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Vitamin D: Testing and supplementation in adults

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Vitamin D is essential for the maintenance of musculoskeletal health through the regulation of calcium and phosphate homeostasis. Severe prolonged deficiency of vitamin D can lead to rickets in children and osteomalacia in adults. Both conditions are now rare in the UK, except in high-risk groups such as those with malabsorption and reduced exposure to sunlight. A much more common situation is 'biochemical' vitamin D deficiency, where circulating 25(OH)D concentrations fall below pre-defined thresholds in the absence of osteomalacia or rickets, making vitamin D deficiency and insufficiency very common in the UK particularly during the winter months and early spring. Biochemical vitamin D deficiency has been associated with various non-skeletal disorders, but it seems likely that the low vitamin D levels in these situations are the result of the underlying condition, rather than the cause.

Clinical case scenario

Carolyn, a 47-year-old female, comes to see you with a 1-year history of generalised aching, particularly of her lower back, thighs, hips and feet, a non-specific feeling of reduced well-being and 'weakness' of her arms and legs. She rarely attends the GP clinic, having not ventured out of her house for many years due to agoraphobia. She now walks to the local shop and GP clinic, but for short visits only. For many years she used illicit drugs and when she achieved abstinence became a vegan. She continues to adhere strictly to this diet. Apart from a brief stay in a drug rehabilitation centre 15 years ago, she has no other past medical history and is not on regular or over-the-counter medication.

On examination she walks independently with a normal gait. Her body mass index (BMI) is 19.3 kg/m². Cardiovascular, respiratory and gastrointestinal systems appear normal. Generalised tenderness is evident on palpation over her lower back, hips, pelvis, thighs and feet. Tone, power and reflexes are normal at all four limbs.

Bloods tests are arranged and you conclude that osteomalacia secondary to vitamin D deficiency is the most likely cause of her symptoms based on her clinical presentation, presence of risk factors (strict adherence to a vegan diet and lack of sunlight exposure) and blood biochemistry results (low vitamin D and raised alkaline phosphate and parathyroid hormone).

You recommend 10 000 IU of vitamin D daily, but she is very wary and wants to know if this supplement is derived from animal products. You reassure her that you can prescribe a vegan-friendly product. You discuss the importance of increasing sunlight exposure and she agrees to sit at her patio occasionally. Repeat blood tests at 1 month show normal phosphate and calcium. Alkaline phosphatase (ALP) has risen to 250 u/L, which is consistent with healing osteomalacia. At four months 25(OH)D and parathyroid hormone (PTH) levels are normal. You reduce the dose of vitamin D to 800 IU daily and advise continuing this life-long. Eight months after starting treatment her symptoms have resolved.

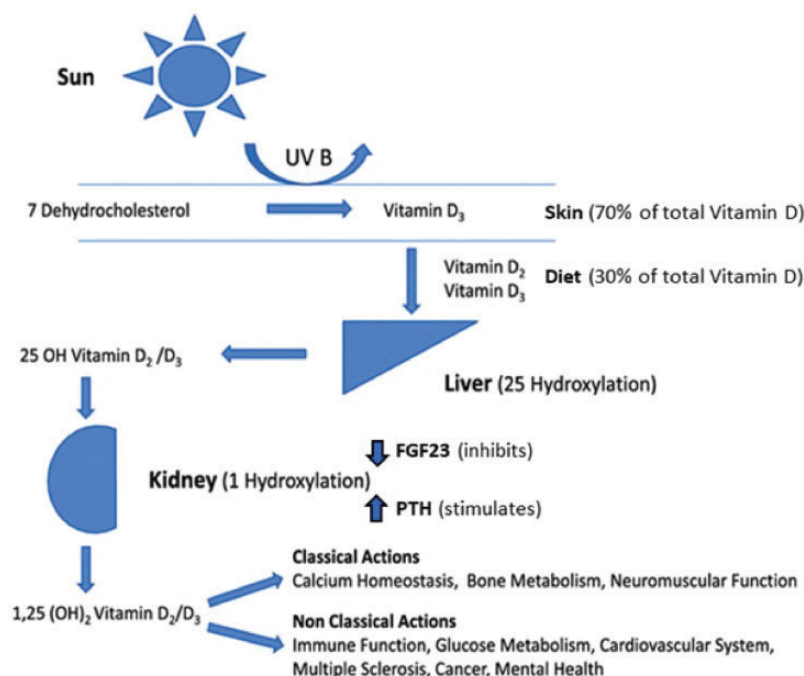
Vitamin D physiology

Vitamin D is a fat-soluble vitamin. Around 70% comes from sunlight exposure where 7-dehydrocholesterol in the skin is converted by the action of ultraviolet light into cholecalciferol (vitamin D₃) (Firth et al., 2020). The remaining 30% is derived by dietary intake of both ergocalciferol (vitamin D₂) and cholecalciferol. Cholecalciferol undergoes 25-hydroxylation in the liver, resulting in the production of calcidiol (25-hydroxyvitamin D or 25(OH)D). This is a biologically inactive metabolite, but is the one that is measured in vitamin D assays; 25(OH)D is present at nanomolar concentrations (10^{-6} molar) in the blood. A further hydroxylation step occurs in the kidneys through the action of 1- α -hydroxylase to produce calcitriol (1,25(OH)₂D), the metabolically active form of vitamin D, which is present in picomolar (10^{-9} molar) concentrations in the blood (Firth et al., 2020; Hobson et al., 2018).

Currently, serum 25(OH)D levels below 25 nmol/L are considered consistent with vitamin D deficiency, whereas

'insufficiency' is the term used to describe the situation where values lie between 25 and 50 nmol/L. Calcitriol increases intestinal absorption of calcium and phosphate and regulates differentiation of osteoblasts (bone-forming cells) and osteoclasts (bone-resorbing cells). Synthesis of calcitriol is tightly regulated by PTH and fibroblast growth factor 23 (FGF23). PTH is produced by the parathyroid glands in response to lowered blood calcium concentrations. The increased levels of PTH help to maintain serum calcium values within the normal range by increasing calcium reabsorption by the renal tubule and by promoting calcitriol synthesis. FGF23 is produced by osteocytes; it plays a major role in promoting phosphate excretion by the kidney by acting on the renal tubule and also suppresses calcitriol production by the kidney. Many inherited forms of rickets and osteomalacia are caused by genetic mutations that increase circulating levels of FGF23 (Hobson et al., 2018). Figure 1 provides a visual representation of vitamin D metabolism.

Figure 1. Pathway of vitamin D production.



Reprinted by permission from Springer Nature, Calcified Tissue International, Vitamin D Assays: Past and Present Debates, Difficulties, and Developments, Fraser WD, Milan AM, 92, 118–127 (2013).

Sources of vitamin D

Biochemical vitamin D deficiency is common in the UK population, due to its northerly position. Latitude and season affect the quantity and quality of solar radiation reaching the Earth. In people located in the UK, there is very little synthesis of cholecalciferol from sunlight between October and March, but thereafter synthesis increases reaching a peak in September after exposure during the summer months. Many factors including degree of skin pigmentation, time of day, season, latitude, use of sunscreens and social circumstances influence the length of time that an individual is exposed to sunlight, which in turn influences vitamin D production. The National Institute for Health and Care Excellence (NICE) recommend that people are encouraged to spend at least two short periods per week from April to October in direct sunlight exposing their legs, arms and face or to consider taking foods or dietary supplements such as cod-liver oil that are rich in vitamin D. It is, however, essential to remember the risk of skin cancer from excessive exposure to sunlight (NICE, 2018).

The most common sources of dietary vitamin D include oily fish, red meat, liver and egg yolks. Milk and dairy products in the UK are relatively poor sources of vitamin D because they are not routinely fortified. In the UK, all margarine sold for domestic use was fortified on a mandatory basis between 1940 and 2013. Voluntary fortification continues in many fat spreads, breakfast cereals, and dried milk. EU Law safeguards ensure mandatory fortification of infant formula (Scientific Advisory Committee on Nutrition (SACN), 2016).

Risk factors for vitamin D deficiency

It is important to consider vitamin D status in people at all ages and stages of life, ranging from before birth until old age. Infants are dependent on vitamin D reserves built up throughout

pregnancy and via intake of milk and food. Direct exposure to sunlight is not recommended for infants younger than 1 year of age, so sunlight cannot be relied upon. Breastmilk is not a significant source of vitamin D, so infants who are exclusively breastfed or taking <500 mls of infant formula daily are potentially at risk of deficiency (NICE, 2014). Vitamin D status in infants is proportionate to maternal reserves; therefore, exclusively breastfed infants of mothers with untreated osteomalacia are at particularly high risk of vitamin D deficiency and hypocalcaemia (Hatun et al., 2005). Maternal osteomalacia is often asymptomatic, making it important to be aware of risk factors for vitamin D deficiency when considering health promotion discussions with pregnant women. See Table 1 for details of risk factors for vitamin D deficiency.

People with darker skin are more likely to have low vitamin D status, as they require longer exposure of their skin to the sun to produce the same amount of vitamin D as people with paler skin (NICE, 2014). In addition, people of African descent may have low 25(OH)D levels in the absence of true deficiency of vitamin D, due to genetic variations in the level of vitamin D binding protein (Powe et al., 2013). Older, frail, hospitalised or imprisoned people are at increased risk, as they are more likely to spend time indoors with less exposure to sunlight (Macdonald et al., 2011; NICE, 2014).

It is important to think about the need for a discussion around vitamin D-related health in people with risk factors. These discussions can take place as health promotion during a routine GP consultation and it is in this context that you can actively promote good health and prevent future complications.

Clinical consequences of vitamin D deficiency

In the majority of cases, vitamin D deficiency is asymptomatic (Hobson et al., 2018; NICE, 2018). Severe and prolonged

Table 1. Risk factors for vitamin D deficiency.

Risk factor	Details
Reduced sunlight exposure	Low or no exposure to the sun, the covering of skin for religious or cultural reasons, excessive use of sunscreen over SPF 15
Reduced oral intake	Infrequent consumption of fish products, eggs, red meat and liver, vegetarian and vegan diets
Reduced intestinal absorption	Malabsorption syndromes, short bowel syndrome, cholestatic liver disease, gastric bypass surgery
Obesity	BMI >30 kg/m ²
Medications	Certain anticonvulsants, highly active antiretrovirals, glucocorticoids, cholestyramine, rifampicin
Genetics	Genetic variation of the vitamin D binding protein and other genes involved in vitamin D metabolism
Pregnancy	Particularly those with multiple short interval pregnancy or those exclusively breast-feeding without oral vitamin D supplementations

Source: Francis et al. (2018); Liu et al. (2018); Information (2020); Excellence (2014); Hatun et al. (2005); Pereira-Santos et al. (2015); Pearce and Cheetham (2010); NICE (2018).

deficiency of vitamin D results in rickets in children and osteomalacia in adults. It is important to remember that there is no single threshold for serum 25(OH)D that is diagnostic of either disorder and large scale studies have shown that most people, even with very low 25(OH)D levels, do not have evidence of impaired mineralisation of bone on histological analysis of bone biopsies (Priemel et al., 2010).

Osteomalacia and rickets are most commonly linked to inadequate exposure to sunlight. Malabsorption syndromes can predispose to deficiency through reduced absorption of vitamin D and calcium. Loss of 1,25-hydroxylation can occur secondary to chronic renal failure. Osteomalacia and rickets can also arise as the result of inherited disorders of renal phosphate reabsorption, which are typically associated with raised FGF23 levels and mutations in the vitamin D receptor or the genes involved in converting 25(OH)D to 1,25(OH)2D3 (Hobson et al., 2018).

Rickets

Rickets leads to softening of the bones, which then become prone to deformity and fractures. Skeletal features include progressive bowing of the legs and knock-knees, softening of skull bones and frontal bossing, delayed eruption of teeth and enamel hypoplasia, and growth plate enlargement seen as wrist swelling and rachitic rosary (swollen costochondral junctions at the chest wall). Skeletal deformities can present as early as 6 months of age (Wharton and Bishop, 2003). Muscle weakness can present as difficulty climbing stairs, waddling gait and difficulty rising from a seated position. Vitamin D deficiency rickets usually presents after 6 months of age on depletion of intrapartum reserves, and is associated with weakness, drowsiness, tetany and seizures (Hobson et al., 2018). Older children can be affected by bone pain, short stature, a tendency to lower respiratory tract infections secondary to a compliant chest wall and muscle weakness, chest pain and skeletal deformities such as scoliosis (Pearce and Cheetham, 2010).

Osteomalacia

In adults the most common complication of severe vitamin D deficiency is osteomalacia. Osteomalacia is characterised by impaired mineralisation of bone. When vitamin D deficiency is severe and prolonged, PTH levels become chronically elevated in an attempt to maintain serum calcium values within the normal range (secondary hyperparathyroidism). The elevated PTH levels increase osteoclastic bone resorption, increased calcium reabsorption from the renal tubules and promote phosphate excretion. If 25(OH)D deficiency persists, there is a gradual failure of 1,25(OH)D production, resulting in defective absorption of calcium and phosphate from the gut. Eventually this leads to demineralisation of bone, which is the defining feature of osteomalacia (Bordelon et al., 2009). Osteomalacia presents with weakness at the pelvic girdle muscles in up to 30% of people, resulting in difficulties rising to stand and walking often mobilising with a waddling gait (Firth et al., 2020; Sievenpiper et al., 2008). Muscle tenderness on pressure and focal bone pain can arise secondary to fissure fractures at the ribs and pelvis (Hobson et al., 2018). In older

adults, vitamin D-related orthostatic hypotension can result in a greater risk of falls, institutionalisation, and death (Duval et al., 2015).

Generalised bone pain can be mistaken for fibromyalgia or somatisation of depression (Firth et al., 2020; Hobson et al., 2018; Sievenpiper et al., 2008). It is important to bear this in mind when seeing people with long-standing chronic pain issues, as misdiagnosis can lead to years of preventable suffering and disability. Having said that, many people with fibromyalgia and chronic pain have low vitamin D levels as a consequence of their health condition, due to poor diet and limited sunlight exposure, rather than it being the cause of their symptoms.

Non-skeletal conditions

There is much current debate around potential associations between low circulating vitamin D levels and various diseases including most types of cancer, chronic kidney disease, hypertension, diabetes, multiple sclerosis, chronic inflammatory diseases, age-related macular degeneration, depression, psychosis and all-cause mortality (Hobson et al., 2018). Reverse causality could be responsible where these conditions have predisposed people to lower vitamin D status secondary to less sunlight exposure and poor diet (Hobson et al., 2018; SACN, 2016). Awareness of this debate can be useful when you are asked about the significance of low vitamin D status.

Investigations

There is no universal consensus of what is optimal vitamin D status, as many people with vitamin D 'deficiency' or 'insufficiency' are in perfectly good health (Aspray et al., 2014). Therefore, it is important to be mindful of the need to reduce unnecessary healthcare costs, prescribing and resultant anxiety caused by performing a vitamin D level only when it is clinically indicated (Pilz et al., 2019). Figure 2 provides a visual illustration of the clinical significance of vitamin D deficiency by clinical group.

Where testing is appropriate, serum 25(OH)D is the recommended test. It closely measures uptake from the diet and sunlight and has a half-life of 2 to 3 weeks (Aspray et al., 2014; Firth et al., 2020; NICE, 2018). If vitamin D levels are low, serum PTH, serum calcium, phosphate and ALP are useful investigations to help determine if the low 25(OH)D is of clinical significance. People with osteomalacia and rickets always have secondary hyperparathyroidism and usually have raised ALP values. Serum calcium and phosphate values tend to be low, but can be in the normal range. It is important to remember that a low 25(OH)D value can occur due to genetic variations in the levels of vitamin D binding protein in the absence of physiological vitamin D deficiency.

There has been a substantial increase in requests for measurement of 25(OH)D in the UK over recent years, despite the lack of clarity over which people to test and how to interpret low levels. This is likely to be related to increased public awareness of the prevalence of vitamin D deficiency, as well as current debates about the extent of the role of vitamin D in

Figure 2. Schematic representation that helps to define broad groups for clinical consideration and decision making.

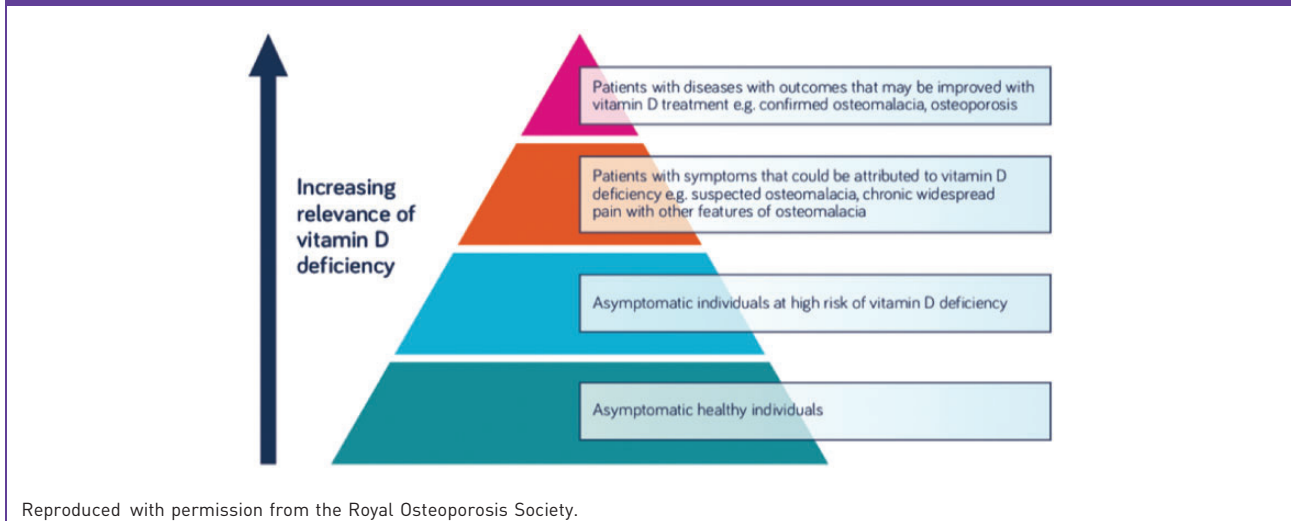


Table 2. Recommendations for vitamin D testing.

25(OH)D testing is recommended	<ul style="list-style-type: none"> • Clinical symptoms or signs to suggest osteomalacia or rickets (Francis et al., 2018; NICE, 2018) • People who are being treated with bisphosphonates or other antiresorptive drugs (testing may not be required in people receiving vitamin D or combined calcium and vitamin D supplements) • People at high risk of vitamin D deficiency due to their lifestyle, ethnic background or co-existing diseases
25(OH)D testing is not recommended	<ul style="list-style-type: none"> • Asymptomatic people without clinical risk factors (Francis et al., 2018; NICE, 2014) • People with other diseases where testing is unlikely to influence clinical management

Source: Francis et al. (2018) and NICE (2014).

disease. Good practice means that testing should only be performed where the result of the test is aligned with current clinical guidance, if it will change your clinical management plan, and where you as the clinician are aware of how to interpret the result correctly (Francis et al., 2018). See Table 2 for recommendations on vitamin D testing to help guide clinical decision making.

Differential diagnosis

When a person presents with symptoms and signs of rickets or osteomalacia, it is important to be aware of other diseases that could cause similar presentations, as this will help to guide further investigation. Where bone pain and muscle weakness are the predominant features, consider bone or soft tissue cancer, myeloma, fibromyalgia, fracture, osteomyelitis, Paget's disease, parathyroid disease, polymyalgia rheumatica and rheumatoid arthritis (NICE, 2018). Alternative causes of painless muscle weakness include polymyositis, dermatomyositis, thyroid disease and muscular dystrophies (NICE, 2018).

Other blood tests

Appropriate use of blood tests, depending on the clinical presentation, can help to secure a diagnosis. A bone profile including adjusted calcium, phosphate, PTH and ALP will assess for hypocalcaemia and markers of bone disease. Renal, liver and thyroid function, full blood count and ferritin, malabsorption screen, rheumatoid or other autoimmune screening and inflammatory markers might also be appropriate depending on the clinical history (NICE, 2018). In children consider referring to local clinical guidance for specialist input.

How to interpret 25(OH)D and bone profile

National guidelines provide recommendations with regard to the interpretation of vitamin D levels. For recommendations see Table 3 for interpretation of vitamin D levels and Table 4 for bone profile.

Table 3. Interpretation of vitamin D level.

25(OH)D <25 nmol/L: Treat	Prolonged deficiency significantly increases the risk of rickets in children and osteomalacia in adults, as well as association with immunosuppression, muscle weakness and potential increased risk of colon cancer (Firth et al., 2020). It is recommended that all people in the UK should not fall below 25 nmol/L at any time in the year (SACN, 2016).
25(OH)D 25–50 nmol/L: Consider treatment in those at risk of developing frank vitamin D deficiency	<ul style="list-style-type: none"> • Malabsorption • Ethnic groups/low sunlight exposure • Prior to administration of bisphosphonates or other antiresorptive agents
25(OH)D >50 nmol/L: Reassure	

Source: Firth et al. (2020) and Pilz et al. (2019).

Table 4 Biochemical features of metabolic bone diseases.

Disease	Serum calcium	Serum phosphate	Serum creatinine	Serum PTH	Serum 25(OH)D	Serum alkaline phosphatase
PHPT	↑	↓	↔	↑	↔	↔/↑
Osteomalacia	↓	↓	↔	↑	↓↓	↑
Paget's	↔	↔	↔	↔	↔	↑/↑↑
CKD-MBD	↑	↓	↑↑	↑↑	↔	↑
Osteoporosis	↔	↔	↔	↔	↔	↔

PHPT – Primary hyperparathyroidism, CKD-MBD – Chronic kidney disease – metabolic bone disease.

↑ - elevated; ↑↑ - markedly elevated; ↓ - reduced; ↔ within reference range.

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Treatment

Consider referral to a specialist if there are features other than dietary or lifestyle factors responsible for deficiency or the person is pregnant (NICE, 2018). Some vitamin D supplements are produced by irradiating sheep wool, whereas others do not require the use of animal products. It is important when considering vitamin D supplementation to ensure that the product chosen is acceptable to people depending on their religious and dietary backgrounds (Francis et al., 2018; NICE, 2018).

Oral vitamin D3 is the recommended preparation relating to consistent concentrations and efficacy in raising serum 25(OH)D levels. Where the person is a strict vegan, vitamin D2 is recommended, as this is not derived from animal sources (UKMi, 2020). There is very limited evidence base to guide dosing of vitamin D and several regimens can be used successfully. In general, it is best to avoid giving large doses of vitamin D, as this has been associated with an increased risk of falls and fractures in older people for reasons that are incompletely understood (Bischoff-Ferrari et al., 2016; Law et al., 2006; Trajanoska and Rivadeneira, 2018).

Monitoring of treatment

Excessive oral intake of vitamin D can lead to toxic effects such as hypercalcaemia (due to increased intestinal calcium absorption and mobilisation of calcium from the bones), which can then result in deposition of calcium in the soft tissues, diffuse mineralisation of bones, and irreversible renal and cardiovascular toxicity (SACN, 2016). Caution should be exercised in people with poor renal function and those with sarcoidosis and other granulomatous diseases where extra-renal production of calcitriol can occur leading to vitamin D intoxication. The administration of vitamin treatment can also unmask primary hyperparathyroidism. In these circumstances, for both cases, it is important to be vigilant for potential features of hypercalcaemia (NICE, 2018; Roger et al., 2018).

It is recommended that clinicians consult local prescribing guidance with regard to the specific dose of vitamin D supplementation, as there is many variations of preparation schedule and practice should be specific to the local area. Apart from these specific conditions, the risk of toxicity is small, due to homeostatic mechanisms. Monitoring is not

necessary in people started on low-dose vitamin D supplements of up to 1600 units /day.

In people receiving treatment with higher doses for osteomalacia or rickets, it is customary to check serum calcium, phosphate and ALP after 1 month and then 3–6 monthly until values have returned to normal. Measurements of 25(OH)D and PTH may be considered after 6–12 months to ensure that secondary hyperparathyroidism has been corrected and vitamin D levels have increased.

Prevention

All people living in the UK aged 1 year and above should be encouraged to take a daily supplement of 10 µg (400 IU) of vitamin D all year, and 8.5–10 µg (340–400 IU) daily in babies aged up to 1 year (Chief Medical Officer, (CMO), 2017; NICE, 2018). However, evidence of the benefit of this supplementation has not yet been established.

Pregnant and breastfeeding women are eligible for free vitamin supplementation through the UK-wide Healthy Start scheme. People who are concerned about vitamin D deficiency can be advised to buy over-the-counter supplementation and calculate calcium intake using on-line tools. Where daily calcium intake is <700 mg/day, then offer dietary advice to increase calcium intake or consider calcium supplementation if they are unable to make dietary changes. Where calcium supplements have been initiated, check adjusted calcium level a month after initiation (NICE, 2018).

Conclusion

Vitamin D deficiency is a common condition in the UK population. In the majority of people this will be asymptomatic and investigation is not required. Those people who develop symptoms specific to vitamin D deficiency should be investigated with treatment and monitoring initiated according to national guidance. There is debate over potential implications

of vitamin D deficiency in non-skeletal disease, and as yet little confirmatory evidence to suggest a causal relationship. It is of great importance that GPs are aware of the current guidance and debate surrounding vitamin D, as this is a common and important issue for the UK population.

KEY POINTS

- Vitamin D deficiency is common in the UK and is mostly commonly asymptomatic
- Severe and prolonged vitamin D deficiency may lead to osteomalacia in adults or rickets in children
- There is no evidence as yet that vitamin D supplements are effective in the prevention or treatment of other medical conditions
- 25(OH)D is the recommended test to determine vitamin D status, but it should only be used in specific clinical circumstances
- National UK clinical guidance now recommends that all people take a daily vitamin D supplement, but this is not based on any evidence of benefit
- Treatment of osteomalacia and rickets should be accompanied with monitoring of calcium, phosphate, ALP, PTH and 25(OH)D levels. It is not necessary to monitor people treated with low-dose vitamin D

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AKT answer relating to cardiovascular disease in people with intellectual disability

Answer A. Hypertension

There is a higher prevalence of cardiovascular disease in those people with an intellectual disability. This is caused by a number of different factors including an accelerated ageing process, poor lifestyle choices including indulging in cigarettes and alcohol, having a poor diet and lack of

adequate exercise. Hypertension is actually less common in this population; however, it is usually under diagnosed.

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