REVIEW

Global vitamin D status and determinants of hypovitaminosis D

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Abstract

Summary This review describes the vitamin D status in different regions of the world with the objective of understanding the scope of hypovitaminosis D and the factors related to its prevalence that may contribute to the pathogenesis of osteoporosis and fragility fractures.

Introduction Vitamin D status has been linked to the pathogenesis of hip fractures as well as other skeletal and non-skeletal disorders. The purpose of this review is to provide a global perspective of vitamin D status across different regions of the world and to identify the common and significant determinants of hypovitaminosis D.

Methods Six regions of the world were reviewed—Asia, Europe, Middle East and Africa, Latin America, North America, and Oceania—through a survey of published literature.

Results The definition of vitamin D insufficiency and deficiency, as well as assay methodology for 25-hydroxyvitamin D or 25(OH)D, vary between studies. However, serum 25(OH)D levels below 75 nmol/L are

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prevalent in every region studied whilst levels below 25 nmol/L are most common in regions such as South Asia and the Middle East. Older age, female sex, higher latitude, winter season, darker skin pigmentation, less sunlight exposure, dietary habits, and absence of vitamin D fortification are the main factors that are significantly associated with lower 25(OH)D levels.

Conclusion Reports from across the world indicate that hypovitaminosis D is widespread and is re-emerging as a major health problem globally.

Keywords Prevalence · Serum 25-hydroxyvitamin D · Vitamin D deficiency

Introduction

Vitamin D plays a primary physiological role in maintaining extracellular calcium ion levels in the human body. Extracellular calcium is vital for the functioning of many metabolic processes and neuromuscular activities. Vitamin D influences calcium levels primarily by controlling the absorption of calcium from the intestine, through direct effects on bone and also through its effects on parathyroid hormone (PTH) secretion [1, 2]. Furthermore, vitamin D deficiency, resulting in decrease bone mineralisation, secondary hyperparathyroidism, and increased cortical bone loss, has been linked to the pathogenesis of osteoporosis and hip fractures [3, 4]. Vitamin D is acquired both through nutritional means (10–20%) and by the cutaneous synthesis under the action of sunlight (80–90%) [5]. Vitamin D_3 or cholecalciferol, after formation in the skin, and vitamin D_2 or D_3, from dietary sources, undergo hydroxylation in the liver, resulting in formation of 25-hydroxyvitamin D or 25(OH)D, the chief circulating form. 25(OH)D subsequently undergoes hydroxylation in the kidney under the influence of 1α-hydroxylase enzyme to yield the biologically active, dihydroxylated form of vitamin D, calcitriol or $1,25(OH)_2D$, which acts through specific vitamin D receptors to regulate not only calcium metabolism, but also differentiation and division of various cell types. It has been suggested that in addition to its pivotal role in bone mineralisation, calcium homeostasis, and its related disorders, vitamin D may play a role in muscle strength [6, 7], pathogenesis of psoriasis [8], certain cancers [9, 10], multiple sclerosis (MS) [11], diabetes [12], and blood pressure [13], among other physiological and pathophysiological processes.

Determining vitamin D status of a population can be a challenging task. While $1,25(OH)_2D$ is the biologically active, "hormonal" form of the vitamin, many health effects correlate better with circulating 25(OH)D levels. Indirect evidence suggests that this may be due to widespread (extrarenal) presence of the enzyme 1α-hydroxylase, which leads to intracellular formation of $1,25(OH)_2D$ in many target tissues, resulting in high local concentrations and cell or tissue specific effects [14]. Therefore, this report will focus only on 25(OH)D levels. However, methods for measuring 25(OH)D levels vary widely. Two commonly used assays presented up to 80% differences in vitamin D levels, especially at lower values [15]. Therefore, comparing vitamin D levels between studies is not reliable unless the same assay is used or the assays are appropriately cross-calibrated.

Earlier observational studies have measured serum 25(OH)D levels in healthy population cohorts to determine reference values for sufficient levels of vitamin D. However, these are known to be influenced by lifestyle and environmental characteristics and, therefore, may not be applied clinically and worldwide [2, 4]. Defining different levels of vitamin D according to health consequences rather than population means is the preferred method but has led to an ongoing debate about what constitutes "normal" or "optimal" 25(OH)D levels. Several criteria have been used to define sufficient 25(OH)D levels, including the level associated with optimal suppression of circulating PTH levels, greatest calcium absorption, highest bone mineral density (BMD), lowest rates of bone loss, falls, or fractures [16]. Hypovitaminosis D is the condition below this level where a population is insufficient or deficient in vitamin D, depending on the severity of its health consequence. Clinical hypovitaminosis D is associated with rickets in infancy and osteomalacia in adults, which causes muscle weakness and contributes to falls and bone fractures. Defining categories of vitamin D insufficiency and deficiency will affect the prevention strategies employed in a clinical setting. These are oral vitamin D supplementation, increased exposure to UV light (especially sunlight), and a better dietary intake.

The aim of this report is to describe 25(OH)D levels in different population groups across the world and highlight what determinants influence vitamin D status. To provide a truly global perspective, six regions (Asia, Europe, Latin America, Middle East/Africa, North America, and Oceania) have been included, and the effect of age, gender, ethnicity, latitude, clothing, nutrition, skin pigmentation, cultural practises, living conditions, and physical activity on vitamin D status of these populations has been emphasised.

Asia

As early as the 1970s, studies clearly showed that migrant populations from Asian countries, when exposed to higher latitudes, were unable to maintain optimal vitamin D levels [17–19]. Frank rickets and osteomalacia were not uncom-

mon in these migrants. More recently, studies carried across different countries in South and Southeast Asia showed, with few exceptions, widespread prevalence of hypovitaminosis D in both sexes and all age groups of the population.

Several studies have demonstrated low serum vitamin 25 (OH)D levels in populations across India [20–22]. In North India (27°N), 96% of neonates [23], 91% of healthy school girls [24], 78% of healthy hospital staff [20], and 84% of pregnant women [23] were found to have hypovitaminosis D. The criteria used for defining hypovitaminosis D in most of the studies was a serum 25(OH)D level below 50 nmol/L.

A major concern is the high prevalence of hypovitaminosis D among pregnant women and children. Maternal serum 25 (OH)D levels correlated negatively with PTH levels and positively with cord blood 25(OH)D levels [23]. Seasonal variation in serum 25(OH)D levels, reflected as winter hypovitaminosis D, has been demonstrated in several studies [25, 26]. Air pollution probably also plays a role in large cities [27]. Hypovitaminosis D is equally prevalent among rural and urban subjects, [23] but in some studies, urban subjects are found to be more deficient [24, 28].

In South India (13°N), hypovitaminosis D is equally prevalent among different population groups [28, 29]. In a population-based study showing the inverse relationship between measured serum 25(OH)D levels and PTH levels, vitamin D levels were significantly higher in rural compared to urban subjects [30].

Similar data have been obtained from Pakistan, most disturbingly from infants [31, 32]. In Bangladesh (24°N), hypovitaminosis D is common in women regardless of age, lifestyle, and clothing [33]. Prevalence of hypovitaminosis defined as 25(OH)D levels below 37.5 nmol/L was 38% in Bangladeshi women from high-income group and increased slightly to 50% in women from low income groups [34]. In Sri Lanka (7°N), mean 25(OH)D among healthy females was 35.3 nmol/L, and 40.5% of them had 25(OH)D values below 25 nmol/L [35].

High prevalence of hypovitaminosis D in South Asia can be explained by skin pigmentation and traditional clothing. Air pollution and limited outdoor activity further compounds this problem in the urban population.

Vitamin D status of the population in Southeast Asian countries has received relatively less attention. However, the problem seems to be less severe [36, 37]. Most studies used serum 25(OH)D level of 75 nmol/L as the cut-off. Prevalence of hypovitaminosis D (25(OH)D <75 nmol/L) in postmenopausal women was 47% in Thailand, 49% in Malaysia, 90% in Japan, and 92% in South Korea [38]. The mean serum 25(OH)D concentration was 48 nmol/L in premenopausal women from Indonesia (6°S) and Malaysia (2°N) [39]. In the Oslo immigrant study, prevalence of hypovitaminosis D was higher in those born in Pakistan and lower in those born in Vietnam compared to the other

ethnic groups. Fatty fish intake and cod liver oil supplements were important determinant factors of vitamin D status in the groups studied [40]. One small study in Thailand showed high serum levels of 25(OH)D [37], possibly related to its geographical location close to the equator. Further studies are needed to confirm this. To some extent, these variations can be attributed to the differences in serum 25(OH)D assay methodology in various studies.

Rickets appears to be common in Mongolia and China (40°N) [41], and this is probably related both to poor vitamin D status and low calcium intake. In a study from North China (Beijing), 89% of Chinese adolescent girls had hypovitaminosis D (serum 25(OH)D <50 nmol/L) [42], and 48% of old men had severe hypovitaminosis D/frank vitamin D deficiency (<25 nmol/L) [43]. Among postmenopausal women, serum 25(OH)D level was found to be lower amongst the Malays (44 ± 11 nmol/L) than the Chinese (69 ± 16 nmol/L) [44]. The relatively lower serum 25(OH)D level among Malays can be explained by their skin pigmentation, lower outdoor activity levels, or greater fat mass. In Hong Kong, the mean serum 25(OH)D was 71 ± 27 nmol/L in adults over 50 years of age [45], but hypovitaminosis D was common among elderly patients with fracture neck of femur [46]. In bottle-fed infants of Hong Kong (on vitamin D fortified milk), serum 25(OH)D levels were normal at 18 months [47]. A dual-centred study in China showed that more than 90% of young women in Beijing and Hong Kong had 25(OH)D levels ≤50 nmol/L. However, the mean values were much lower in the north (Beijing) as compared to the south (Hong Kong; 34 versus 9 nmol/L; $p < 0.001$) and 40% compared to 18% of young women in Beijing and Hong Kong, respectively, had 25 (OH)D levels ≤25 nmol/L [48].

Hypovitaminosis D in Japan (35°N) is more common in inactive elderly (mean 30 nmol/L) and in women younger compared to older than 30 years of age (mean 34 nmol/L) [49]. Overall, the vitamin D status in Japan is relatively better in the regions in South Asia and positively related to fish consumption [49–51]. Prevalence of hypovitaminosis D (<30 nmol/L) in women over 30 years old is only 10.3% [49] and in active elderly (25(OH)D <75 nmol/L) is below 5% [50].

This widespread prevalence of vitamin D deficiency/ insufficiency has a deleterious effect on bone mineral homeostasis and peak bone mass achieved and may subsequently reflect as low BMD [20, 42, 47, 52]. Intervention studies with vitamin D supplements are underway in several of these populations.

Europe

The vitamin D status within different European countries shows a high variation [53]. A serum 25(OH)D lower than

25 nmol/l was found in 2% to 30% of adults, but this percentage may increase to 75% or more in older persons in institutions [4]. Some international studies used one central laboratory, i.e., one radioimmunological method, for all measurements of serum 25(OH)D. The European Action on Nutrition and Health-Survey (EURONUT-SENECA) on independent older persons showed mean serum 25(OH)D levels of 20 to 30 nmol/l in Southern European centres to 40 to 50 nmol/l in Northern Europe [54]. The levels usually were higher in men than in women. The strong positive correlation between serum 25(OH)D and latitude in this survey was rather unexpected because ultraviolet irradiation is more effective in Southern than in Northern European countries. A similar positive correlation ($r^2 = 0.42$) between serum 25(OH)D and latitude was found in the baseline data of the Multiple Outcomes of Raloxifene Evaluation (MORE) study, a clinical trial on the effect of raloxifene in postmenopausal women with osteoporosis, which also used a central laboratory facility [55]. Within countries, the variation in vitamin D status also is very high. The *supplementation en vitamins et mineraux antioxydants* (SUVIMAX) study in French adult men and women between 35 and 65 years showed a mean serum 25(OH)D of 43 nmol/l in the north and 94 nmol/l in the southwest of France [56]. In this study, the correlation between serum 25(OH)D and latitude was negative as expected. In the Netherlands, the Longitudinal Ageing Study Amsterdam (LASA) showed a serum 25(OH)D lower than 25 nmol/l in 8% of men and 14% of women, and lower than 50 nmol/l in 45% of men and 56% of the women [57]. Similar data were found in the population-based Hoorn study and the Swiss Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project [58, 59]. A study of Swiss nursing homes observed that 90% of elderly women had serum 25(OH)D levels below 50 nmol/l compared to 57% in non-institutionalised elderly women [60]. Mean serum 25(OH)D was 45 nmol/l in Italian postmenopausal women, and levels were lower than 25 nmol/l in about 30% [61, 62]. Very low levels were also found in Spanish elderly and institutionalised persons [63], confirming the prevalence in Southern Europe of poor vitamin D status in this social group. Mean serum 25(OH)D was about 25 nmol/l in breast-fed children and about 30 nmol/l in their mothers in Greece [64]. In adolescents in Greece, serum 25(OH)D was lower than 25 nmol/l in 47% in winter [65].

Immigrants from Asian countries and asylum seekers carry a high risk for severe vitamin D deficiency [40, 66–68]. Serum 25(OH)D was lower than 25 nmol/l in 40% of non-Western immigrants in the Netherlands [69]. Pregnant non-Western women even carry a higher risk: a study in midwife practices in The Hague showed a serum 25(OH)D lower than 25 nmol/l in more than 80% of Turkish and Moroccan immigrants. Remarkably, 25(OH)D was below the detection limit in 22% of the Turkish women [70].

Determinants of vitamin D status explaining the higher serum 25(OH)D in Northern Europe are the high consumption of fatty fish and cod liver oil equivalent to almost 400 IU or 10 μg of vitamin D per day [71]. In the Hoorn study in the Netherlands, the determinants of vitamin D status were time spent outdoors, body mass index, the consumption of fatty fish and margarine (fortified with 3 IU per gramme), and the use of vitamin D supplements [58]. Limited time spent outdoors as a predictor of low vitamin D levels was even higher in patients >65 years old, according to a Swiss population study [59]. People in Northern Europe may have a more sun-seeking behaviour, combined with a white skin, while people in Southern Europe may avoid the sun and have a more pigmented skin, which, for the same sunlight exposure, results in less vitamin D production in the skin. In the LASA study, serum 25(OH)D levels below 50 nmol/l were positively related to physical performance score, a sum of walking test, chair stands, and tandem stand scores [72]. Serum 25(OH)D below 25 nmol/l was a predictor of falls in LASA, but the relationship was significant only in those younger than 75 years of age [73]. In a similar way, serum 25(OH)D below 30 nmol/l predicted fractures in persons between 65 and 75 years [74]. However, a relationship between vitamin D status and fracture risk was not observed in the European Prospective Investigation into Cancer and Nutrition (EPIC) study [75].

It can be concluded that vitamin D deficiency (serum 25(OH)D <25 nmol/l) is more common in Southern than in Northern Europe. Risk groups are the elderly (especially the institutionalised and housebound), adolescents, and non-Western immigrants. Dependent on the required serum 25(OH)D level, either 50 or 75 nmol/l, the percentage of the population with vitamin D insufficiency is high or very high in most European countries.

Latin America

In year 2006, the population of Latin America and Caribbean region was 556 million, from diverse ethnic origins. Mean life expectancy is 73 years and, therefore, a significant growth of elderly population is anticipated all over the region. Hip fracture incidence (an average of published data) is 192/100,000 persons aged 50 years and older. Latitudes range from 33°N to 55°S. Dietary habits show ample variations between regions, and a deficient nutritional status is common in the poorer regions [76]. A few studies have addressed the status of vitamin D among small samples of diverse populations, and a review on the subject raises concern about hypovitaminosis D among different population groups in Latin America [77].

A study in healthy elderly men and women from different regions of Argentina showed significant differences in mean values of 25(OH)D between habitants of northern (52 nmol/L) and southern (36 nmol/L) provinces. This study showed a cut-off level of 25(OH)D of 68 nmol/L at which serum PTH began to increase [78]. Another study in ambulatory women from Buenos Aires showed differences in 25(OH)D levels in summer (63 nmol/L) and winter (53 nmol/L) [79]. Neonates and mothers from the southernmost province had lower 25(OH)D than those from Buenos Aires [80], and a proposal for a supplementation scheme for children in that province (twice single doses of 100,000 IU ergocalciferol every 3 months during autumn and winter) resulted in a safe recovery of 25(OH)D levels [81].

An international epidemiological investigation conducted in postmenopausal women with osteoporosis from Mexico ($n = 149$), Chile ($n = 115$), and Brazil ($n = 151$) found lower values of 25(OH)D in Mexico than in Chile and Brazil [82]. The percentage of persons with inadequate levels of 25(OH)D (<75 nmol/L) in the mentioned countries were 67%, 50%, and 42%, respectively. A further study of postmenopausal women screened for a clinical trial on osteoporosis from four different cities in Mexico, who were not taking any supplements, showed a very low value of serum 25(OH)D [83]. Prevalence of hypovitaminosis D depended on its defined threshold and varied from 2%, 31%, 62%, to 97% for 25(OH)D levels below 22.5, 27.5, 50, and 75 nmol/L, respectively. Finally, another very recent report showed that osteoporotic women from Mexico City taking calcium and vitamin D supplements had higher values (84 nmol/L) of 25(OH)D than those not taking any (64 nmol/L) [84]. Differences found in results from small-scale studies suggest methodological differences in patient selection, including the use or not of vitamin supplements, seasonal variations, and sun exposure habits.

Middle East and Africa

Despite ample sunshine, the Middle East (15°-36°N) and Africa (35°S-37°N) register the highest rates of rickets worldwide. This is in large part explained by limited sun exposure due to cultural practises and prolonged breast-feeding without vitamin D supplementation in the Middle East [85], and by dark skin colour and calcium deficiency, rather than vitamin D deficiency, in several countries in Africa [86]. However, both regions also have a high prevalence for hypovitaminosis D.

Hypovitaminosis D is very common in this region and does not spare the paediatric age [87, 88]. A large proportion of adolescent girls, up to 70% in Iran [89] and 80% in Saudi Arabia [90], had 25(OH)D levels below 25 nmol/L. The reported proportions were 32% in Lebanese girls and between 9% and 12% in Lebanese adolescent boys [91, 92]. Diarrhoea and maternal vitamin D status in infants [93, 94] and gender, clothing style, season, and socioeconomic status in older children were independent risk factors for 25(OH)D levels [89–91, 95]. Several were also predictors for calcium and vitamin D intake [96].

The first study in adults from the region was conducted in university students and elderly from Saudi Arabia and revealed a mean 25(OH)D level ranging between 10 and 30 nmol/L [97]. The mean 25(OH)D level was near 25 nmol/L in Lebanese, Saudi, Emirati, and Iranian women [98–101]. A similar mean was recorded in elderly Lebanese [102]. The proportion of subjects with vitamin D levels below specific cut-offs varied. It was 35% for a vitamin D level below 25 nmol/L in a study of elderly subjects from a geriatric hospital in Israel [103]; and between 60% and 65% in Lebanon, Jordan, and Iran [98, 104, 105]; and was 48% for a cut-off less than 37.5 nmol/L in subjects from Tunisia [106]. In the elderly Lebanese, 37% of men and 56% of women had vitamin D levels below 25 nmol/L. In the similar international study conducted in women with osteoporosis, the highest proportion of hypovitaminosis D was noted in the Middle East [82]. In a study of hip fracture patients and elderly from Israel, up to 80% of subjects had hypovitaminosis D [107, 108]. Inadequate vitamin D intake, urban dwelling, female gender, wearing the veil, winter season, age, and high parity were independent predictors of low vitamin D levels [99, 104–106, 109, 110].

Neonates born to mothers with low D levels have lower cord vitamin D levels and may be at risk for rickets and other complications [87, 111]. Studies from Saudi Arabia, Kuwait, United Arab Emirates, and Iran reveal that 10–60% of mothers and 40–80% of their neonates had undetectable low vitamin D levels (0–25 nmol/L) at delivery [112–115]. Neonatal outcomes were not detailed in most studies. Higher socioeconomic status, antenatal care, and vitamin D intake were associated with higher vitamin D levels [115].

The negative impact of low vitamin D on mineral metabolism is illustrated in the inverse relationship between vitamin D and PTH levels noted in Lebanese of all age groups and in Emirati and Iranian women ($R = -0.2$–0.25) [101, 116, 117]. A positive correlation between 25(OH)D and spine, but not hip BMD (Z-score) was noted in postmenopausal Iranian women [118]. Similar correlations were noted in elderly Lebanese with spine, hip, and forearm BMD ($R = 0.13$–0.3) but were not present after adjustment for age, height, lean mass, and PTH levels [102], consistent with findings in Iranian women [116]. Neonatal size or bone mass may be affected by maternal vitamin D status [87]. No effect of maternal vitamin D levels on neonatal birth weight was detected in a sample of 50 mothers-

neonates from Iran after adjusting for maternal height, age, and parity [112]. Conversely, in a larger sample of 449 women and their newborns from Tehran, neonates of mothers with adequate calcium and vitamin D intake were 0.9 cm taller and had a better Apgar at birth [119]. Vitamin D supplementation for 1 year increased lean mass, bone area, and bone mass in a randomised controlled trial in Lebanese adolescent girls [92].

In summary, vitamin D levels are quite low across age groups in this region. Consistent predictors of low levels are older age, female gender, multi-parity, the winter season, conservative clothing style, low socioeconomic status, and urban living. The negative impact of low vitamin D levels on indices of mineral bone metabolism and the positive effect of replacement in adolescents are consistent with observations worldwide and support recommendations to optimise vitamin D status.

North America

In the USA, serum 25(OH)D levels have been assessed in a representative sample of 20,289 non-institutionalised, civilian males and females in the national health and nutrition examination survey (NHANES) over the period of 2002–2004 [120, 121]. Among males in selected age categories of 1–5, 20–49, and 70 years and older, the prevalence of 25(OH)D levels considered by some to be deficient (<37.5 nmol/L) were 2%, 13%, and 11%, respectively [120]. The proportions of males with levels below 50 nmol/L for the same age groups were 8%, 29%, and 27%, respectively. The proportions with serum 25(OH)D concentrations below the level considered by many to be optimal for older adults (<75 nmol/L), for the same age groups, were 50%, 73%, and 78%, respectively. Among females, 25(OH)D levels below 37.5 nmol/L were present in only 3% of those aged 1–5 years but more common in young adults aged 20–49 years (19%) and in women aged 70 years and older (16.5%). Serum 25(OH)D levels below 50 nmol/L were present in 8.5%, 35%, and 34% of females in the same three age groups, respectively. The proportions with serum 25(OH)D levels below 75 nmol/L were 56%, 73%, and 77% in these age groups, respectively.

Within these 25(OH)D categories, however, prevalence of low serum 25(OH)D levels vary dramatically by race/ethnicity. For example, among males aged 70 years and older, the prevalence of levels below 50 nmol/L was 23% for non-Hispanic whites, 45% for Mexican Americans, and 58% for non-Hispanic blacks. By age 70 years and older, the prevalence of levels below 75 nmol/L in these three groups were 76%, 88%, and 93%, respectively. Among women, the corresponding prevalence of values below 50 nmol/L were 28.5%, 55%, and 68% and of values below

75nmol/L were 73%, 89%, and 95%, respectively. Information on the other age groups and on the impact of season on 25(OH)D levels is also available [120].

Comparison of these values with those in the previous NHANES III conducted in 1988–1994 reveals that secular changes in the 25(OH)D levels have occurred over the last 10 years [120, 122]. The more recent 25(OH)D levels are 5–20 nmol/L lower than those in the 1988–1994 survey [122]. After adjustment for the contribution of assay differences, the newer values remain 5–9 nmol/L lower. The lower values, present more frequently in males than in females, have been explained by the combination of an increase in body mass index, a decrease in the consumption of milk, which in the USA is routinely fortified with vitamin D, and more widespread sunscreen use [120, 122].

National survey data are not available for institutionalised individuals and other high-risk groups in the USA, but investigator-initiated studies reveal that 25(OH)D levels are, as expected, low in those that do not routinely take supplements. For example, in institutionalised elderly not taking vitamin D supplements, 30% had 25(OH)D levels below 37.5 nmol/L [123]. In acute hip fracture patients admitted to a hospital in Boston, the mean serum 25(OH)D level was 32 nmol/L, and half of the patients had extreme vitamin D deficiency, defined as 25(OH)D levels of 30 nmol/L and lower [124]. Of 1,536 postmenopausal women residing throughout the USA who were taking pharmacotherapy for osteoporosis, 18% had 25(OH)D levels below 50 nmol/L and 52% had levels below 75 nmol/L [125].

In summary, despite growing awareness of the multiple health benefits of an adequate vitamin D status, vitamin D insufficiency abounds and is a growing problem in the USA.

Available data indicate that vitamin D concentrations are low in many otherwise healthy Canadian adults, particularly during winter months, and dependent on ethnic origins. An early study of young women (18–35 years of age) in Toronto found that in winter, 21% of white women, 32 of non-white women (a group which combined First Nations peoples, South Asian, Indo Asian, and East Asian ancestries), and 25% of black women had serum concentrations below 40 nmol/L [126].

Seasonal changes were also observed in a population study of 155 residents of long-term care facilities (83 years of age) [127]. Although the study group had limited outdoor exposure, the prevalence of vitamin D deficiency (25(OH)D ≤25 nmol/L) increased from 9% in fall to 18% in winter ($p = 0.03$) and that of vitamin D insufficiency (25(OH)D ≤40 nmol/L) increased from 38% in fall to 60% in spring ($p < 0.001$). Patterns of seasonal variation were also examined in a population of healthy men and women living in Western Canada (Calgary) [128]. At the end of the winter

season, in men and women of mostly European ancestry, 20% had serum concentrations below 40 nmol/L, 39% had serum concentrations below 50 nmol/L, and 86% had serum concentrations below 80 nmol/L. Prevalence of low vitamin D concentrations decreased in the summer to 9%, 14%, and 68%, respectively, which was associated also with travelling to lower latitudes (below 42°N) in that period. However, it should be pointed out that Calgary receives more hours of sunshine per year than any other Canadian city and, therefore, the data may not be generalised to the whole Canadian population.

The Canadian multicentre osteoporosis study, a prospective epidemiology study of 10,000 randomly selected people from across Canada, is in the process of measuring 25(OH)D levels (among other analytes). These data will shed more light on the vitamin D situation across Canada.

Oceania

Several investigations have shown low vitamin D levels in a significant proportion of Australians and a large number of at risk groups within the community. In a prospective study evaluating prevalence of vitamin D deficiency in older people in residential aged-care facilities in the northern Sydney area, vitamin D deficiency (serum 25 (OH)D <28 nmol/L) was present in 68% of men and 86% of women, with a mean serum 25(OH)D level of 17 nmol/L [129]. A case series of elderly patients (mean age 81 years) admitted with a hip fracture to Royal Hobart Hospital, Tasmania, found vitamin D deficiency (<28 nmol/L) in 67% [130]. Importantly, community-dwelling elderly are at risk as well. A cross-sectional study of older Tasmanian subjects (mean age 79 years) reported 17% of the community group to be vitamin D deficient (<28 nmol/L) [131]. A significant predictor of vitamin D level in this study was poor physical function and activity.

Low vitamin D status has been reported to be highly prevalent among housebound elderly and among ethnic communities, especially Asians, including in Australia, which has a multicultural population. In a cross-sectional study involving elderly living in assisted care and the community in Sydney metropolitan area, elderly people of Middle Eastern origin were found to be at fourfold risk and elderly of Vietnamese origin at threefold risk of vitamin D deficiency (defined as <25 nmol/L) compared to their counterparts of European Caucasian origin [132]. The study included recently arrived young middle-aged Chinese immigrants, of whom 28% were vitamin D deficient. In a further study evaluating 25(OH)D levels in community-dwelling elderly of Vietnamese and Australian/British origin, levels <37 nmol/L were found in 63% and 37%, respectively [133]. Data from New Zealand are similar,

with evidence that vitamin D deficiency/insufficiency is a growing problem. Serum 25(OH)D levels in New Zealand reveal much more hypovitaminosis D than expected, especially for those of Pacific Islander and Maori origin [134, 135].

Women who wear a veil for cultural reasons have an increased prevalence of vitamin D deficiency. One study of veiled and dark-skinned pregnant women in an antenatal clinic in Melbourne found that the majority (80%) were actually vitamin D deficient (<22.5 nmol) [136]. A cross-sectional study of a random sample of Muslim women aged 20–65 years living in an urban community in South-western Sydney found vitamin D deficiency (defined as <30 nmol/L) in 68%, hyperparathyroidism in 39%, and high bone turnover in 46% [137].

There is a strong association between disability, sun exposure, and vitamin D status. Greater disability and associated reduced exposure to sun may contribute to the high prevalence of vitamin D insufficiency reported in a population-based MS case sample [138]. Amongst 136 prevalent cases with MS in Tasmania, those individuals with greater disability were more likely to have vitamin D insufficiency than controls with odds ratio (OR) of 3.07 (95% confidence interval (CI), 1.37–6.90) for 25(OH)D levels ≤40 nmol/L. Overall, 34% of people with MS had 25 (OH)D levels ≤40 nmol/L versus 23% of community controls.

Vitamin D deficiency has re-emerged as a significant paediatric health issue in Australia and New Zealand, with complications including hypocalcaemic seizures, rickets, limb pain, and fracture. A major risk factor for infants is maternal vitamin D deficiency. A retrospective audit of medical records of children diagnosed with vitamin D deficiency rickets in Melbourne identified 25(OH)D levels ≤25 nmol/L in 81% of the mothers [139]. Ninety percent had levels ≤40 nmol/L or less. Fifty-four of the 55 children were born to mothers with ethnocultural risk factors (including veiling) for vitamin D deficiency. A population-based study of pregnant women and their neonates from Southeastern Sydney identified vitamin D deficiency (25(OH)D <25 nmol/L) in 15% of women and 11% of neonates [140]. In a study of women presenting to a general practise for antenatal care in Wellington, 87% had 25(OH)D levels <50 nmol/L and 61% <25 nmol/L [141]. Only 22% of the women were veiled, and the group included a diverse ethnic population, including African and Middle Eastern as well as Maori, European, and Polynesian women.

Levels of 25(OH)D tend to be lower at the end of winter compared to the end of summer, as exposure to sunlight is the main source of vitamin D. In a cross-sectional study of a population-based, random sample of women aged 20–92 years in Geelong, 25(OH)D levels were less than

28 nmol/L in 7% overall and 11% in winter [142]. Levels were less than 50 nmol/L in 30% overall and 43% in winter. A comparison of vitamin D status in people below 60 years of age using data from cross-sectional studies of three regions across Australia confirmed vitamin D insufficiency (≤50 nmol/L) to be common over a wide latitude range [143]. Prevalence of vitamin D insufficiency in women in winter/spring was 41% in southeast Queensland (27°S), 37% in the Geelong region (38°S), and 67% in Tasmania (43°S). Season appeared to be more important than latitude in determining serum 25(OH)D levels according to this study. Vitamin D deficiency is common among elderly women with a high risk of fracture living in southern New Zealand. This is most marked in the winter months. In a study involving elderly women living independently in Dunedin, 26% had 25(OH)D levels below the reference range for healthy adults (≤40 nmol/L). In winter, 69% had levels below the reference range [144]. A cross-sectional study conducted in Auckland also concluded seasonal variation significantly affected the prevalence of vitamin D insufficiency [145–147]. Also, gender differences have been suggested in 25(OH)D levels, with men having higher levels of 25(OH)D throughout the year than women, a finding that persisted after adjusting for potential confounding factors. Predicted duration of 25(OH)D concentrations less than 50 nmol/L was 250 days per year in women and 165 days per year in men [146]. Levels of 25(OH)D, in men, peaked in early autumn at 103 nmol/L with a nadir in early spring at 59 nmol/L [145].

Discussion

Defining worldwide what constitutes insufficient or deficient levels of vitamin D has long been debated, and there is currently no standard definition of optimal vitamin D status. It is self-evident that changing the threshold (cut-off point) at which hypovitaminosis D is defined will alter the percentage of people with such condition. Therefore, comparing vitamin D status across different populations will depend on the thresholds set for hypovitaminosis D. It will also depend upon the assays used to measure serum 25(OH)D levels. Regardless, differences between regions are still observed. This review presents six regions of the world (Asia, Europe, Latin America, Middle East/Africa, North America, and Oceania) with various vitamin D status reports depending on age, gender, ethnicity, latitude, clothing, nutrition, skin pigmentation, cultural practises, and living conditions.

Regardless of the definition of vitamin D sufficiency (usually 50 nmol/L or 75 nmol/L), it is apparent that suboptimal 25(OH)D levels are a worldwide phenomenon with hardly any region spared. However, severe hypovitaminosis

D (usually <25 nmol/L) seems to be most common in the Middle East and South Asian regions, despite abundant sunshine and favourable latitude. It is possible that other regions in Asia and Oceania (or even Africa, which remains largely unstudied) may also be similarly affected, but definitive comments cannot be made in absence of more complete data.

Age and gender

Since the discovery of rickets in children and its association to vitamin D deficiency, this disease has been very well controlled in paediatric settings and treated with exposure to UV light and vitamin D supplementation programmes. This report shows, however, that rickets is still a health issue in Asia, Middle East, Africa, and Oceania and in immigrants in Europe. Rickets is still common in neonates whose mothers have low levels of vitamin D and where the sole nutrition of the infant is breast milk. Osteomalacia is a crippling albeit reversible condition, which continues to be common in parts of Asia like the Indian subcontinent [52]. Furthermore, hypovitaminosis D affects all age groups, from the newborn to the elderly, and is dependent on several lifestyle and environmental conditions. In general, the cutaneous production of vitamin D_3 declines with age [148, 149], and often, the elderly have to be confined indoors for prolonged periods of time, which compounds the problem. Not surprisingly, therefore, elderly have lower circulating 25(OH)D levels, as compared to the young population from the same regions and with similar skin colour.

Similarly, hypovitaminosis D affects both men and women in all age groups but mainly depends on external factors. However, there is evidence that women have lower levels than men in elderly Europeans [54, 57, 58], in non-institutionalised American civilians of various ethnical subgroups [122], in young adolescents in Lebanon [91], and in a yearly study of healthy aged men and women in New Zealand [146]. This difference is noted also in rural and urban populations [28]. Moreover, pregnant women [23, 70, 136, 140, 141] and women breast-feeding for long periods of time [64, 85] are at higher risk of hypovitaminosis D. Gender differences also occur due to clothing differences where adolescent girls and adult women wearing the veil have lower levels of vitamin D throughout the year compared to their male counterparts [91, 105].

Genetic traits and cultural behaviour

Population studies in Europe have shown that immigrants and asylum seekers from Asian, Middle Eastern, or African origins have greater risks of low vitamin D levels [66–70]. Country of origin, genetic traits, and cultural behaviour are

important factors in determining vitamin D levels. For example, Vietnamese immigrants in Norway were reported to have lower prevalence of hypovitaminosis D compared to Turkish or Pakistani immigrants [40]. In Canada, young women from Asian and to a lesser extent, African origins, showed lower levels of vitamin D compared to white-Canadian women [126]. In the USA, African Americans, then Mexican Americans, showed more severe vitamin D deficiency compared to non-Hispanic white Americans [122]. Similar results are also found in Australia where in an elderly population, Middle Eastern, then Asian immigrants, had lower vitamin D levels compared to white-Australian and European Caucasians [132, 133]. Finally, New Zealanders of Maori and Pacific Island origins were more vitamin D insufficient compared to European, Asian, and Indian origins [134, 135]. These studies indicate that ethnic differences play a role in the circulating levels of serum vitamin D.

The significant variation of hypovitaminosis D prevalence between people of different origin may partly be explained by differences in skin colour and cultural behaviours. Highly pigmented skins with comparable UV light exposure achieve lesser cutaneous formation of vitamin D_3, hence, dark-skinned individuals require greater duration of exposure than their light-skinned counterparts to synthesise comparable amounts of vitamin D [150, 151]. Skin pigment is probably a major factor in the very low 25 (OH)D levels seen in the Indian subcontinent, despite abundant sunshine [20, 25, 28]. However, more widespread use of sunscreen users in lighter-skinned populations (now also increasingly used by darker-skinned peoples), may also significantly diminish the cutaneous synthesis of vitamin D_3 [152].

Cultural behaviour that may explain vitamin D variations is linked to nutritional and religious differences between people of different origin but living in the same city or country. The consumption of fatty fish and cod liver oil, major sources of dietary sources of vitamin D, were reported to be more common in immigrants from Vietnam and Sri Lanka as compared to Pakistanis [40]. This is further reinforced by Japanese, Dutch, and Norwegian national studies showing the dependence of vitamin D status on consumption of foods rich, or enriched, in vitamin D [49–51, 58, 71]. Ethnic differences in dairy consumption are also reported in African and Asian immigrants in the USA and, in a country where milk is generally fortified with vitamin D, this may contribute in explaining differences in levels of vitamin D. However, the effectiveness of dairy products with low levels of vitamin D fortification in Canada's health programmes is being questioned, as the average serum 25(OH)D concentrations were reported to be similar to those of Europeans, where products are usually non-fortified [127].

Clothing practises affect the photosynthesis of vitamin D_3 from the skin. It is self-evident that the effect of clothing on vitamin D status will be more pronounced in sunny periods, when differences in clothing practises are greater between ethnic populations. The religious practise of the veil (*hijab* or *niqab*), covering totally or all except for the face and arms of women, has been demonstrated to be an independent factor of hypovitaminosis D in the Middle East and Africa [91, 98, 99, 106, 109]. In these regions, however, levels of vitamin D may still be low regardless of clothing practises [33, 105]. In South Asia, clothes usually cover much greater proportion of body surface than is the practise in Europe, Americas, and Oceania, even in summer. Sun-seeking behaviour is uncommon in these populations, both because climate is hot for most of the year and because fair skin is associated with beauty in these cultures. In the most southern and warmest parts of Europe, avoiding the heat and sun had a significant role in reducing 25(OH)D levels [54]. Immigrants living in Australia and New Zealand wearing the veil showed strong tendencies towards low level of vitamin D [136, 137].

Latitude and season

Synthesis of vitamin D_3 in the body depends upon solar radiation of the skin. The amount of UV light at a geographical location depends on the length the sun's rays have to travel through the atmosphere, where it is more or less absorbed. Countries at latitudes nearer to the equator receive more sunlight yearly compared to those nearer the poles, which also changes with seasons. The northern and southern hemispheres are tilted towards the sun from April to September and October to March, respectively. Therefore, both latitude and seasons influence the degree of possible solar radiation a population may receive. The literature reports strong evidence that hypovitaminosis D is greater in winter months for all age groups in Asia [25, 26], Europe [69, 72, 82], Latin America [79], Middle East [91], North America [153], and Oceania [142]. However, in very hot countries and where the majority of women wear veils, vitamin D levels were not significantly higher and were even lower in the summer months, as these women avoided the heat and sun by staying indoors [101, 105].

The measured effect of latitude on levels of vitamin D is pronounced. Theoretically, geographical regions closer to the equatorial latitudes should present higher levels of vitamin D photosynthesis due to longer periods of sunlight. Classic studies from North America first showed this clearly many years ago [154, 155]. Asian migrants that moved to northern countries and Canadian summer holiday takers that travelled closer to equatorial latitudes showed a decrease and increase in their vitamin D levels respectively, confirming this relationship [17–19, 128]. Furthermore, in

Argentina, vitamin D deficiency is significantly lower in populations living in northern regions where mean latitude, temperature, and heliophany (daily hours of solar irradiation) varied from 48°S to 27°S, 3.7°C to 16.1°C, and 3.6 h to 6.3 h of UV irradiation, respectively [78]. The findings from China, although in different population groups, also indicate much lower 25(OH)D levels in northern latitudes [42, 45]. However, a similar Australian study across a latitude range of 27°S to 43°S showed lesser variations, with latitude explaining only 3.9% of the differences in 25 (OH)D levels [143]. In contrast, in Europe, most southern countries (<40°N) demonstrated higher prevalence of vitamin D deficiency in elderly men and women, compared to northern countries (55–60°N) [54, 55] but can be partly explained by the increase of nutritional vitamin D intake and lighter skin pigmentation of these populations. Direct comparative studies between countries lying above latitudes of 45°N or below 45°S and those close to the equator are, however, scarce.

Living condition and outdoor activity

Limiting outdoor activities can further reduce the amount of sun exposure and thus cutaneous vitamin D_3 formation, especially in the elderly population. This global report shows that in many studies of elderly population, hospitalised, institutionalised (nursing home or residential care), housebound, and those with greater disabilities have low or lower vitamin D levels compared to healthy adults as they have limited time spent outdoors [44, 46, 55, 58, 63, 124, 132, 138, 153]. Urbanisation is also a predictor of low levels of vitamin D in Asia and the Middle East, as both men and women dwell and work most often indoors compared to rural communities [24, 28, 99]. Air pollution in cities further acts as a barrier to UV light [27]. In developing countries, higher social economic status and familial income has been shown to decrease the prevalence of hypovitaminosis D in all age groups, explained as better outdoor school activities in adolescents, superior antenatal care facilities in pregnant women, improved overall nutritional diet, and higher accessibility to vitamin D supplementation in the elderly [76, 90, 91, 115].

Conclusion

This global report shows the widespread prevalence of hypovitaminosis D in almost every region of the world studied. There is still paucity of data from some parts of Asia and most of Africa. The re-emergence of vitamin D deficiency as a clinical problem in several parts of the world is a major cause of concern. The degree of hypovitaminosis D varies from region to region. While 25

(OH)D levels below 75 nmol/L are common in most populations, levels below 25 nmol/L that constitute frank vitamin D deficiency are most commonly seen in populations at risk, in particular, the elderly. In some regions, such as South Asia and Middle East, frank vitamin D deficiency is common in all age groups, from neonates to the elderly.

Risk factors for hypovitaminosis D include older age; female sex; lower latitude; winter season; darker skin pigmentation; factors that determine sunlight exposure, such as clothing and cultural practises; dietary habits; and national policies of vitamin D fortification. Skin pigment and cultural practises seem to override the effect of other factors, including latitude, as is evidenced by the higher vitamin D levels in Northern as compared to Southern Europe, and the severity of the problem in South Asia and the Middle East. Seasonal variation is also seen in most populations and at all latitudes, unless individuals cover themselves more extensively during summer in very hot climates. Age seems to have a consistent effect too, but the contributions of fortification and diet are variable.

As prevention of osteoporosis becomes more imperative with the global ageing of the population, the role of non-pharmacological treatments will also become increasingly important. Defining categories of vitamin D deficiencies will affect the prevention strategies employed in a clinical setting. These are vitamin D supplementation, increased exposure to UV light (especially sunlight), fortification of food products with vitamin D, and a better dietary intake. Given the proposed definitions of vitamin D sufficiency, it is possible that populations at high risk will have to resort to supplementation to achieve desired 25(OH)D levels.

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