Assessment, treatment and prevention of vitamin D deficiency.

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Abstract:

Vitamin D deficiency and insufficiency are prevalent in numerous clinical populations in the UK, yet symptoms are non-specific and therefore assessment of vitamin D status is low. A population-wide recommendation of 10μg of vitamin D per day is established with a daily supplement recommended, particularly during winter months. However, supplement usage is poor, compounding the risk of deficiency.

Long-term vitamin D deficiency (through poor dietary intake and insufficient sunlight exposure) causes rickets in children and osteomalacia in adults. Therefore, it is important to understand and identify 'at risk' populations, how to measure and interpret vitamin D status and how to support appropriate clinical management.

Clinical management is dependent on the level of vitamin D insufficiency and involves dietary and lifestyle changes in combination with supplementation.

Aims and intended learning outcomes

The purpose of this article is to enable nurses to identify and improve management of patients at high risk of vitamin D deficiency and insufficiency.

After reading the article and completing the CPD questions you should be able to:

- Understand the relevance of vitamin D synthesis and physiology to patient care
- Explain why specific patient groups are at increased risk of deficiency
- Understand the symptoms and long-term consequences of vitamin D deficiency
- Recognise the importance of assessing for vitamin D status in clinical populations
- Support the management and treatment of patients with vitamin D deficiency and insufficiency

TIME OUT QUESTIONS

1) **Considering the patient groups you work with, who would be most at risk of vitamin D deficiencies and what symptoms would you look out for?**
2) **On a day-to-day basis, how could you acquire an understanding of sunlight exposure and vitamin D production in your patients? Consider what question you might ask them.**
3) **If a 65-year-old woman arrived on your ward with fractured wrist from a fall, how would you assess their vitamin D deficiency? Familiarise yourself with trust protocols and procedures.**
4) **Can you summarise the population-level advice for the prevention of vitamin D deficiencies?**
5) **How would you identify patients who need additional dietary support and require referral to a dietitian?**
6) **Consider how you would describe the benefits of vitamin D treatment to individuals to help increase supplement uptake.**

Introduction

Vitamin D deficiency is prevalent across many sub-groups in the UK. These include pregnant and breastfeeding women; infants and young children under 5 years of age; teenagers and younger adults; people following a vegan or restrictive diet; people with long term conditions (e.g., obesity, malabsorptive disorders, end-stage liver or kidney diseases); those with low sunlight exposure (e.g. housebound), people with higher levels of skin pigmentation and older people aged 65 years and over.

Despite evidence of the widespread prevalence and risk of vitamin D insufficiency in the UK, lack of awareness of supplementation recommendations in UK adults is high, and supplementation usage is poor (BNF, 2021).

Providing a healthy and active lifestyle is maintained, the majority of vitamin D is produced in the skin from regular sunlight exposure. Therefore, due to few foods containing vitamin D, the dietary contribution to vitamin D status is low.

Vitamin D is available in two main forms: vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). Vitamin D_3 is the most common form found in the human diet. Upon exposure to UVB radiation, vitamin D_3 is synthesised in the skin (Norman, 2008). Small amounts of Vitamin D_2 is present in some mushrooms and similar products through UVB irradiation (SACN, 2016).

Long-term vitamin D insufficiency and deficiency can have adverse effects on musculoskeletal health as well as other potential conditions (Giustina et al., 2023) which led to widespread free supplementation of 'clinically extremely vulnerable' populations in the UK during the Covid-19 pandemic (DHSC, 2021). The treatment and management of vitamin D insufficiency is in the form of supplementation and lifestyle changes.

Vitamin D sources and dietary intake

Vitamin D_3 is synthesised in the skin from exposure to sunlight and obtained from foods or dietary supplements. If the skin is regularly exposed to sunlight, the cutaneous synthesis of vitamin D_3 is most important source of vitamin D (Holick, 2004). When cutaneous production is limited, dietary sources of vitamin D become more important (SACN, 2016). Vitamin D_2 has a minimal contribution towards vitamin D status in the UK because it is only found in limited plant-based foods and dietary supplements (SACN, 2016).

The National Diet and Nutrition Survey Rolling Programme in the UK indicates that there is a low intake of dietary vitamin D within the population, with very few people meeting the Reference Nutrient Intake (RNI) of 10µg/day. Mean vitamin D intakes from food sources were below the RNI in all age groups. When supplements were considered, mean intakes increased to 29-40% of the RNI in children, 54% for adults aged 19-64 and 91% of 65-74 and 60% of adults aged 75 years and over (PHE, 2020).

Sunlight Exposure

The duration and frequency of UVB radiation exposure from sunlight, and the efficiency of the production, determines the amount of cutaneous vitamin D_3 synthesis (Webb, 2006). The process is influenced by time of day, latitude, cloud cover, season, clothing practice and sunscreen use (Engelsen, 2010; Webb, 2006). Therefore, vitamin D status tends to be lower in northern parts of the UK, between October and March. Vitamin D production is optimal when the sun is highest in the sky during the spring and summer months, but is affected by the amount of cloud cover, clothing practice and sunscreen use. Research indicates that between April to September, 10-15 minutes of daily unprotected sunlight exposure protects people with lighter skin from vitamin D deficiency, while reducing the risk of erythema (sunburn) and skin cancer. For people with darker skin pigmentation, 25-40 minutes is recommended (British Skin Foundation, 2023).

Food Sources

Vitamin D is present in some foods, which are usually of animal origin. Egg yolk is high in vitamin D_3 (12.6µg per 100g) but oily fish (e.g., mackerel, salmon and sardines) is the richest source of vitamin D_3 (5-16µg per 100g) (Finglas et al., 2015). However, the content of vitamin D_3 varies widely due to farming conditions and geographical location (Jakobsen et al., 2019). Lower levels of vitamin D_3 are found in some animal products such as meat, fat and offal (0.1-1.5µg per 100g) (Finglas et al., 2015).

Mushrooms are a natural source of vitamin D_2. However, the vitamin D_2 content varies widely (1- 57µg per 100g) due to growing conditions and whether the mushrooms have been treated with UVB light. (Mattila et al., 2002; Cardwell et al., 2018).

Commercially produced foods in the UK, such as breakfast cereals and some eggs, milk and bread are fortified on a voluntary basis with either vitamin D_2 or D_3 (SACN, 2016). Vitamin D supplements in the UK mainly contain D_3.

Vitamin D synthesis, metabolism and physiological role

Vitamin D_3 is formed by the UVB irradiation of 7-dehydrocholesterol found in the skin or is absorbed at the intestine from ingested food sources containing vitamin D. Vitamin D_3 is bound in circulation to carrier proteins for transport. The side chain of vitamin D_3 is hydroxylated in the liver to form 25(OH)D. The 25(OH)D is further hydroxylated at the kidney to form the active hormone (1, $25(OH)_2D$) (see Figure 1). Vitamin D_2 from dietary sources undergoes similar metabolic transformations post-absorption.

The active vitamin D metabolite is important for normal bone mineralisation through the regulation of calcium and phosphate metabolism (Christakos et al., 2019). Calcium concentrations are tightly regulated to optimise healthy bone mineralisation and maintain neuromuscular function (Giustina et al., 2023).

There is evidence that vitamin D also has other extra skeletal effects (Caprio et al., 2017; Bouillon et al., 2019). Observational studies have associated vitamin D deficiency with an increased risk of infection, including upper respiratory tract infections such as Covid-19 (Chiodini et al, 2021) and randomised controlled trials (RCTs) provide some evidence that vitamin D supplementation may prevent infections in vitamin-D-deficient populations (Martineau et al., 2019; SACN, 2021).

There is a wide collection of observational studies that have linked low levels of vitamin D with Covid-19 incidence, severity of infection and recovery (Jordan et al., 2022). However, these studies have many confounding variables that may drive this association, such as BMI and age. Additionally, many observational studies have overlooked that the main carrier protein for vitamin D (Vitamin D Binding Protein [VDBP]) is an acute phase reactant and so with a large systemic infection (such as Covid-19), the concentration of this carrier protein will fall (Silva et al., 2015). If there is less VDBP to carry the vitamin D in circulation, then vitamin D concentrations will fall (i.e., the infection may be a cause of deficiency) (Subramanian et al., 2022). There is no evidence from more recent RCTs that vitamin D supplementation significantly benefits hospitalized patients with moderate to severe Covid-19 (Brunvoll et al., 2022; Joliffe et al., 2022; Murai et al., 2021), but further data is still required to fully elucidate the relationship between vitamin D and Covid-19.

A positive relationship between total 25(OH)D and physical performance has been reported in some studies (Vaes et al., 2019). The impact of vitamin D supplementation on physical function and falls is controversial, but a recent consensus statement suggests that regular low dose supplementation is likely to reduce falls risk in older people, particularly in those with a baseline total 25(OH)D of <50nmol/l (Giustina et al., 2023).

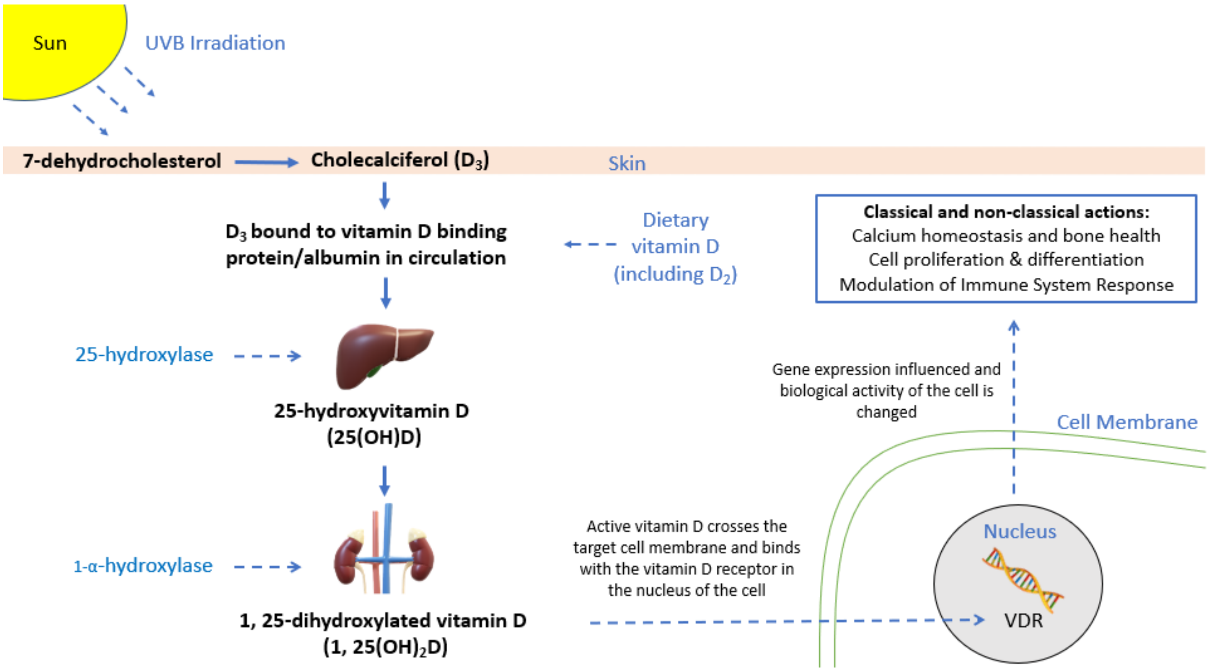

Figure 1: An overview of vitamin D physiology

Prevalence in high risk groups

Younger adults and the elderly or institutionalised have the highest prevalence of vitamin D deficiency in the UK (Lanham-New et al., 2011). In older age groups, the causes of vitamin D deficiency are likely to be multifactorial. There is reduced cutaneous synthesis of vitamin D (Chalcraft et al., 2020). Older adult groups may have less time spent outdoors due to lower levels of physical activity (DHSC, 2008) compared to younger age groups. People following a vegan diet have a low dietary intake of vitamin D and are therefore at increased risk of insufficiency (Bakaloudi et al., 2021).

In the UK, there is high risk of deficiency and insufficiency among certain ethnic groups, particularly in those of South Asian and African-Caribbean origin (Darling, 2020; Darling et al., 2021; Smith et al., 2021). Factors including, less sunlight exposure, more skin pigmentation and wearing of religious or traditional clothing that block UVB sunlight all contribute to lower vitamin D production. (Darling et al., 2013).

Vitamin D levels have been observed to be lower in those living with obesity due to a higher proportion of vitamin D being stored in the excess fat mass as opposed to circulating in the bloodstream. This is known as volumetric dilution effect (Walsh et al., 2017).

Those living with chronic malabsorption disorders (e.g., Crohn's Disease) or following bariatric surgery, and those with chronic liver or end stage kidney disease are also at heightened risk of deficiency (ROS, 2018).

Therefore, reinforcing preventative supplementation usage and assessment of vitamin D status in those who present with symptoms is worthwhile in nearly all patient groups.

According to the latest NDNS, 2% of 4–10-year-olds, 19% of 11-18 year olds, 16% of 19-64 year olds and 13% of those over 65 years have a 25(OH)D concentration of <25nmol/l (PHE, 2020). In a recent study of UK-dwelling south Asians, 55 % had 25(OH)D <25 nmol/l and 92% had 25(OH)D <50 nmol/l (Darling et al., 2021).

Consequences of vitamin D deficiency and insufficiency

Older adults are likely to have low vitamin D which can lead to adverse consequences for calcium metabolism, such as secondary hyperparathyroidism. Secondary hyperparathyroidism is the main cause of bone loss in vitamin D deficiency (Lips & van Schoor, 2011). This, in turn, is deleterious to bone health and may lead to rickets (in children), osteomalacia and osteoporosis.

When vitamin D deficiency is prolonged, PTH remains raised, promoting high bone turnover which can lead to osteoporosis (Lips & van Schoor, 2011). In severe vitamin D deficiency (<12.5nmol/l), osteomalacia occurs when more than 5% of the bone tissue is new (osteoid) bone, (Lips & van Schoor, 2011). In children, severe vitamin D deficiency can lead to rickets (SACN, 2016). Lower 25(OH)D has been associated with lower bone mineral density and bone quality (Zhu et al., 2019) and an increased risk of falls (Snijder et al., 2006) and fractures (van Schoor et al., 2008).

Prevention

In the UK, for individuals aged 4 and over, there is an RNI of 10µg (400IU) per day (SACN, 2016). This is the average amount needed to prevent vitamin D deficiency in 97.5% of the UK population when exposure to sunlight limited. The RNI includes pregnant and lactating women and other at-risk population sub-groups. As there is no RNI for 0–3-year-olds, safe intake levels of 8.5µg/d for 0 – 12-month-olds (including exclusively breastfed babies and those receiving less than 500ml of infant formula milk per day) and 10µg/d for 1 to <4 year olds are used (SACN, 2016).

Due to the prevalence of vitamin D deficiency in many clinical populations, a vitamin D supplement of 10 μg (400 IU) is recommended for all 'at risk' populations, particularly during the winter months (NICE, 2017). However, supplement usage is poor, even when free supplements are available (e.g., through the Healthy Start scheme for pregnant women and children under 5, with less than 10% of eligible people taking the supplements due to lack of knowledge, awareness, poor motivation and poor accessibility to the supplements) (Jessiman et al., 2013). Less than a third of all adults' report vitamin D supplement usage across all age groups (PHE, 2020).

Clinical Assessment

Non-specific symptoms (in children)	Symptoms of rickets (in children)	Non-specific symptoms (in adults)	Symptoms of osteomalacia (in adults)	Symptoms of osteoporosis
• long-standing (> three months), unexplained bone pain • muscular weakness • tetany due to low blood calcium • seizures due to low blood calcium (usually in infancy) • infantile cardiomyopathy	• progressive bowing of legs • progressive knock knees • wrist swelling • rachitic rosary (swelling of the costochondral junctions) • craniotabes • delayed tooth eruption and enamel hypoplasia	• muscle weakness (particularly lower limb) • muscle aches • fatigue/lethargy • chronic pain • bone pain	• lower back pain • bone pain in the shoulder, ribs, pelvis or legs • muscle pain and weakness • waddling gait • impaired physical function	• fragility fractures and falls

Table 1: Symptoms and clinical presentation of vitamin D deficiency and associated diseases (ROS 2018 and 2020)

It is difficult to determine vitamin D deficiency from symptoms alone, due to their generic nature. Therefore, a 25(OH)D measurement is required (ROS, 2018). Routine screening for vitamin D deficiency is not recommended.

The Royal Osteoporosis Society (ROS) recommend that assessment of vitamin D status should be considered in patients with bone diseases which may be improved with vitamin D treatment or prior to beginning a specific treatment where correcting a vitamin D deficiency is essential (ROS, 2018).

Total 25(OH)D is commonly used to assess vitamin D status as it reflects the combined cutaneous synthesis and dietary intake (ROS, 2018). The ROS currently endorses a threshold of 25(OH)D <25nmol/l for deficiency and <50nmol/l for insufficiency. These thresholds are widely used by UK health professionals (ROS, 2018).

Treatment and monitoring of vitamin D deficiency

The latest ROS clinical guidelines for the treatment of vitamin D deficiency are summarised in Figure 2 and are determined of serum 25(OH)D levels. In patients with a serum 25(OH)D <25nmol/l treatment is recommended. In patients with a serum 25(OH)D between 25-50nmol/l treatment is also advised if they have symptoms of vitamin D deficiency, are taking antiresorptive medication (e.g., bisphosphonates), malabsorptive conditions, are at increased risk of osteoporotic fracture, or have elevated secondary hyperparathyroidism (ROS, 2018). For those patients with a serum 25(OH)D >50nmol/l, lifestyle advice on maintaining adequate vitamin D levels should be provided.

The priorities for correction of deficiency are to use an appropriate level of supplementation to raise 25(OH)D above 50nmol/l and provide a timely resolution of clinical consequences, in addition to preventing toxicity (ROS, 2018).

However, there is debate over the optimal way to treat vitamin D deficiency. Compliance with daily oral supplementation can be an issue in certain population groups (Sanfelix-Genoves et al., 2009) and so larger bolus doses may be preferable. However, optimal frequency and size of the bolus dose are still contested and is therefore not used in practice unless there is a need for urgent correction of vitamin D status (ROS, 2018).

Patients who receive pharmacological doses of vitamin D supplements should have blood calcium concentration measured weekly and if episodes of nausea or vomiting have occurred (ROS, 2018). Vitamin D levels can take 3-6 months to reach a steady state after initiation of treatment (ROS, 2018) and therefore reassessment of vitamin D levels is recommended after 6 months. If levels are still deficient, compliance with supplementation should be reviewed and appropriate referrals made (ROS, 2018).

Successful treatment will improve symptoms, improve PTH level and reduce longer-term risk of osteoporosis. However, the success of treatment depends on several factors including sufficient calcium intake. Therefore, we should encourage patients on vitamin D supplements to maintain dietary calcium intake above the RNI (DoH, 1991). Extra care should be taken to ensure appropriate calcium intake in vegan and dairy intolerant populations. Additionally, high calcium intakes are required for those with malabsorptive disorders and on osteoporosis treatment.

Early identification, diagnosis and management of vitamin D insufficiency or deficiency is more likely to be effective.

Summary

There are a wide range of 'at risk' groups and the prevalence of vitamin D insufficiency is high, therefore health care professionals need awareness of the identification and clinical management. Due to the non-specific nature of vitamin D deficiency symptoms, assessment of vitamin D status can be poor and this can lead to long term consequences to bone health. For most people, safe sunlight exposure is the best way to prevent deficiency, as there are few vitamin D rich foods. Treatment of low vitamin D status depends on the severity of deficiency with over-the-counter oral doses being prescribed for insufficiency and higher bolus doses often recommended for severe deficiency.

<table>
<tr><td>Who to TEST</td><td colspan="6">• Patients with diseases (e.g. osteoporosis) that could be improved with vitamin D supplement
• Patients who have symptoms of vitamin D deficiency</td></tr>
<tr><td rowspan="4">How to INTERPRET the result</td><td colspan="6">25(OH) vitamin D (nmol/l)</td></tr>
<tr><td colspan="2">>50</td><td colspan="2">25-50</td><td colspan="2"><25</td></tr>
<tr><td colspan="2"></td><td colspan="2">Plus one or more of the following:
• fragility fracture/osteoporosis/high fracture risk
• drug treatment for bone disease
• Symptoms of vitamin D deficiency
• Increased risk of developing vitamin D deficiency</td><td colspan="2"></td></tr>
<tr><td colspan="2">MAINTAIN VITAMIN D
through lifestyle advice</td><td colspan="2">TREAT</td><td colspan="2">TREAT</td></tr>
<tr><td rowspan="2">How to TREAT</td><td colspan="3">Rapid correction if:
• Symptoms of vitamin D deficiency
• About to start treatment with a potent antiresorptive agent</td><td colspan="3">• Approximately 300,000 IU vitamin D3 orally in divided doses over 6-10 weeks
• Commence maintenance vitamin D 4 weeks after loading as per elective correction</td></tr>
<tr><td colspan="3">Elective correction in all other cases</td><td colspan="3">• 800-2,000 IU vitamin D3 daily or intermittently at higher equivalent doses</td></tr>
<tr><td>How to MONITOR</td><td colspan="6">• Check serum adjusted calcium one month after treating with loading doses of vitamin D. Vitamin D repletion may unmask primary hyperparathyroidism
• Routine repeat of vitamin D testing is generally unnecessary</td></tr>
</table>

Figure 2: Recommended test, treatment and monitoring process for patients with suspected vitamin D deficiency (adapted from ROS, 2018).

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