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AMPATHCHAT

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Vitamin D overview

After much consideration about the most appropriate cutoffs to define adequate vitamin D status, Ampath has decided to lower the currently reported cutoffs to those proposed by the Institute of Medicine, and recently endorsed by the National Osteoporosis Foundation of South Africa. According to these guidelines, a 25-hydroxyvitamin D level < 12 ng/ml is regarded as vitamin D deficient, with levels between 12 and 19 regarded as insufficient and levels of 20 ng/ml or above as sufficient.

Overt vitamin D deficiency manifesting as osteomalacia or rickets is now uncommon in developed countries. However, the incidence of **subclinical vitamin D deficiency** presenting with low bone mass on bone densitometry, muscle weakness and risk of falls and fragility fractures may be higher than expected, especially in the elderly where both vitamin D stores and the skin's ability to convert 7-dehydrocholesterol to vitamin D decline with age.

The **prevalence of vitamin D deficiency** is dependent on the vitamin D level used to define deficiency. The National Health and Nutrition Survey (NHANES) 2005–2006 has shown that 41.6% of all adults in the United States (aged 20 years and older) have vitamin D levels below 20 ng/ml.[1, 2]

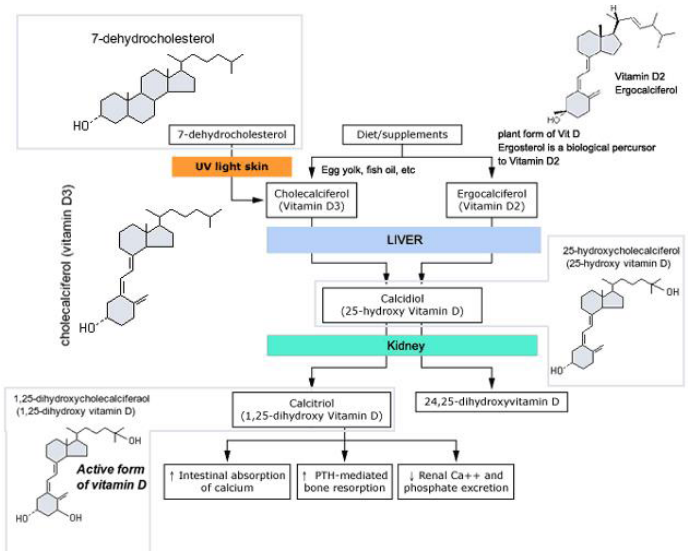
Data for South Africa is limited, with a previous retrospective analysis of laboratory results at Tygerberg Hospital showing a prevalence of 41% for vitamin D results below 15 ng/ml. A more recent study done at the National Health Laboratory Service (NHLS) in Johannesburg in adult patients (aged 18 to 65 years) confirmed expected seasonal, ethnic and sexual differences. The prevalence of vitamin D levels below 12 ng/ml was 28.6% in Indians compared to just over 5% in black Africans. Other ethnic groups were not studied.[3]

Although there is some evidence to support the **benefit of vitamin D on extraskeletal health**, including the immune and cardiovascular systems, most recommendations are based on the beneficial effect of vitamin D on skeletal health, for which consistent and conclusive evidence of benefit exists.[1, 2, 5]

Sources of vitamin D

UVB sunlight exposure is the main source of vitamin D and is influenced by season, latitude, indoor working hours, skin pigmentation, clothing style and use of sunscreen. There is large interindividual variation in the vitamin D synthetic ability of the skin. Only a small part of vitamin D comes from dietary sources, mainly fatty fish, and supplemented food products (such as milk, infant formula and breakfast cereal), but this becomes more important when sun exposure is restricted, e.g. in the aged, infants and disabled persons.

Figure 1: Vitamin D synthesis, metabolism and effects on calcium and phosphate homeostatis



Vitamin D synthesis and metabolism

Previtamin D_3 is synthesized nonenzymatically in the skin from 7-dehydrocholesterol during ultraviolet exposure. It then undergoes a temperature-dependent rearrangement to form vitamin D_3 (cholecalciferol). Vitamin D from the diet or dermal synthesis is biologically inactive and requires enzymatic conversion in the liver (25-hydroxylation) and kidney (1-alpha-hydroxylation) to the active metabolite 1,25-dihydroxyvitamin D (calcitriol). Renal alpha-1-hydroxylase enzyme activity is primarily stimulated by an increase in parathyroid hormone (PTH) secondary to hypocalcaemia, as well as by hypophosphataemia. Fibroblast growth factor 23 (FGF23) inhibits renal production of 1,25-dihydroxyvitamin D. The 1,25-dihydroxyvitamin D production in turn inhibits PTH synthesis and secretion, and stimulates FGF23 production, creating a negative feedback loop.

Both 1,25-dihydroxyvitamin D and 25-hydroxyvitamin D [25(OH)D] are degraded in part by 24-hydroxylation. The liver also has the capacity to metabolise 25(OH)D to other inactive metabolites.[1]

The 1-alpha-hydroxylase enzyme is also expressed in extrarenal sites, which becomes of clinical relevance in granulomatous disorders (such as sarcoidosis, tuberculosis and chronic fungal infections) and some lymphomas where unregulated 1,25-dihydroxyvitamin D production occurs in activated macrophages, resulting in hypercalcaemia and hypercalciuria.

Definition of normal vitamin D status

The recommended test for the assessment of vitamin D status is **serum total 25-OH vitamin D [25(OH)D] levels** as it is believed to reflect both the vitamin D from dietary sources as well as dermal synthesis. There is, however, **controversy** about the **optimal level.**

Some authors advocate levels of 20–40 ng/ml, while others, including the National Osteoporosis Foundation (NOF) and the American Geriatric Society (AGS), favour maintaining levels between 30 and 50 ng/ml, especially in older adults to minimise the risk of falling and fractures.[2] The *Endocrine Society Clinical Practice Guidelines,* published in 2011, define vitamin D deficiency as a level below 20 ng/ml, with an intermediary zone of vitamin D insufficiency from 20–29 ng/ml,[4] and these guidelines have been used by Ampath for reporting since 2014.

The most recent *Revised South African Clinical Guidelines for the Diagnosis and Treatment of Osteoporosis* published by the National Osteoporosis Foundation of South Africa (NOFSA) in 2017, however, supports the Institute of Medicine (IOM) 2010 guidelines[5] that define **vitamin D deficiency** as a level **below 12 ng/ml (30 nmol/l), vitamin D insufficiency** as a level of **12–19 ng/ml** and **vitamin D sufficiency** as a level **of 20 ng/ml (50 nmol/l) and above**.[6] A vitamin D level of 20 ng/ml or above is regarded by the IOM as the level at which 97.5% of the population would achieve an adequate bone health benefit.[5] Ampath will, in future, be using these cutoffs for reporting.

Although several epidemiological studies suggest that a 25(OH)D level above 30 ng/ml may have additional health benefits in reducing risk of common cancers, autoimmune diseases, type 2 diabetes, cardiovascular disease and infectious diseases, these claims have not been substantiated in randomised clinical trials.[4, 5]

There is also debate regarding the **safe upper limit.** An upper limit of 100 ng/ml has previously been advocated.[4, 7] However, recent guidelines point towards a level of **50–60 ng/ml,** due to concerns of adverse outcomes related to all cause mortality, chronic diseases, falls and fractures at higher vitamin D levels.[5] Evidence also exists regarding a potentially increased risk for some cancers (including pancreatic and prostate cancer) with levels above 30 ng/ml to 48 ng/ml.[2, 5] Studies performed with high sun exposure in young adults have shown an apparent physiological ceiling at 60ng/ml.[8] Prolonged exposure of the skin to sunlight does not produce toxic amounts of vitamin D_3 due to photoconversion of previtamin D to inactive metabolites, and induction of melanin production.[1] Although vitamin D intoxication has previously been defined as a 25(OH) vitamin D level above 150 ng/ml,[7] hypercalcaemia and hypercalciuria have been described with levels above 88 ng/ml.[2]

Optimal vitamin D intake to prevent deficiency (assuming minimal sun exposure and adequate calcium intake to obtain beneficial effects on skeletal health)[4, 5, 6]

- The **recommended dietary allowance (RDA)** for **adults** aged 19–70 years is 600 IU/d of vitamin D (daily calcium requirement: 1 000 mg 19–50 years old and males 51–70 years, 1 200 mg for females 51–70 years).
- **Older persons** (>70 years) confined indoors and other **high-risk** groups may have higher requirements:
  - The NOF and AGS recommend a daily vitamin D intake of 800 and 1 000 IU/d respectively in older persons to reduce the risk of fractures and falls (daily calcium requirement: 1 200 mg for >70 years old).

  - **Pregnant and lactating women** require at least 600 IU/d, although 1 500 to 2 000 IU/d may be needed to maintain adequate levels (daily calcium requirement: 1 000 to 1 300 mg).
  - **Obese** patients, those with **malabsorption** syndromes or on **medications** affecting vitamin D metabolism (including long-term glucocorticoids, anticonvulsants, antifungals such as ketoconazole and antiretroviral treatment), require a 2 to 3 times higher dose for their age group.
- The **maintenance tolerable upper limit** of vitamin D, which is not to be exceeded without medical supervision, is 4 000 IU/d for healthy adults.[1, 4, 5] The applicable level for calcium is 2 500 mg/day for adults aged 19 to 50 years, and 2 000 mg/day for those older than 50 years.[5, 6]

Causes of vitamin D deficiency or resistance

- **Decreased availability** of vitamin D due to inadequate dietary intake, fat malabsorption disorders and/or lack of sunlight.
- **Decreased endogenous synthesis** via decreased 25-hydroxylation by the liver (liver failure) or decreased 1,25-hydroxylation by the kidneys (vitamin D-dependent rickets type 1, chronic renal insufficiency).
- **Increased hepatic catabolism** due to drugs inducing P450-enzyme activity, including phenytoin, phenobarbital, carbamazepine, oxcarbazepine, isoniazid, theophyllin and rifampicin.
- **Increased renal loss** of vitamin D-binding protein (e.g. nephrotic syndrome).
- **End organ insensitivity** to vitamin D metabolites (hereditary vitamin D-resistant rickets/HVDRR, vitamin D-dependent rickets type 2).

Clinical manifestations and biochemistry of vitamin D deficiency

Clinical manifestations depend on the duration and severity of vitamin D deficiency. The majority of patients with **moderate to mild vitamin D deficiency** are asymptomatic and have normal serum calcium, phosphorus and alkaline phosphatase (ALP) levels.

With **prolonged severe vitamin D deficiency** [25(OH)D levels 5–8 ng/ml], intestinal absorption of calcium and phosphorus is decreased, and during early stages, **hypophosphataemia** is more pronounced than hypocalcaemia. As vitamin D deficiency persists, **hypocalcaemia** will occur, leading to **secondary hyperparathyroidism**, which causes phosphaturia, demineralisation of bones and eventually osteomalacia in adults, and rickets and osteomalacia in children.[1, 2, 6]

Additional laboratory testing to consider with vitamin D deficiency includes serum calcium, phosphorus, ALP, PTH, electrolytes, urea and creatinine.[2]

Determination of **1,25-dihydroxyvitamin D** is reserved for the monitoring of specific conditions, such as acquired or inherited diseases of vitamin D and phosphate metabolism.

High-risk groups for vitamin D deficiency requiring screening

Most experts agree that widespread screening for vitamin D deficiency is unnecessary, but that screening should be aimed at the following high-risk groups:[4]

- Older adults, in particular the frail institutionalised elderly
- Limited effective sun exposure due to dark skin, clothing, consistent use of sunscreens, being institutionalised/ hospitalised
- Obesity (fat tissue serves as a reservoir for vitamin D_3 and usually less sun exposure)
- Osteoporosis
- Medication accelerating vitamin D metabolism, e.g. phenytoin
- Malabsorptive diseases, including inflammatory bowel disease and celiac disease
- Pregnant patients with any of the above risk factors

Treatment of vitamin D deficiency

The amount of vitamin D required to treat vitamin D deficiency depends on a number of factors, including the baseline 25(OH) vitamin D level, absorptive capacity, liver capacity for 25-hydroxylation and unknown genetic factors.

In a patient with normal absorptive capacity, serum 25(OH)D concentrations increase by approximately 0.7–1.0 ng/ml for every 100 units (2.5 µg) of added vitamin D, with the larger increment seen with lower baseline vitamin D levels. For example, a patient with a 25(OH)D level of 15 ng/ml would require an additional daily input of about 1 500 IU vitamin D to reach and sustain a level of 30 ng/ml.

Although there has been some debate about the preferred form of vitamin D to be used for supplementation, several studies have shown that both vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) are effective in maintaining serum 25(OH)D levels, and are therefore recommended by the Endocrine Society and NOFSA guidelines.[4, 6] Vitamin D supplementation is mainly administered via the oral route, and can be taken on an empty stomach or with food, as it does not require dietary fat for absorption.[4] Multiple dosing regimens have been shown to be effective in the treatment

of vitamin D deficiency. Dosing frequency at intervals up to once monthly seems to be less important than the cumulative dose.[2] Intermittent high dose supplementation given every three or six months intramuscularly (IMI) has, however, been shown to increase the risk of falls and fracture, and is therefore not advised.

The following treatment guidelines, as proposed by *UpToDate*[2] based on the Endocrine Society Guidelines,[4] are supported by the 2017 NOFSA guidelines:[6]

- Patients with severe vitamin D deficiency (< 10 ng/ml) are usually treated with 50 000 IU of vitamin D_2/D_3 once weekly for 6 to 8 weeks, or its equivalent of 6 000 IU daily, followed by maintenance of 800 IU daily thereafter.
- Patients with 25(OH)D levels of 10 to 20 ng/ml may be given prophylactic vitamin D of 800–1 000 IU daily with a follow up vitamin D level after three months.
- Individuals with 25(OH)D levels above 20 ng/ml are maintained on RDA levels appropriate for their age.
- Obese patients, patients with malabsorption syndromes and those taking medication affecting vitamin D metabolism require a higher dose of 6 000–10 000 IU daily to achieve a blood level of 25(OH)D of 20 ng/ml, followed by maintenance of 3 000–6 000 IU daily.

Follow-up 25(OH)D levels are recommended three to four months after initiation of therapy.

Patients who do not show an increase in their serum 25(OH)D level should be worked up for celiac disease or occult cystic fibrosis, assuming that they were compliant with treatment.

Some patients with vitamin D deficiency may have **co-existing primary hyperparathyroidism**, with calcium being normal or at the upper limit of the normal range in the presence of increased PTH. In these individuals, vitamin D supplementation should be provided to prevent bone loss, but with caution as hypercalcaemia and hypercalciuria may rarely develop. Urinary calcium excretion may be useful for monitoring purposes as it shows a rapid increase with vitamin D repletion in these patients, and higher values may identify patients at risk for nephrolithiasis.

In patients with **granulomatous disease** needing vitamin D supplementation, vitamin D levels should not be increased to above 30 ng/ml, as this may be associated with hyper-calciuria and hypercalcaemia.

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