Vitamin D deficiency: a global perspective

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The prevalence of clinical vitamin D deficiency (rickets and osteomalacia) is high in many parts of the world, and there is a resurgence of rickets among children of ethnic minority groups in Europe and Australasia. Plasma 25-hydroxyvitamin D concentration (25OHD) is a useful risk marker of clinical vitamin D deficiency. This review summarizes the factors that contribute to differences in 25OHD among populations and provides an overview of the prevalence of low vitamin D status worldwide. It discusses the controversies that surround the interpretation of 25OHD, other proposed indices of vitamin D adequacy and dietary reference values for vitamin D, and describes the emerging evidence that a very low calcium intake may contribute to the etiology of rickets in Africa and Asia. There is an urgent need for action to address the global burden of rickets and osteomalacia.

INTRODUCTION

Vitamin D deficiency causes rickets in children and osteomalacia in children and adults. Rickets is characterized by a failure or delay in endochondral ossification at the growth plates of long bones that, in children old enough to stand, results in characteristic bone deformities of the lower limbs. Osteomalacia is defective mineralization of osteoid on the trabecular and cortical surfaces of bone and is associated with widened osteoid seams and the presence of Looser zones. Both conditions may be associated with pain, hypocalcemic fits, and muscle weakness in the limbs, heart, and respiratory systems. Low vitamin D status, above that associated with clinical deficiency, has also been linked with an increased risk of other diseases, most notably osteoporosis, cardiovascular disease, diabetes, some cancers, and infectious diseases such as tuberculosis.

Clinical vitamin D deficiency was commonplace in many countries until the middle of the last century. Fortification programs and improvements in air quality have largely eradicated rickets and osteomalacia from the general populations of North America and Europe. The prevalence of rickets, however, remains scandalously high in many parts of Asia, Africa, and the Middle East (Table 1). Moreover, a resurgence of rickets has been recorded in recent years among ethnic and cultural minority groups in some Northern European countries, notably in the United Kingdom, The Netherlands, and Denmark, and in Australasia. The global prevalence of osteomalacia in adults is more difficult to gauge because there are few reports in the literature and because it may be asymptomatic and go undetected. However, it is reasonable to assume that in regions where rickets is prevalent in children, adult osteomalacia is likely to be common, especially among pregnant women and the elderly.

RISK OF VITAMIN D DEFICIENCY

The long-lived plasma metabolite of vitamin D, 25-hydroxyvitamin D (25OHD), is a useful risk marker of vitamin D deficiency. It is produced in the liver and reflects the supply of vitamin D from skin synthesis and the diet. Vitamin D deficiency rickets and osteomalacia are associated with low circulating concentrations of 25OHD, generally less than 20 nmol/L (8 ng/mL; 2.5 nmol/L = 1 ng/mL). The plasma concentration of
25OHD has been used to identify individuals at risk of vitamin D deficiency disease and, on a population basis, to consider the adequacy of vitamin D supply. In the UK, a plasma 25OHD concentration \(< 25 \text{nmol/L (10 ng/mL)}\) is commonly used in clinical practice and in the definition of dietary reference values. In the USA, a value \(< 27.5 \text{nmol/L (11 ng/mL)}\) is used. Over the last 10–15 years there have been many proposals to redefine this lower threshold of adequacy upwards in order to accommodate the possible link between vitamin D status, at 25OHD concentrations above those associated with clinical deficiency, and health outcomes other than rickets and osteomalacia. Most recently, there have been calls to define vitamin D sufficiency as a plasma 25OHD concentration \(> 50 \text{nmol/L (20 ng/mL)}\), \(> 75 \text{nmol/L (30 ng/mL)}\), \(> 80 \text{nmol/L (32 ng/mL)}\), and \(> 100 \text{nmol/L (40 ng/mL)}\). In addition, there have been calls, supported by recent safety data, for a revision upwards of the current tolerable upper intake level (UL) for vitamin D of 50 \(\mu g/\text{day}\) in order for such plasma concentrations to be achievable through dietary means.

**MEASUREMENT OF PLASMA 25OHD CONCENTRATION**

The measurement of 25OHD in plasma is challenging. There are several methods available, including ones based on competitive protein binding assay (CPBA), radioimmunoassay (RIA), enzyme-linked immunoassay (EIA, ELISA), random access automated assay using chemiluminescence technology (RAAA), high-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS). There is a lack of standardization and results vary among methods, among commercially available versions of the same method, and among laboratories. Some assays also differ in their detection of 25OHD\(_3\) and 25OHD\(_2\). It is important, therefore, to exercise caution when comparing results from studies or surveys conducted in different laboratories or with different methods and when interpreting individual results against a universal threshold value. An international vitamin D external quality assessment scheme (DEQAS) is helpful in evaluating different methodologies and individual laboratory performance. However, the lack of international reference materials and the incompatibility of the various methods makes it difficult to undertake robust assessments of the global prevalence of vitamin D deficiency or comparisons of adequacy across different countries and population groups.

**VITAMIN D STATUS IN THE UK (LATITUDE 50°N–58°N)**

Relatively few countries have nationally representative data on the vitamin D status of their population and the risk of vitamin D deficiency, as estimated by plasma 25OHD concentration. The National Diet and Nutrition Survey (NDNS) of the UK has included 25OHD measurements since 1992. The most recent nationally representative data from the UK are available from samples collected between 1992 and 2001 from all age groups between 18 months and 85 years and over, including older people living in residential institutions. All the plasma 25OHD measurements were taken using RIA (Incstar-Diasorin) with DEQAS external quality assurance and were performed in one laboratory (MRC Human Nutrition Research, formerly at the Dunn Nutrition Unit, Cambridge, UK). To date, data for children aged \(< 18\) months, women who are pregnant or breastfeeding, and representative data from ethnic minority groups have not been included in NDNS. However, data are available from children aged 2 years in British Asian families (an ethnic minority group from India, Pakistan, and Bangladesh) from a separate population study.

These collective data (Figure 1) show that, when judged on a year-round basis and using a 25OHD concentration of \(< 25 \text{nmol/L (10 ng/mL)}\) as the criterion for risk of deficiency, the prevalence of low vitamin D status in the UK during 1992–2001 averaged between 5% and 20% in most age groups, but was in the range of 20–40% in young men and women (age range, 19–24 years), in women over the age of 85 years, in residents of care homes over the age of 65 years, and in children of British Asians. In all age groups, except elderly men and women in residential institutions, the prevalence was higher in the winter and lower in the summer. If 50 nmol/L (20 ng/mL) is used as the lower threshold of sufficiency, the prevalence of low status was 20–60% throughout the population and exceeded 75% in young adults.
the elderly, and British Asian children (Figure 1). If
>80 nmol/L (32 ng/mL) is used, 90% of the UK popula-
tion had a plasma 25OHD concentration below the
threshold. No new national data have been collected in
the UK since 2002, but data will be available from the
newly constituted NDNS rolling programme, starting in
2008.

VITAMIN D STATUS IN THE USA (LATITUDE 25°N–47°N)
The assessment of vitamin D status using plasma 25OH
concentration on a nationally representative basis is also
a component of the National Health and Nutrition
Examination Survey (NHANES) of the United States of
America. An analysis of the 25OHD data obtained in the
third NHANES (1988–1994) is available.40,41 Samples
were collected from individuals aged ≥12 years. The
housebound and those living in residential institutions
were excluded. Measurements of 25OHD were per-
formed using the Incstar-Diasorin RIA method in one
laboratory (National Center for Environmental Health,
CDC, Atlanta, Ga, USA) and monitored using the inter-
national DEQAS. The design of the survey was such that
samples from northern regions were collected during
the summer (April–October) and those from southern
regions were obtained during the winter (November–
March). This makes it difficult to separate the indepen-
dent effects of season and latitude in these data. The
prevalence of low vitamin D status in 1988–1994, using
<25 nmol/L (10 ng/mL) as the criterion for risk of defi-
cency, was 1–5%, depending on season/latitude and age
group, and was, therefore, lower than that recorded in the
UK. The prevalence using 50 nmol/L (20 ng/mL) as the
threshold of adequacy was 10–40%, with no conspicuous
peak of prevalence in young adults or the elderly. In most
age groups, the prevalence of low status was greater in
the winter/southern latitudes than in the summer/
northern latitudes, in females than males at all ages, and
in black and Mexican Americans compared to the white
population.

VITAMIN D STATUS IN PREGNANT WOMEN
FROM ETHNIC MINORITIES
In the last few years there has been increasing recognition
of a high prevalence of low vitamin D status (<25 nmol/L;
10 ng/mL) among pregnant women from ethnic minority
groups in Northern Europe, Australasia, and the United
States, suggesting a high risk of vitamin D deficiency dis-
ease.2,42 Typically, women from these ethnic groups have a
dark complexion, customary dress that restricts or pre-
vents exposure of the skin to sunshine, and a low uptake
of vitamin D supplementation. Some examples of preva-
ience rates collected from such women at antenatal clinics
are given in Table 2.17,43–46 The vitamin D status of the
mother in pregnancy is a key determinant of the vitamin
D status of her infant, and poor maternal vitamin D status
is likely to be a primary factor in the resurgence of rickets
seen among children from these ethnic minority
groups.2,47–49 This problem is not confined to pregnant
women from these ethnic groups in temperate climates,
however; there are also reports of a high prevalence
of low vitamin D status among pregnant women in the
Middle East, India, Pakistan, and Ethiopia.42

Figure 1  Vitamin D status in the UK (50°N–58°N). Percentage of males (M) and females (F) with a plasma 25-hydroxyvitamin
D concentration below (a) 25 nmol/L (10 ng/mL) and (b) 50 nmol/L (20 ng/mL). From the National Diet and Nutrition Survey
1992–2001, all seasons combined,35–38 plus a population sample of British Asian Children.39
DETERMINANTS OF PLASMA 25OHD CONCENTRATION

There are two primary sources of vitamin D for the human: endogenous skin synthesis and diet.\textsuperscript{18–21} Cholecalciferol (D₃) is synthesized in the skin when exposed to ultraviolet light in the range of 290–315 nm (UVB). Vitamin D is provided from the diet as cholecalciferol (D₃, from animal sources) or as ergocalciferol (D₂, from plant sources). The relative contributions of sunshine exposure and diet to the vitamin D status of an individual depend on many factors. These are described briefly below and reviewed in detail elsewhere.\textsuperscript{2,18–21,25}

Skin exposure to sunlight at the required wavelengths

a) \textit{Latitude, season, and time of day}. The more oblique the angle at which sunlight passes through the earth’s atmosphere, the more UVB light is absorbed. The further from the equator, the fewer months of the year that sunlight contains the required wavelengths.\textsuperscript{18,19,21} For example, at latitudes above about 40°, sunlight is only effective for cholecalciferol synthesis between April and October. As a consequence, vitamin D status at these latitudes tends to be higher at the end of summer than at the end of winter. For example, in the UK, the mean 25OHD concentration in the summer is approximately twice that in the winter in most age groups.\textsuperscript{35–38} In addition, at temperate latitudes, only sunlight produced in the middle of the day (between about 10:00 and 15:00) is effective for cutaneous synthesis of vitamin D.\textsuperscript{19}

b) \textit{Cloud cover and atmospheric pollution}. These filter or block sunlight of the necessary wavelengths, and can lead to variations in vitamin D status at the same latitude. An example from India described marked differences in the prevalence of 25OHD concentration <25 nmol/L (10 ng/mL) among children living in different districts of Delhi (28°N), depending on the level of pollution.\textsuperscript{50}

c) \textit{Time spent outdoors}. The frequency and duration of skin exposure to UVB sunlight is a primary factor determining vitamin D status. The housebound and those who spend little time out of doors have few opportunities for skin sunshine exposure. In addition, sunshine that passes through glass or Plexiglas does not contain UVB and so is ineffective for skin synthesis of cholecalciferol.\textsuperscript{18,19}

d) \textit{Customary dress and sunscreen use}. Individuals who wear clothes that cover most of the body, including the face, head, and arms, or who liberally use sunscreen, have minimal skin sunshine exposure.\textsuperscript{18} Current campaigns on skin cancer prevention often emphasize the importance of protecting the skin from sunshine without promoting safe sunshine exposure for the skin synthesis of vitamin D.\textsuperscript{18,19}

Customary dress that conceals much or all of the body is associated with a high prevalence of low vitamin D status, even in sunny areas of the world at low latitudes (e.g., Beirut and Bekaa Valley, Lebanon, 33°N–34°N\textsuperscript{21}).

e) \textit{Skin pigmentation and age}. Darker-skinned individuals and the elderly produce less cholecalciferol in the skin for the same exposure to UVB light than lighter-skinned individuals and young adults, respectively; they therefore require longer exposures to achieve the same plasma 25OHD concentration.\textsuperscript{18,19,21}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
\textbf{Country} & \textbf{Latitude} & \textbf{Assay} & \textbf{Group} & \textbf{25OHD nmol/L} \\
\hline
The Netherlands & 52°N & Diasorin RIA & Turkish & <25 nmol/L <37.5 \%
\hline
(\textit{The Hague}) Van der Meer et al. (2006)\textsuperscript{44} & & & Moroccan & 81% \%
\hline
UK & 51°N & Incstar RIA & Non-European & >50% \%
\hline
(\textit{Cardiff}) Datta et al. (2002)\textsuperscript{45} & & & & \\
\hline
New Zealand & 41°S & Diasorin RIA & Mixed ethnicity & 61% \%
\hline
(Wellington) Judkins and Eagleton (2006)\textsuperscript{17} & & & & \\
\hline
Australia & 38°S & Incstar RIA & Veiled/dark skin & >80% \%
\hline
(Melbourne) Grover and Morley (2001)\textsuperscript{16} & & & & \\
\hline
USA & 40°N & IDS ELISA & White & 5% \%
\hline
(\textit{Pittsburgh}) Bodnar et al. (2007)\textsuperscript{43} & & Black & 29% \%
\hline
\end{tabular}
\caption{Prevalence of low vitamin D status in pregnant women from ethnic minority groups in different countries.}
\end{table}
Inclusion of rich sources of vitamin D in the diet

a) There are relatively few foods that are natural sources of vitamin D and are eaten regularly. The most common are oily fish and egg yolk. Meat contains measurable quantities of vitamin D and its metabolites and can make an important contribution to dietary vitamin D intake. However, although it has been included in the NDNS estimates of vitamin D intake since 1995, to date, the contribution of meat has rarely been included in dietary assessments in other countries because of the scarcity of analytical data. Recent analyses from Ireland have added to the available data on the vitamin D content of meat.

b) Dietary vitamin D supplements, in the form of fish liver oils (D3) or synthesized vitamin D (D2 or D3), are increasingly available and can make significant contributions to intake for those individuals who consume them on a regular basis. In some countries, supplement use is recommended for specific population groups that are vulnerable to vitamin D deficiency. For example, in the UK, supplements are recommended for infants, children aged <3 years, pregnant and lactating women, people aged ≥65 years, those in ethnic minority groups, and those who are frail and with restricted sunshine exposure.

c) In some countries, vitamin D is added as a fortificant to specific foods in the national food supply, either on a mandatory or an optional basis. Examples include the addition of vitamin D to margarine (mandatory) and spreading fats in the UK to milk in the USA, and to some juices and breakfast cereals in both countries. Vitamin D is a fortificant of some foods manufactured for special purposes, e.g., infant formula milks. Fortification policies vary widely among countries.

Influence of other factors on vitamin D supply or metabolism

a) The vitamin D status of the mother in pregnancy influences the vitamin D status of her infant in the first months of life.

b) Calcium and phosphate intake influence vitamin D metabolism and a low calcium intake may influence vitamin D status. This is discussed later.

c) Adiposity. Obese individuals tend to have a lower 25OHD concentration than those of normal weight. This may be due to differences in lifestyle but may also be because vitamin D, a fat-soluble compound, is taken up by adipose tissue.

d) Ethnic and genetic differences in physiology and vitamin D metabolism may affect the vitamin D requirements and status of different populations, such as have been reported in Chinese, Asians, Indians, and African Americans.

e) Poor renal function may reduce the conversion of 25OHD to its active metabolite in the kidney, resulting in poor availability of active vitamin D in target tissues and elevated parathyroid hormone (PTH) concentrations. This can lead to higher concentrations of 25OHD in the circulation. Conversely, hyperparathyroidism secondary to poor renal function may decrease the half-life of 25OHD, and thus decrease its concentration in the circulation. Poor liver function may result in decreased production of 25OHD and its binding protein.

f) Some diseases, such as tuberculosis, appear to increase the requirement for vitamin D and are associated with low plasma 25OHD concentrations.

RELATIVE CONTRIBUTIONS OF SUNSHINE EXPOSURE AND DIET

The relative contributions of sunshine exposure and dietary intake to vitamin D supply and the achievement of adequacy in an individual, therefore, depend on many factors. These are not necessarily obvious from first principles. For example, in Europe (latitude 36°N to 63°N) it might be expected that there would be a higher risk of low vitamin D status in the north than in the south because exposure to UVB sunlight would be restricted to fewer months of the year. However, studies conducted in Europe during the last 20 years, in which samples were collected from different countries but measured in centralized laboratories, have shown that the prevalence of low vitamin D status is greater in the countries of the Mediterranean and Central Europe than in Scandinavia and other northern regions. This is thought to reflect the higher vitamin D intakes in Northern European countries coupled with differences in skin exposure to UVB sunlight.

There have been few quantitative assessments of the relative contributions of sunshine exposure and dietary intake to vitamin D supply in different populations. However, some indication can be obtained by examining the relationship between plasma 25OHD concentration and dietary intake in nationally representative data. In the NHANES III data, vitamin D status among African Americans was associated with the consumption of
vitamin D-fortified foods (milk and breakfast cereals) and supplements. Similarly in the UK, significant positive correlations were observed between 25OHD and dietary vitamin D intake in NDNS data when considered on a year-round basis. However, more detailed analyses, using NDNS data from young children and the elderly, showed that the relationship was only significant in the winter, spring, and autumn, not in the summer (July–September). Furthermore, the plasma 25OHD concentration associated with an intake of about 10 \( \mu g \) /day (400 IU/day) in older people during these months was similar to the mean value achieved in the summer (Figure 2). This supports the UK’s Reference Nutrient Intake of 10 \( \mu g \) /day for people 65 years of age and those in the general population with limited exposure to summer sunshine. In countries where the general lifestyle limits skin sunshine exposure and where there is a high prevalence of low 25OHD concentration, such as Lebanon, vitamin D status has also been shown to depend on vitamin D intake.

VITAMIN D STATUS IN THE TROPICS

The body regulates the amount of cholecalciferol produced by skin synthesis that appears in the circulation, thereby preventing vitamin D intoxication. It is reasonable to assume that, providing no factors limit vitamin D biological effectiveness, the range of plasma 25OHD concentrations achieved through abundant exposure to sunshine at the required wavelengths is indicative of optimal vitamin D status.

In the NDNS, mean plasma 25OHD concentrations measured in the summer were as follows: children aged 1½ to 4½ years, 66 nmol/L (26 ng/mL); children aged 4–18 years, 79 nmol/L (32 ng/mL); adults 19–64 years, 65 nmol/L (26 ng/mL); people aged 65 years and over (free-living), 69 nmol/L (28 ng/mL). However, summer 25OHD concentrations in countries where sunshine only contains UVB light for a limited period of the year, such as the UK, may not represent those that would be attained if individuals were exposed for a longer period. On these grounds, therefore, it would be anticipated that populations living in the tropics with abundant all-year UVB sunshine and a lifestyle that does not restrict skin sunshine exposure would have plasma 25OHD concentrations that could act as a reference range for vitamin D status. However, relatively little data are available from such populations.

The Gambia, West Africa (latitude 13°N) has abundant, tropical sunshine all year. There is a short rainy season from June to October, but characteristically, there are periods of sunshine between the episodes of heavy rainfall. Maximum daily temperatures range from a low

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**Figure 2** Relationship between plasma 25-hydroxyvitamin D concentration and dietary vitamin D intake among older people in the UK at different seasons of the year. Data from Bates et al. (2003) using values from the National Diet and Nutrition Survey: People Aged 65 Years and Over. They are for men and women combined living in the community (n = 773). Reproduced from Bates et al. (2003) with permission.
of around 25°C in December to a high of around 40°C in April. Much of The Gambia is orchard savannah, with only sparse tree cover. The rural people are farmers, and men, women, and children spend much of their time outdoors. The adult dress does not restrict sunshine exposure of the arms, face, or head and, not infrequently, the shoulders and upper back are uncovered, especially during farming.

As part of our ongoing program of research into the calcium requirements of rural Gambian people, my group at MRC Human Nutrition Research (formerly at the MRC Dunn Nutrition Unit) has measured plasma 25OHD concentration in several age groups during the period 1990–1999, using the Incstar-Diasorin method performed in the same laboratory as the NDNS measurements (Table 3). These were small studies, conducted for a separate purpose, and the results cannot be taken as representative of the Gambian population. However, they do provide insight into the likely range of plasma 25OHD concentrations among individuals living in the tropics with abundant skin exposure to sunshine.

As shown in Table 3, the mean concentrations in these studies were between 80 and 100 nmol/L (32 ng/mL and 40 ng/mL, respectively). Interestingly, small but significant effects of age and season were observed in older Gambian women in the same direction as those observed in temperate climates, but at higher concentrations overall. Lower mean 25OHD concentrations were recorded among breastfeeding mothers (measured at 13 weeks postpartum), suggesting there may be a physiological effect of lactation on vitamin D metabolism. In the Gambian studies, no individual was identified with a plasma 25OHD <25 nmol/L (10 ng/mL) and, except for breastfeeding women, few had a concentration <50 nmol/L (20 ng/mL). However, as can be seen in Table 3, a substantial proportion had a concentration <80 nmol/L (32 ng/mL). The mean 25OHD concentrations recorded in these Gambian studies were lower than those recorded in the UK during the summer using the same methodology. They may, therefore, be more representative of average population concentrations achievable when exposure to UVB sunlight is not restricted.

**DIETARY INTAKES OF VITAMIN D**

In countries where there is restricted skin exposure to sunshine of the necessary wavelengths, a dietary supply of vitamin D is important. Vitamin D intake varies from one country to another depending on dietary habits, the use of dietary supplements, and the extent to which the national food supply is fortified with vitamin D. For example, in the UK the mean vitamin D intake, as measured in NDNS, is around 2 μg/day for children and 3–5 μg/day for adults. The main food sources are oily fish, fortified breakfast cereals, meat, eggs, and fortified margarine. In adults aged 19–64 years, measured in 2001–2002, dietary supplements provided 25% of daily intake for women and 12% for men. This contrasts with the USA where the mean vitamin D intake is higher, at around 7 μg/day for women and 8 μg/day for men, and where supplements and fortified milk are the main sources of vitamin D. In Japan, where the mean intake of vitamin D is similar to in the USA, supplement use is not widespread, and over 90% of daily intake comes from oily fish.

**DIETARY REFERENCE VALUES/RECOMMENDATIONS FOR VITAMIN D**

Dietary reference values/recommendations for vitamin D from national authorities differ among countries. Examples are given in Table 4. However, closer inspection shows that the recommendations are, in fact, broadly similar but differ in how they are presented. In the UK, no reference nutrient intake (RNI) is given for the general population aged 4–65 years, with the caveat that an RNI of 10 μg/day is set for those at risk of vitamin D.


deficiency, such as those with limited skin exposure to sunlight.\textsuperscript{2,23,75} In contrast, the USA and Canada set an adequate intake (AI) of 5 mg/day for the general population under 50 years, with the caveat that this applies only to those with “limited but uncertain sun exposure and stores, with a safety factor for those unable to obtain sunlight”.\textsuperscript{24} In the European Union, the population reference intake (PRI) for vitamin D is given as 0–10 mg/day, depending on the extent of exposure to UVB sunlight.\textsuperscript{86} In addition, most authorities recognize infants, young children, pregnant and lactating women, and the elderly as being vulnerable to vitamin D deficiency, and make specific dietary recommendations for these groups. Thus, all the recommendations are based on the assumptions that the main source of vitamin D for the general population is skin synthesis during the summer and that a dietary supply of vitamin D is necessary when skin exposure to sunlight of the appropriate wavelengths is restricted and to protect vulnerable groups against deficiency.

However, as can be appreciated from Table 4 and from the description of population dietary intakes above, regardless of how they are expressed, it is difficult for the dietary recommendations to be met from food sources, even when fortification is widely practised. Consequently, many authorities advocate supplement use for those at risk of restricted sunshine exposure at the effective wavelengths.

**FUNCTIONAL MARKERS OF VITAMIN D STATUS**

Plasma 25OHD concentration is a marker of vitamin D supply and does not necessarily provide an indication of the availability of active vitamin D for use by target tissues. In addition, the functional consequences of, or biological need for, a specific 25OHD concentration in the circulation may depend on several factors, such as the stage of life, metabolic differences, renal function, and the supply of other nutrients such as calcium.

There is, therefore, interest in identifying an index of vitamin D status that is linked to function and that could be used to define vitamin D sufficiency beyond the avoidance of clinical deficiency. PTH has been proposed as such an index because of its role in the conversion of 25OHD to the active metabolite of vitamin D, 1,25-dihydroxyvitamin D \([1,25(OH)_2D]\). Plasma PTH concentration is inversely related to 25OHD concentration in many population groups,\textsuperscript{23,84} and decreases in response to vitamin D supplementation.\textsuperscript{87,88} In addition, primary hyperparathyroidism is linked clinically to bone disease and, in older people in Western countries, an elevated plasma PTH concentration is a risk factor for osteoporosis.\textsuperscript{4} However, in practice, PTH has not proved particularly useful as a functional index of vitamin D adequacy.\textsuperscript{23,84} Some studies have identified a plasma concentration of 25OHD below which PTH concentration starts to rise, and such concentrations have been proposed as a lower threshold of vitamin D sufficiency.\textsuperscript{89,90} However, where such a cut-point was identified, the threshold of 25OHD concentration varied between 20 nmol/L and 110 nmol/L.\textsuperscript{23,84,91} Other studies, while showing a significant inverse relationship between PTH and 25OHD, have been unable to identify a cut-point between a rise in PTH and a lower plateau.\textsuperscript{74,88,92} Furthermore, some studies have shown an increase in PTH at high 25OHD concentrations, possibly reflecting poor renal function.\textsuperscript{74}

One of the main drawbacks, however, of using plasma PTH concentration as a functional index is the wide variation among individuals at any given plasma 25OHD concentration.\textsuperscript{74,83} Furthermore, much of the interest in PTH as a functional index of vitamin D adequacy has been for use in the elderly in Western countries. It is likely that the interpretation of plasma PTH concentration and its relationship with 25OHD differs among countries and stages of life. The relationship between PTH and 25OHD is age dependent\textsuperscript{92} and influenced by renal function.\textsuperscript{68} Physiologically, plasma PTH concentration is reduced during pregnancy and lactation\textsuperscript{93} and may be increased in puberty in association with the higher calcium requirement for skeletal growth.\textsuperscript{94} A chronically low calcium intake may also elevate PTH con-

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**Table 4. Dietary reference values for vitamin D (µg/d) in UK, USA/Canada, and European Union.**

<table>
<thead>
<tr>
<th>Country</th>
<th>DRV</th>
<th>Young children</th>
<th>Children and adults</th>
<th>Pregnancy + lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.6–3 years</td>
<td>&lt;50 years</td>
<td>≥50 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(µg/d)</td>
<td>Group (µg/d)</td>
<td>Group (µg/d)</td>
</tr>
<tr>
<td>UK 1991, 1998</td>
<td>RNI</td>
<td>7</td>
<td>All*</td>
<td>50–64 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>USA/Canada 1997</td>
<td>AI</td>
<td>5</td>
<td>All†</td>
<td>50–70 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>≥70 years</td>
</tr>
<tr>
<td>EU 1993</td>
<td>PRI</td>
<td>0–10</td>
<td>All</td>
<td>0–10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11–18 years</td>
<td>0–15</td>
<td></td>
</tr>
</tbody>
</table>

* For general population; 10 µg/day for those with limited skin sunshine exposure.
† For those in the population with limited or uncertain skin sunshine exposure.

*Abbreviations: DRV, dietary reference value; RNI, reference nutrient intake; AI, adequate intake; PRI, population reference intake.

Data from references \textsuperscript{2,23,24,86}. 

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centration independently of vitamin D supply. In The Gambia, for example, where mean calcium intakes are very low at 200–400 mg/day, our studies have shown higher plasma PTH concentrations than in the UK throughout adult stages of life, and they are not inversely related to 25OHD concentration. Whether such alterations in PTH should be considered pathological or an integral part of a physiological compensatory mechanism is a question that needs more research.

**INTERDEPENDENCE OF VITAMIN D, CALCIUM, AND PHOSPHATE**

Vitamin D and calcium metabolism are highly interdependent, with PTH being the key hormone that maintains plasma ionized calcium by regulating the renal synthesis of 1,25(OH)₂D. When the concentration of plasma ionized calcium falls, PTH rises and stimulates 1,25(OH)₂D synthesis. This active vitamin D metabolite promotes calcium supply into the bloodstream by increasing intestinal calcium absorption, renal calcium reabsorption and calcium release from the skeleton. This also promotes phosphate supply into the bloodstream, because intestinal phosphate absorption and renal phosphate reabsorption are enhanced by 1,25(OH)₂D and phosphate is released along with calcium from skeletal mineral. It has been recognized for many years that the body must be able to excrete this additional phosphate rapidly to prevent it from accumulating. However, it has only recently been appreciated that 1,25(OH)₂D plays a central role in an integrated calcium-phosphate-vitamin D system that promotes renal phosphate excretion when calcium and phosphate flux from intestine and bone is increased (Figure 3). Physiologically, 1,25(OH)₂D stimulates the cells of the skeleton to produce fibroblast growth factor 23 (FGF23) which, along with other factors, promotes urinary phosphate excretion. This integrated metabolic system is considered to be essential for the maintenance of plasma ionized calcium and phosphate within their physiological ranges during the everyday fluctuations in the supply of these nutrients.

Perturbations in any part of the calcium-phosphate-vitamin D system might, therefore, be expected to cause disease. Vitamin D deficiency causes rickets by preventing sufficient calcium being absorbed in the intestine for skeletal mineralization. It is, therefore, plausible that calcium deficiency might also cause rickets in the absence of primary vitamin D deficiency. There is evidence, from our studies in The Gambia, and from other studies in Nigeria, South Africa, and Bangladesh, that this may be the case. Cases of rickets in these countries have been reported in which plasma 25OHD concentration is >25 nmol/L (10 ng/mL), PTH and 1,25(OH)₂D concentrations are normal or elevated, plasma calcium is normal, but plasma phosphate concentration is low. Characteristically, these children also come from populations where calcium intake is very low, suggesting that calcium deficiency, possibly combined with other predisposing factors, may precipitate disease. Treatment with calcium has been associated with clinical improvements. Recently, we demonstrated abnormally elevated circulating concentrations of FGF23 in Gambian children with rickets and lower concentrations of 25OHD than in children from the local community, although at concentrations above those associated with primary vitamin D deficiency. We hypothesized that calcium deficiency leads to chronically elevated PTH and 1,25(OH)₂D, which, in turn, elevates FGF23, leading to urinary phosphate-wasting, hypophosphatemia and rickets, and that the increased production of 1,25(OH)₂D leads to an increased biological requirement for vitamin D.

**Figure 3** Schematic representation of an integrated calcium-phosphorus-vitamin D homeostatic system. Reproduced from Prentice (2007) with permission.
GLOBAL PERSPECTIVE

Clinical vitamin D deficiency, manifested as rickets and osteomalacia, is a major public health problem in many parts of the world. Action is urgently needed to reduce the risk of clinical vitamin D deficiency worldwide among infants, young children, pregnant mothers, and other vulnerable groups. Effective ways to do the following need to be found and implemented at the population level: 1) promote safe skin exposure to UVB sunlight; 2) improve dietary intake of vitamin D; and 3) increase awareness among policy makers, health professionals, and the general public about the importance of vitamin D.

CONCLUSION

Primary deficiency is highly prevalent, even in countries with abundant sunshine, when skin exposure to UVB sunlight is limited by lifestyle and other factors. Secondary deficiency may also be prevalent in populations where very low calcium intakes or other factors, such as underlying disease, may increase the biological requirement for vitamin D. Plasma 25OHD at concentrations <25 nmol/L (10 ng/mL) is a useful marker of the risk of clinical deficiency, despite limitations caused by the lack of methodological standardization. The usefulness of 25OHD as a risk marker for health outcomes other than rickets and osteomalacia may be more limited and functional indicators are needed. However, while the legitimate debate continues about which plasma 25OHD concentrations to select as yardsticks of vitamin D adequacy with respect to other health outcomes,25–27 we need to be cautious that this does not delay action to reduce the global burden of frank vitamin D deficiency.

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