associations between 25(OH)D level and blood pressure amongst men only (p<0.05).	[174]
Cardiovascular disease	1,006 adults (≥65 yrs) were examined for serum 25(OH)D levels and cardiovascular disease mortality risk.	Subjects in lowest quartile (<26.2 nmol/l) had increased risk of cardiovascular disease mortality (HR 2.64; 95% CI, 1.14-4.79; p=0.02).	[175]
	9578 subjects at baseline and 5469 at 5-yr follow-up were assessed for 25(OH)D levels in association with CVD mortality.	25(OH)D concentrations <30 nmol/l were associated with increased cardiovascular mortality risk (hazards ratio 1.39; 95% CI, 1.02-1.89).	[176]
Diabetes	524 non-diabetics (40-69yrs at baseline), were assessed for serum 25(OH)D and various diabetic risk markers at baseline and at 10 years of follow-up.	Baseline 25(OH)D was inversely associated with 10-year risk of hyperglycaemia (fasting glucose p = 0.019; 2-h glucose: p = 0.006), insulin resistance (fasting insulin p = 0.010; and metabolic syndrome z score p = 0.048).	[260]
	1,000 insulin-requiring diabetics and matched controls were examined between 2002–2008 for serum 25(OH) D levels.	Serum 25(OH)D concentrations were lower in subjects who developed diabetes (62.2 nmol/l) than controls (72.5 nmol/l) (p< 0.0001). A 3.5-fold lower risk was associated with a serum 25(OH)D concentration ≥ 60 nmol/l.	[261]
Stroke	464 women who developed ischemic stroke and 464 controls were examined for 25(OH)D level status.	Results found lower 25(OH) D levels associated with an elevated risk of ischemic stroke when comparing women in the lowest versus highest tertiles odds ratio 1.49 (95% CI, 1.01-2.18; p = 0.04).	[262]
	Plasma 25(OH)D levels were measured in 10,170 individuals. After 21 years of follow-up, 1,256 and 164 persons developed ischemic and haemorrhagic stroke, respectively.	Results found decreasing plasma 25(OH)D concentrations were associated with increasing risk of ischemic stroke using stepwise analysis (p≤ 0.002).	[263]
Osteoporosis	1,292 menopausal women with osteoporosis had their serum 25(OH) D levels assayed and analysed into four 25(OH)D groups (30, 50, 75, and 80 nmol/l).	90.3% of women with osteoporosis had serum 25(OH)D levels lower than 80 nmol/l and 46.2% lower than 50 nmol/l.	[264]
	1,311 older men and women were examined to determine whether low serum 25(OH)D levels were associated with osteoporotic fractures.	Results found a significant relationship between serum 25(OH)D levels lower than or equal to 29.95nmol/l and fractures in subjects 65–75yrs (HR 3.1; 95% CI, 1.4-6.9).	[265]
Multiple Sclerosis	98 multiple sclerosis patients, 17 healthy age-sex-matched controls were examined for associations with serum 25(OH)D concentrations.	Serum 25(OH) D concentration was significantly lower in patients with multiple sclerosis, especially those categorised as having severe multiple sclerosis, compared with controls (p = 0.047).	[26]
	Dietary vitamin D intake (food and supplement) was examined in relation to risk of multiple sclerosis in two large cohorts of women (n = 92,253 & 95,310).	Intake of vitamin D from supplements was inversely associated with risk of multiple sclerosis; the relative risk comparing women with intake of ≥400 IU/day against no supplement intake was 0.59 (95% CI, 0.38-0.91; p = 0.006).	[266]
Obesity	410 women, with body mass index ranging from 17–30 kg/m^2 underwent a total body scan using dual-energy x-ray absorptiometry examining total body fat and nonfat soft tissue weight to determine % body fat. Serum 25(OH) D was measured.	Level of serum 25(OH)D inversely correlated with percentage body fat (correlation −0.13; p = 0.013) after adjusting for race, age, season, and dietary vitamin D intake.	[267]
	Plasma concentrations of 25(OH) D were determined and body composition was evaluated by bioelectrical impedance in a group of 43 women with morbid obesity, 28 non-morbidly obese, and 50 non-obese women matched for age for the association between 25(OH) D and body fat.	Morbidly obese women showed lower 25(OH)D concentrations compared to non-morbidly and non-obese women (p = 0.001). 51% of morbidly obese women had vitamin D deficiency [25(OH) D <38 nmol/l] compared to 22% of non-obese patients, (p = 0.004). Correlation analysis found 25(OH)D inversely associated with weight (r=-0.41, p = 0.001), body mass index (r=-0.432, p = 0.001), body fat (r=-0.53, p = 0001).	[12]
Colorectal cancer	16,818 subjects (from 1988–1994 to 2000) were examined for the relationship between serum 25(OH) D levels and total cancer mortality and specific cancer mortality.	Results found colorectal cancer mortality was inversely related to serum 25(OH)D level, with levels 80 nmol/l or higher associated with a 72% risk reduction (95% CI = 32% to 89%) compared with lower than 50 nmol/l, p = 0.02.	[190]
	Female only (46-78 yrs) study identified 193 colorectal cancer cases, diagnosed up to 11 years after blood collection between 1989-2000. Two controls were matched per case.	Results found a significant inverse linear association between plasma 25(OH)D and risk of colorectal cancer (p = 0.02). A protective effect was observed for higher 25(OH)D concentrations in distal colon and rectum cancers (p = 0.02).	[191]

Breast cancer	1,800 early breast cancer patients had their 25(OH) D measured by radioimmunoassay and tumour characteristics assessed for rates of overall survival, disease-specific survival , and disease-free interval.	Lower 25(OH)D serum levels were significantly associated with larger tumour size at diagnosis (p = 0.0063). Serum 25(OH)D was significantly correlated with breast cancer-specific outcome in postmenopausal women [hazards ratios for 25OHD >75 mmol/L versus ≤75 mmol/L were 0.15 (p = 0.0097) and 0.43 (p = 0.0172) for disease-specific survival , and disease-free interval, respectively.	[268]
	194 women who underwent breast cancer surgery and 194 cancer-free controls had 25(OH)D levels measured between 2009-2010.	Significantly lower 25(OH)D levels were found in breast cancer cases compared with cancer free controls (breast cancer: 82.29mmol/L vs. cancer free: 93.35 nmol/l; p = 0.02).	[269]
Pancreatic cancer	118,597 participants were followed from 1986 to 2006. 25(OH)D levels were analysed and examined in relation to pancreatic cancer risk.	During 20 years of follow-up, 575 pancreatic cancer cases were identified. Higher 25(OH)D levels were associated with a significant reduction in pancreatic cancer risk (p = 0.001).	[270]
	A study of male smokers (50-69 yrs) were examined to determine whether serum 25(OH)D concentrations were associated with lower pancreatic cancer risk. 200 pancreatic cancer cases (between 1985-2001) were matched with 400 controls.	Results found higher serum 25(OH)D concentrations were associated with a 3-fold increased risk for pancreatic cancer (highest versus lowest quintile, >65.5nmol/l vs. <32.0 nmol/l); odds ratio, 2.92; 95% CI, 1.56-5.48, (p = 0.001).	[271]
Prostate cancer	622 prostate cancer cases and 1,451 matched controls were examined for serum 25(OH)D levels.	Results found both low (≤19 nmol/l) and high (≥80 nmol/l) serum 25(OH)D concentrations were associated with higher prostate cancer risk.	[272]
	After 13-yr follow-up of 19,000 middle-aged men, 149 prostate cancer cases were identified. Subjects and matched controls were analysed for serum 25(OH)D levels.	Results found men with 25(OH)D concentrations below the median had an odds ratio of 1.7 compared to men above the median level. Prostate cancer risk was highest among men <52 yrs and low serum 25(OH)D (odds ratio 3.1 non-adjusted and 3.5 adjusted).	[273]

Table 2: A selected list of recent studies that implicate vitamin D status with a range of chronic degenerative disorders.

advanced ageing due to increased bone loss. Females are at significant risk of osteoporosis post-menopause due to the decrease in oestrogen levels. Oestrogen stimulates bone remodelling, and thus a reduction in oestrogen status results in higher bone losses through increased bone resorption [192]. Other risk factors linked to osteoporosis include fragility or low impact fracture, low body weight, smoking, use of corticosteroid medication and decreased physical activity (especially weight bearing) [193]. Globally, it is estimated that one in three women and one in twelve men, aged 50 years and older, will suffer from osteoporosis [194]. In Australia, there are currently 1.2 million people affected by osteoporosis, with many undiagnosed. Without intervention, osteoporosis rates are anticipated to increase to 3 million by 2021, a result of an ageing population [195]. Treatment and ultimately prevention of osteoporosis usually involves vitamin D and calcium supplements. It has been proposed that the dose of vitamin D should be targeted to maintain serum levels >75 nmol/l, obtained via a regular dose of 1,000 IU/day [196]. Calcium supplementation is recommended at a dose of 1.2 gm/d [197]. However, recent concerns of potential cardiovascular risks associated with calcium supplementation have altered the practice by highlighting the importance of dietary calcium and of decreasing the recommended calcium dose to 50% [198]. Despite this, other studies have shown a protective effect of calcium [199]. Two studies highlighting the significance of vitamin D in the prevalence of osteoporosis can be found in (Table 2).

Vitamin D Molecular Biology and Human Health in the Context of Degenerative Disorders

The role of vitamin D in cancer aetiology has also been studied widely, as Vitamin D functions to decrease cellular proliferation, increase apoptosis and inhibit invasion, migration, metastasis and angiogenesis [200-202]. The possible role of this vitamin in tumour growth and aggression has been linked to numerous case-controlled studies relating to pathways involving VDR genes. The molecular genetics of vitamin D are also significant in risk for various cancers and several VDR single nucleotide polymorphisms (SNP) have been examined with respect to CRC risk [203-208], prostate cancer [209-218] breast cancer [219-227], MM and SCC [228-234]. A selection of studies regarding VDR SNPs and cancer are given in Table 3. In the last decade, vitamin D has also been studied in relation to several autoimmune diseases, including MS. In vitro, this vitamin is a potent immune modulator, capable of ameliorating, and possibly curing animal models of MS [235]. SNPs in the VDR gene also appear to influence the vulnerability to bone fragility, disability and deformity. Extensive reviews have revealed a growing importance of the VDR in association with bone disorders [236-240]. Details of these studies are listed in (Table 3).

Vitamin D and the genome

To obtain vitamin D, the body is dependent upon dietary sources and more so synthesis from UV exposure to the skin. It is firmly recognized that the major function of vitamin D is the maintenance of calcium and phosphorus homeostasis, supporting skeletal health. However in recent years, vitamin D metabolism and VDR genetics have been increasingly examined. Vitamin D action is mediated by the nuclear VDR receptor, and while 25(OH)D may bind to the VDR, $1,25(OH)_2D$ is the main ligand that induces activation [241].

After undergoing two hydroxylations the newly formed $1,25(OH)_2D$, which circulates bound to the DBP, reaches the target cell. After entering the cell, the VDR is able to form a heterodimer with the RXR following binding by 9-cis-retinoic acid. In the nucleus, this heterodimer recognises and binds in complex with a transcription factor to a VDRE in promoter regions of vitamin D target genes, enabling the execution of transcriptional effects [242,243]. The Entrez SNP database of the National Centre for Biotechnology Information lists over 2250 polymorphisms within the VDR gene. Of these, 1867 have an active human ref SNP (RS) and 80 have been cited in PubMed. The VDR gene is located on chromosome 12 (12q13.11) and contains 8 introns and 9 exons. The first exon contains a promoter region of the gene, which has the ability to generate multiple tissue specific transcripts. The DNA binding domain occurs on exon 2-3, whilst exon 6-9 contains the ligand binding domain [244]. Located at the 3'-end of the gene are the ApaI, BsmI and TaqI polymorphisms. Both ApaI (G>T substitution) and BsmI (A>G substitution) are restriction fragment length polymorphisms (RFLP) located at the intron between exon 8-9. The ApaI and BsmI RFLP are considered

Disorder/outcome	25(OH)D/ calcium influence	VDR SNP	Decreased risk/protective effect/risk factor	Ref
Prostate cancer		*BsmI*	Protective effect– BB & Bb genotypes	[214]
	25(OH)D-Low	*BsmI*	Risk factor– B allele	(215)
		TaqI	Risk factor– T allele	[216]
		FokI; Cdx-2	Risk factor– ff genotype; GA & AA genotype	[217]
		FokI	Risk factor– ff genotype	[213]
	25(OH)D-High	*TaqI*	Risk factor– t allele	[218]
Breast cancer		*FokI*	Risk factor– ff genotype	[221,222]
		BsmI	Risk factor– bb genotype	[223,224]
		ApaI; TaqI	Risk factor– a allele; T allele	[226]
		ApaI	Risk factor– AA genotype	[227
	25(OH)D-Low	*BsmI*	Risk factor– bb genotype	[225]
	Calcium-High	*BsmI*	Decreased risk– bb genotype	[274]
Colorectal cancer		*Tru91*	Decreased risk– Uu & uu genotypes	[203]
		ApaI	Risk factor– aa genotype	[205]
		FokI	Risk factor– Ff & ff genotypes	[206]
	25(OH)D-Low	*TaqI*	Risk factor– TT genotype	[207]
	25(OH)D-Low	*BsmI*	Decreased risk– BB genotype	[208]
Basal or squamous cell carcinoma		*FokI*	Risk factor– ff genotype	[229]
		TaqI	Risk factor– Tt genotype	[230]
	25(OH)D-High	*BsmI*	Risk factor– BB genotype	[231]
Malignant melanoma		*A1012G*	Risk factor– A allele	[232]
		FokI	Decreased risk– F allele	[233]
		TaqI; FokI	Decreased risk– Tt & tt genotypes; Risk factor– Ff genotype	[234]
Multiple Sclerosis		*BsmI; ApaI*	Risk factor– b allele; A allele	[236]
		ApaI	Risk factor– A allele	[237]
		TaqI; ApaI	Risk factor– t allele; A allele	[238]
		Cdx-2	Risk factor– G allele	[239]
Osteoporosis		*Cdx-2*	Protective effect– A allele	[240]
		BsmI	Risk factor– BB genotype	[275]
		ApaI; BsmI; FokI; TaqI	Risk factor– aa genotype; bb genotype; FF genotype; TT genotype	[276]

Table 3: A selected list of some known VDR nutrient-gene interactions and their clinical correlates.

to be silent SNPs, as they do not change the amino acid sequence of the encoded VDR protein [244,245]. They may, however, alter gene expression through regulation of messenger RNA [235,245].

The VDR gene TaqI (T>C substitution) is a RFLP at codon 352 in exon 9 of the VDR gene, and depending on the absence or presence of a TaqI restriction site in each allele, products are digested into two fragments of 495 and 245bp (T allele: absence of a restriction site) or three fragments of 290, 245 and 205 bp (t allele: presence of the restriction site). Individuals are classified as one of the following genotypes TT; Tt or tt [245]. The FokI polymorphism (T>C) substitution is situated at the start of the codon in exon 2 of the VDR gene and is the fourth polymorphic gene in this region [65]. FokI can be detected by RFLP using the FokI restriction enzyme, altering an ACG codon located ten base pairs from the translation start codon, and resulting in the addition of a start codon. If translation is initiated at this alternative site, the generation of an extended VDR protein of 427 amino acids occurs; referred to as the f allele. The f allele exerts much lower transcriptional activity than the F allele, which is 1.7-fold more active [235,244,245]. Studied to a lesser extent is the VDR polymorphism Tru91 (G>A substitution) within the intron 8 region [203,245]. Other polymorphisms in the 1A promoter region; Cdx-2, A1012G and G1520C have also recently been reported on, although studies mostly focus on these polymorphisms at the 3'-end of the gene [246].

Vitamin D and epigenetic modification: Epigenetics is a phenomenon that affects gene expression without altering the genomic sequence. DNA methylation is vital as an epigenetic effector of gene expression, DNA synthesis and epimutations. Errors in the epigenetic process or epimutations represent epigenetic silencing of a gene that is not normally silenced or epigenetic activation of a gene that is normally silent [247]. Epidemiological research has highlighted many different mechanisms that occur in utero and in early-life such as DNA methylation, which heavily impact human health later in life [248]. Recently, demonstrations have shown that impairment of intrauterine growth and development are connected to increased susceptibility to disease in adult life, a paradigm referred to as foetal programming or developmental origins of health and disease [67]. DNA methylation is an epigenetic occurrence which occurs on cytosine bases at the carbon-5' position in CpG nucleotide residues [247]. Other than nutrients such as folic acid and vitamin B12, which act directly as methyl –group donors, epigenetic activity of vitamin D is mediated via interaction with the VDR. Additionally, this may be related to expression of the key enzymes calcidiol 1-hydroxylase (CYP27B1) and calcidiol 24-hydroxylase (CYP27A1). Both of these are encoded by cytochrome P450 genes, and are involved in the metabolism of vitamin D_3 to 25(OH)D and 1,25$(OH)_2$D respectively.

DNA methylation is necessary for regulated embryogenesis and early foetal growth to ensure optimal homeostasis and life-long health.

Impairment of this via an inadequate maternal diet, including one with low vitamin D may possibly provoke pediatric developmental diseases and illness later in life [66]. The active form of vitamin D, $1,25(OH)_2D$ has been shown to be epigenetically active, as the gene encoding the CYP27B1 (which completes the final step from 25(OH) D to $1,25(OH)_2D$), can be repressed by epigenetic mechanisms at its promoter site, mediated by $1,25(OH)_2D$ levels [67]. Furthermore, it has been shown that the 24-hydroxylase, which is responsible for the degradation of $1,25(OH)_2D$ is under epigenetic control in the placenta [67]. The role of vitamin D in epigenetic modification and foetal programming may explain why vitamin D is important for a number of health benefits. Future studies investigating particular epigenetic markers may provide risk assessment tools which target early intervention strategies for those at increased risk for a particular disease [67].

Optimal level recommendations for vitamin D

There are numerous factors which may affect the plasma concentration of 25(OH)D in the body, including sun exposure, dietary intake, level of adiposity and muscle, age, disease, the 25-hydroxylase activity and DBP production/concentration in the liver, the efficiency of cellular uptake of 25(OH)D and its rate of conversion to $1,25(OH)_2D$ or $24,25(OH)_2D$ [45,66]. Therefore, the optimal levels for vitamin D recommendations need to allow for these various confounders.

Despite this, the concentration of serum 25(OH)D is widely recognized as the best measure of vitamin D status. Deliberation about a sufficient requirement for optimal health has occurred in the past; a minimal level of 75nmol/l per day was recommended for both bone and general health. Recently, a level of 50nmol/l per day has been established as sufficient. A level of <25 nmol/l per day is associated with mild to severe deficiency [39,44].

The potential health effects of vitamin D may be relevant at all ages and stages of the human life cycle. For example, the adequacy of the vitamin D supply to tissues might be particularly important for conception and subsequently the developing foetus, again it may be important during childhood and adolescence for bone mineral accrual and somatic growth, and in later life for reducing susceptibility to chronic degenerative diseases [249].

Attempts to shed light on a safe level of sun exposure has led to researchers using models based on skin types and erythemal dose [253], which is the time taken for UVR to cause a slight reddening of the skin [250]. The Cancer Council of Australia has released broad recommendations on achieving adequate vitamin D synthesis while remaining "sun safe". For example, fair-skinned individuals are suggested to expose their hands, arms and face to a few minutes of sunlight either side of the peak sunlight hours (10.00-15.00 hours), or when the UV index is low. In winter, maintenance of vitamin D requires sun exposure to increase to 2-3 hours a week [251].

Sunlight is by far the best and most reliable source of vitamin D for most humans, and at the above recommendations, the beneficial effect of sunlight, while preventing the damaging consequences due to excessive exposure, is possible.

Natural dietary sources of Vitamin D

Few foods in nature contain vitamin D, but those that do include oily fish such as mackerel and salmon, and cod liver oil. Mushrooms and other fungi and yeast contain ergosterol, the provitamin form of vitamin D, which when subject to UVR converts to vitamin D_2, depending on irradiation dose and temperature [252]. Variation between the levels of vitamin D in dietary sources can occur. For example, farmed salmon can contain up to 25% less vitamin D when compared to wild-caught salmon [35]. It has also been demonstrated that seasonal variation in the vitamin D level in oily fish can occur, with higher vitamin D levels in the summer compared to winter. The absorption of dietary vitamin D is generally high at all stages of life [254], but is reduced when the intake of fat is low [200]. Overall, however, dietary intake of vitamin D from food is not sufficient to meet an adults needs, leading to growing interest in vitamin fortification and dietary supplementation as a way to improve vitamin D status.

Contemporary dietary fortification trends in Australia

Foods naturally containing vitamin D are limited in Australia, and are insufficient to allow for adequate intake. A fortified food is one which has had one or more essential nutrients added, whether normally present or not, in order to prevent or rectify a nutrient deficiency. In Australia it is mandated that margarine contains vitamin D at a level of no less than 55µg/kg [255]. Limited voluntary fortification of food products with vitamin D occur in low-fat milk, powdered milk, cheese and yoghurt [256]. The level of vitamin D Australians receive from food sources is low. In 2002, Australians were only consuming 2-3µg of vitamin D per day from dietary sources and, of that, 50% was from fortified margarine products [38]. Data from a recent study by the present authors assessed the dietary [including fortified] and supplemental micronutrient intake from an Australian Retirement Village population [257]. The average intake of vitamin D was only 24% of the recommended daily allowance (RDA) [257]. Therefore, currently dietary sources of vitamin D alone challenge sufficiency in maintaining optimal vitamin D levels in an elderly Australian population where requirements are increased over younger members of society.

Contemporary dietary fortification trends worldwide

The United States and Canada are dependent on fortified foods and dietary supplements to meet vitamin D needs as foods naturally rich in this vitamin are not frequently consumed. Vitamin D fortification is highly regulated in the United States, with fluid milk and evaporated milk mandatorily fortified. Other foods voluntarily fortified include cereal flours, yoghurt, cheese and some fruit juices. In Canada, milk and milk alternatives and margarine are mandatorily fortified. Other food including eggs, meal replacements, nutritional supplements and formulated liquid diets are presently permitted to be fortified with vitamin D [258].

In Europe, fortification may be mandatory, optional, or absent, with most countries permitting fortification of margarine with vitamin D. In the United Kingdom, breakfast cereals are voluntarily fortified, providing 13% of vitamin D intake for adults, representing a major source of vitamin D [259].

Conclusion

Vitamin D is a unique micronutrient which has complex biological functions throughout the human lifecycle, with recent evidence suggesting that vitamin D is associated with reduced risk for a variety of degenerative disorders. This has been highlighted by the identification that most tissues and cells contain a VDR, and that a number of genes may directly or indirectly be influenced and/or regulated by $1,25(OH)_2D$.

Vitamin D deficiency and its consequences are extremely subtle, but have significant implications for human health and disease. It is for this reason that vitamin D deficiency continues to go unrecognized by a majority of health care professionals. Humans rely on UVR exposure, a known carcinogen, to enable adequate vitamin D synthesis, as dietary sources can be minimal. The optimal wavelength of UVB exposure for vitamin D synthesis is 290-315nm, but availability varies according to season and latitude. The ability to synthesize vitamin D is related to the level of melanin pigmentation in the skin, and as a consequence the vitamin D-folate sunlight hypothesis has been developed to help partially explain the evolution of skin pigmentation. The hypothesis suggests depigmentation evolved to allow vitamin D synthesis at higher latitudes, while nearer the equator pigmentation evolved to protect against UVR folate destruction. Both folate and calcium are important to reproductive processes; and hence may have provided selection pressures for depigmentation/pigmentation to evolve.

The positive and negative effect of UVR exposure creates a health dilemma, and it is for these reasons that the question of whether vitamin D fortification should be mandated arises. It is particularly relevant in sunny countries such as Australia, where reduced UVR exposure to protect against skin cancer rates has led to the paradox that such a sunny country can yield high vitamin D deficiency rates. Mandatory fortification or more widespread supplementation may be the most practical measure to alleviate vitamin D deficiencies and suboptimal levels, particularly in at risk groups. Further research will ultimately elucidate the importance of achieving optimal vitamin D status and/or mandatory fortification especially in western societies and ageing populations.

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