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VITAMIN D OVERVIEW

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INTRODUCTION

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. Identification and treatment of vitamin D deficiency is important for musculoskeletal health.

The **prevalence of vitamin D deficiency** is dependent on the vitamin D level used to define deficiency. The National Health and Nutrition Survey (NHANES) 2011-2014 has shown that 23% of all adults in the United States (aged 20 yr and above) 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 (37.5 nmol/l). A more recent study done at the NHLS in Johannesburg in adult patients (aged 18-65 yr) confirmed expected seasonal, ethnic and sexual differences. The prevalence of vitamin D levels below 12 ng/ml (30 nmol/l) was 28.6% in Indians (27.9% for Indian females only) compared to just over 5% in Black Africans. Other ethnic groups were not studied.[3]

Although there is some evidence supporting 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.

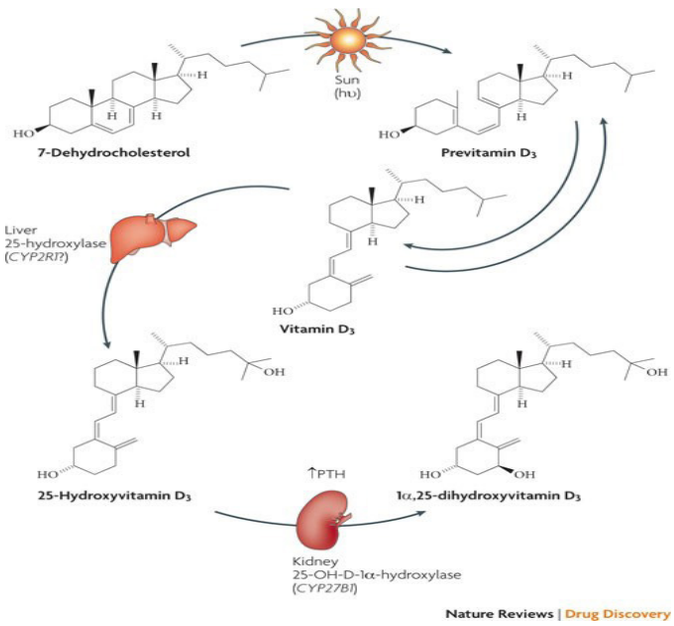

FIGURE 1: DERMAL SYNTHESIS AND METABOLISM OF VITAMIN D_3

VITAMIN D 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. 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]

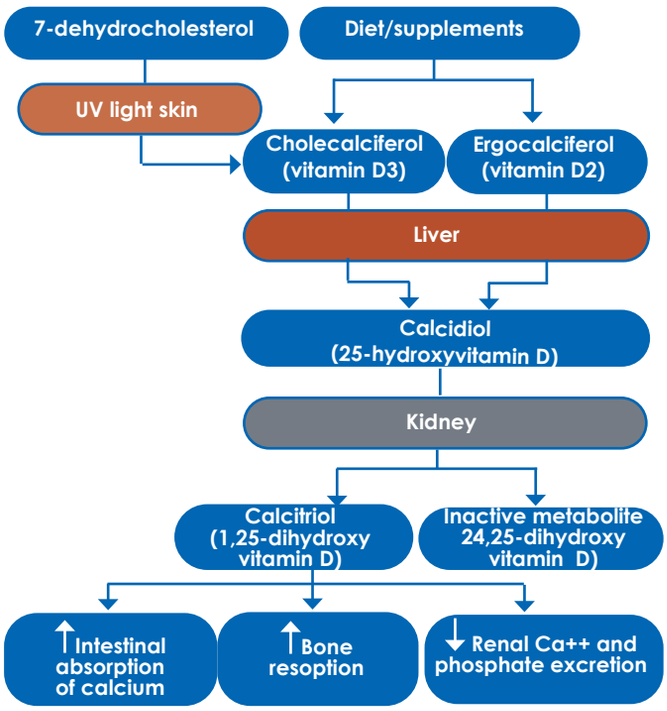

FIGURE 2: METABOLIC ACTIVATION OF VITAMIN D TO CALCITRIOL AND ITS EFFECTS ON CALCIUM AND PHOSPHATE HOMEOSTASIS

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 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**.

The National Academy of Medicine(NAM) and the revised South African Clinical Guidelines for the diagnosis and treatment of osteoporosis published in 2017 by the **National Osteoporosis Foundation of South Africa (NOFSA)** supports the **Institute of Medicine (IOM)** 2010 guidelines[5] defining **vitamin D deficiency** as a level below 12 ng/ml, vitamin D insufficiency as a level of 12-19.9 ng/ml and vitamin D sufficiency as a level of 20 ng/ml 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]

The American Geriatric Society (AGS) and International Osteoporosis Foundation (IOF) suggest a minimum level of 30 ng/ml in older adults to decrease the risk of fractures.[2.]

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 randomized 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) 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, which reduces vitamin D_3 production.[1] Although vitamin D intoxication has previously been defined as a 25(OH) vit 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 children aged 1 to 18 years and **adults** up to 70 yr is 600 IU/d of vitamin D (daily calcium requirement: 1000 mg 19-50 yr old and males 51-70yr, 1200 mg for females 51-70 yr.
- **Older persons (>70 yr)** confined indoors, and other **high-risk** groups may have higher requirements:
  - In 2010, The National Academy of Medicine (NAM) recommended a daily vitamin D intake of 800 IU/d **in older persons** to reduce the risk of fractures and falls (daily calcium requirement: 1200 mg for >70 yr old).
  - **Pregnant and lactating women** require at least 600 IU/d (daily calcium requirement: 1000-1300 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 higher dose for their age group.

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 upon 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, demineralization 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 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, particularly the frail institutionalized 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 several 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 1500 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_3 (cholecalciferol) and vitamin D_2 (ergocalciferol) are effective in maintaining serum 25(OH)D levels and are therefore recommended by the Endocrine Society and NOFSA guidelines.[4,6] However, it is suggested **that D_3 (cholecalciferol) is used when available.**

Vitamin D supplementation is mainly administered orally can be taken on an empty stomach or with food, as it does not require dietary fat for absorption.[4] Many different dosing regimens have been shown to be effective in treatment of vitamin D deficiency. The cumulative dose is the most important factor in treatment.[2] Intermittent high dose supplementation given every 3 or 6 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] and largely based on the Endocrine Society Guidelines,[4] are supported by the 2017 NOFSA guidelines.[6]

- Patients with severe vitamin D deficiency (< 12 ng/ml) are usually treated with 25 000 to 50 000 IU of vitamin D_2/D_3 once weekly for 6 - 8 weeks, or its equivalent of 6000 IU daily, followed by maintenance of 800 IU daily thereafter. **D_3 is preferred**, if available.
- Patients with 25(OH)D levels of 12 – 19.9 ng/ml may be given prophylactic vitamin D of 800 -1000 IU daily with a follow up vitamin D level after 3 months.
- Individuals with serum 25(OH)D levels of ≥20 to 30 ng/mL, 600 to 800 IU daily are sufficient to maintain levels in the target range.
- Individuals with 25(OH)D levels above 30 ng/ml are maintained on RDA levels appropriate for their age.
- In pregnant women, the safety of 50,000 international units of vitamin D weekly for six to eight weeks has not been adequately studied. The American College of Obstetricians and Gynaecologists (ACOG) recommends 1000 to 2000 international units (25 to 50 micrograms) of vitamin D daily.[1] Urinary calcium excretion increases in pregnancy, and it should be monitored when treating vitamin D deficiency, especially in women with a history of kidney stones.

Follow up 25(OH)D levels are recommended **3 - 4 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 **coexisting 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 hypercalciuria and hypercalcaemia.

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