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How to do it: Vitamin D supplementation

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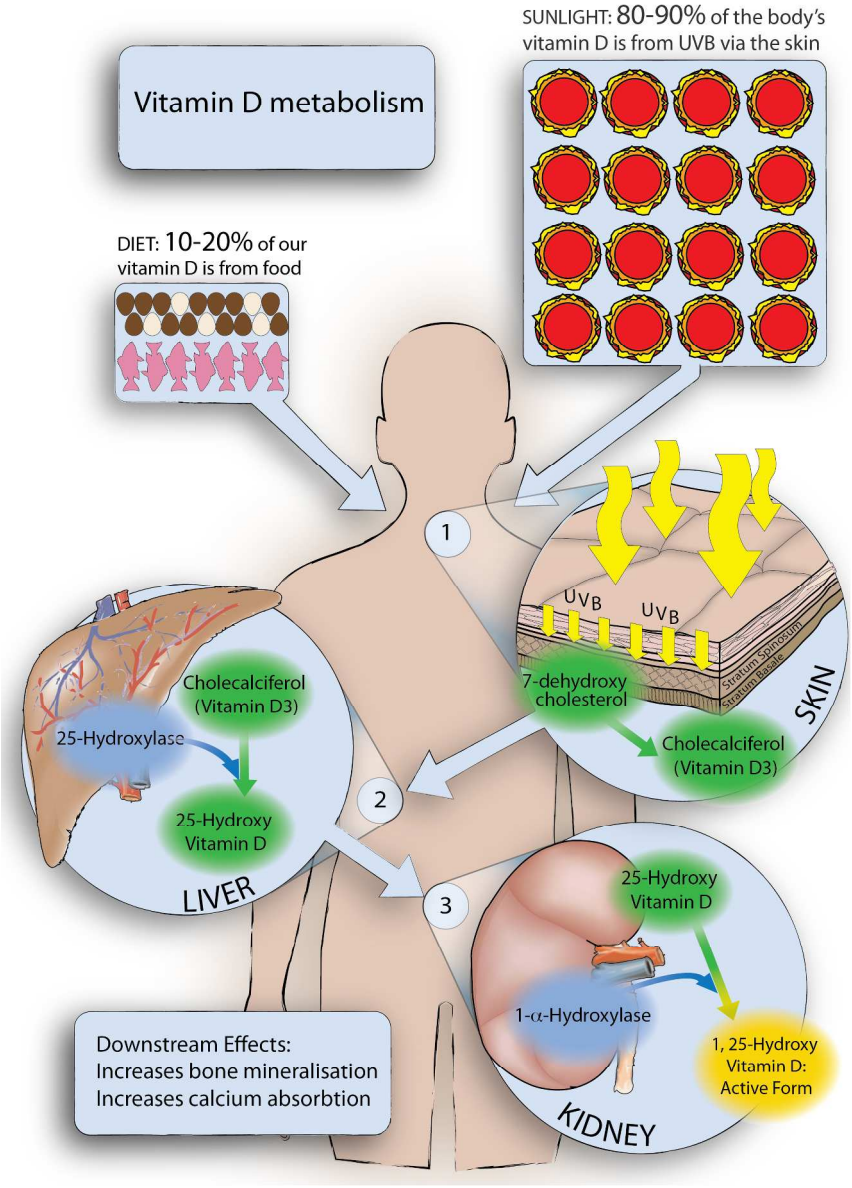

Absorption and metabolism of vitamin D in humans (taken from reference 18)

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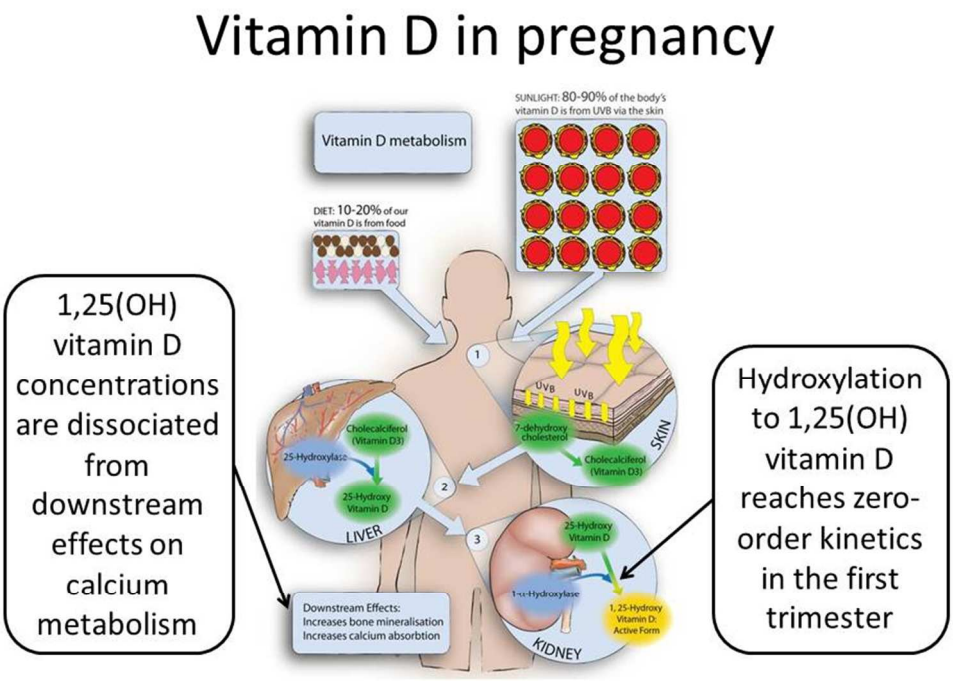

Alterations to vitamin D metabolism during pregnancy – these changes are established by the end of the first trimester, and at no other time in life are concentrations of 25(OH) vD so closely linked to those of 1,25(OH)vD. Figure adapted from reference 18.

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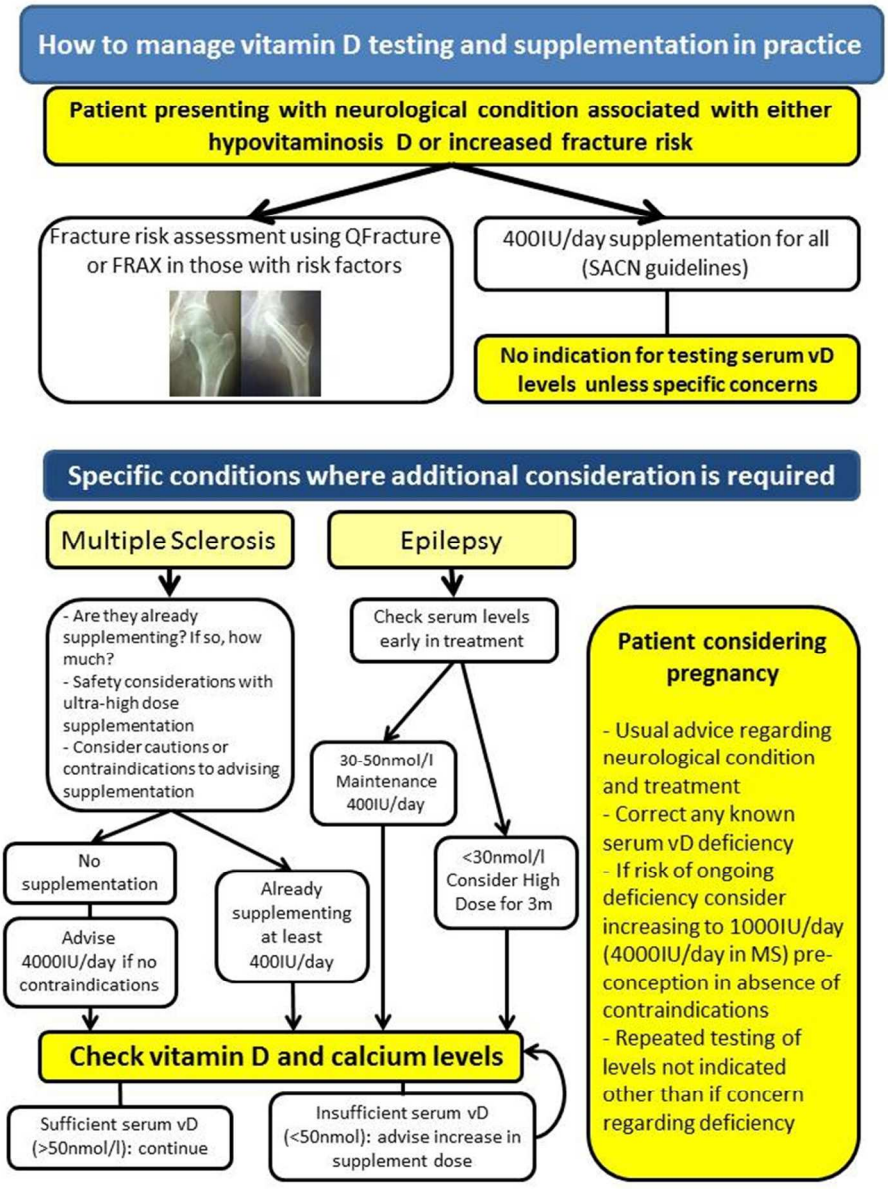

Infographic detailing a suggested approach to vitamin D testing and supplementation in the neurology clinic

190x254mm (96 x 96 DPI)

How to do it: Vitamin D supplementation

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Abstract

Vitamin D testing and supplementation is of great interest to neurologists and their patients. Recommended nutritional intakes of vitamin D in the UK remain focussed on bone health, despite increasing evidence for a role outside this area. Here we discuss how neurologists might approach vitamin D testing and supplementation, focusing on two conditions associated with vitamin D deficiency that have an increased risk of downstream complications resulting from this: multiple sclerosis and epilepsy. We set out a rationale for testing serum 25-hydroxyvitamin D concentrations and discuss our personal practice in terms of supplementation, with evidence where available.

1. Background to vitamin D testing

There has been a recent explosion of interest in the role of vitamin D in health and disease [1]; however, current guidelines for supplementation are inconsistent between the UK and Europe. The European Food Safety Authority guidelines in 2003 [2] re-evaluated intake levels for vitamin D; their further guidance in 2016 addressed serum concentrations of vitamin D, and made supplementation recommendations [3]. Vitamin D intakes below 10,000 IU/day (250 µg) are not associated with adverse events—the 'no observed adverse event limit' (NOAEL)—and vitamin D toxicity is rare; when it occurs, its primary manifestation is hypercalcaemia resulting from the displacement of 1,25(OH)D from its binding protein by 25(OH)D. The European Food Safety Authority recommends an intake of 600 IU (15 µg)/day in healthy adults, with a maximum recommended intake of 4000 IU/day (100 µg). The UK Scientific Advisory Committee on Nutrition recently recommended a nutritional intake for vitamin D of 400 IU (10 µg)/day for all [4]. So why is there such a discrepancy, and what should we recommend to patients in the neurology clinic?

The discovery of vitamin D was intrinsically linked to rickets; prevention trials in 1917 involved feeding babies between one half and six teaspoons of cod liver oil per day [5], although without understanding the reason for its benefit. Vitamin D was discovered in 1922, and the Nobel Prize for chemistry in 1928 was awarded to Adolf Windaus "for his studies on the constitution of the sterols and their connection with vitamins". Recommended dietary allowances for dietary vitamin D intake were first proposed in 1941.

All the current recommendations are based on bone health. The 'estimated average requirement' for vitamin D is the median requirement, whereas the 'recommended dietary allowance' estimates the highest end of vitamin D requirements; thus 97.5% of the population requires an intake below this

recommended amount [6]. The recommended dietary allowance of 400 IU/day (10 µg) was initially derived from the amount of vitamin D in a teaspoon of cod liver oil [7]. The UK Scientific Advisory Committee on Nutrition states that a serum 25-hydroxyvitamin D (25(OH)D) concentration of 30 nmol/L (12.5 µg/L) is sufficient to maintain bone health in the general population, and that a serum concentration should not fall below 25 nmol/L at any time of year. However, this does not address serum concentrations in the presence of other insults to bone health, such as corticosteroid use; where there are additional risk factors, it can be argued that a serum 25(OH)D concentration above 50 nmol/L is safer [8].

Despite increasing evidence for a role of vitamin D outside bone health, the recommended dietary allowance has not changed, due to concerns regarding vitamin D toxicity. Whilst there is a negative feedback system for 25(OH)D formation by the skin, no such system regulates dietary vitamin D uptake (figure 1). Supplementation with >10,000 IU day for > 3 months may result in toxicity in those without risk factors for hypercalcaemia, such as primary hyperparathyroidism and granulomatous disease. Studies linking long-term adverse health outcomes, such as malignancy, to high dose vitamin D supplementation are inconsistent in terms of both supplementation/serum concentration and outcome; hence we cannot draw any reliable conclusions. The European Food Safety Agency concluded that daily doses of vitamin D up to 10,000 IU are safe if there are no predisposing comorbidities, with no convincing evidence linking vitamin D intake and long-term adverse health outcomes [2]. The logic behind not increasing the recommended dietary allowance thus seems inherently flawed—any potential beneficial effects of vitamin D outside of bone health are ignored.

Serum vitamin D concentrations are not only dictated by intake and absorption; there are several genetic polymorphisms that control vitamin D metabolism and contribute to serum vitamin D concentrations and hence to physiological requirements [9]. There is thus no ‘one size fits all’, and

everyone probably requires their own (personalised) level of supplementation. This argues against blanket guidelines at a population level.

In this article we discuss the current recommendations around vitamin D measurement, supplementation and fracture risk assessment, and give guidance on how to approach specific groups of neurological patients—namely those with multiple sclerosis, those with epilepsy, and those considering pregnancy.

2. Vitamin D in general neurology patients

***When should I test vitamin D levels*?**

Many neurological and systemic conditions have been indirectly linked to vitamin D deficiency, including multiple sclerosis (MS), type 1 diabetes mellitus, metabolic syndrome, asthma, infectious diseases, and many malignancies. However, many of the associations between systemic illness and vitamin D deficiency derive from observational studies, and reverse causality remains a concern.

The National Osteoporosis Society recommends measuring serum 25(OH)D concentrations in those patients with bone diseases that may be improved with vitamin D supplementation, and in those patients with musculoskeletal symptoms that are possibly attributable to vitamin D deficiency [8]. The UK National Institute for Health and Care Excellence (NICE) epilepsy guidelines recommend “bone profile” blood tests every 2–5 years: 25(OH)D is arguably inferred rather than specified. We know of no other nationally agreed guidelines for testing. In addition, patients who are predisposed to hypercalcaemia who are also supplementing with vitamin D should have their serum 25(OH)D and calcium concentrations monitored, for example patients with sarcoidosis. UK guidelines recommend population-wide supplementation, regardless of serum 25(OH)D [10]; as such, there is an argument not to test, and instead to supplement the entire population with 400 IU/day. It is important that a focus on

supplementation does not lead clinicians to overlook personal and demographic factors contributing to vitamin D deficiency, such as socioeconomic group, cultural factors (sunblock and cosmetic usage, covering up, reduced outdoor activity, level of skin pigmentation), smoking and obesity [4] as well as important dietary sources (milk, oily fish).

Serum 25(OH)D testing and supplementation is not free; the typical cost for measuring serum 25(OH)D is £12–£20. Standard-dose vitamin D supplements are relatively cheap (c. £6/year for adults in 2014 [11]); the cost of higher dose supplementation is significantly greater at £15–£65/year for 4000 IU/day.

If I do test serum 25(OH)D concentrations in my patients, what do the results mean?

The development of a reference range for serum 25(OH)D in 1971 used standard techniques: gathering a diverse population, measuring serum 25(OH)D concentrations, and defining a reference range against a Gaussian distribution. There have since been attempts to define physiologically normal serum 25(OH)D concentrations. Calcium absorption by the gut is suboptimal and secondary parathyroidism occurs at serum concentrations <50 nmol/L (20 µg/L). There is also evidence for an increased risk of adverse musculoskeletal and pregnancy-related health outcomes at serum 25(OH)D concentrations <50 nmol/L [3]. In the UK, deficiency is defined as serum 25(OH)D concentration <30 nmol/L, and insufficiency as a serum concentration of 30–50 nmol/L.

Which patients in neurology clinics are at risk of vitamin D deficiency and/or increased fracture risk?

Clinicians should evaluate patients' fracture risk and serum 25(OH)D concentrations where there is a scientific rationale that supplementation may improve disease-related or disease-associated outcomes; this includes treatment effects, such as an increased fracture risk in patients taking long-term

corticosteroids. Patients at increased risk of fracture for other reasons, such as post-stroke patients, post-menopausal women and those with a strong family history of fracture, should have serum 25(OH)D concentrations measured [8]. However, in these patients there is at present insufficient evidence to recommend treatment over that recommended by the National Osteoporosis Guideline Group.

Vitamin D deficiency is relatively common in patients with Parkinson's disease [12], a condition also associated with increased fracture risk [12,13]. However, we have no biological evidence linking vitamin D deficiency to the development of Parkinson's disease. There is no evidence to guide serum 25(OH)D testing in these patients outside of standard National Osteoporosis Society advice, which is that given the increased fracture risk in these patients, clinicians should consider formal fracture risk calculation and consideration of serum vitamin D testing [8].

A detailed discussion of the management of fracture risk is beyond the scope of this article, and has previously been covered in this journal [13]. NICE recommend correcting reversible factors associated with poor bone health (smoking, hypothyroidism, alcohol excess, etc.) together with an assessment of fracture risk using clinically validated tools such as FRAX or QFracture in all women aged 50–64 years and all men aged 50–74 years with risk factors for fracture (NICE CKS – osteoporosis) followed by a bone densitometry scan where fracture risk lies within a threshold associated with osteoporosis (National Osteoporosis Guideline Group). As such, the role of vitamin D supplementation in managing fracture risk is limited to correcting deficiency and insufficiency, with additional treatments as indicated for osteopenia/osteoporosis.

How should vitamin D supplements be given?

As above, the UK Scientific Advisory Committee on Nutrition recommends a nutritional intake for vitamin D of 400 IU (10 µg)/day for all. They also specify that whilst this refers to intakes from all sources, it is difficult to achieve the recommended nutritional intake from natural food sources alone, and recommend that the Government consider population-wide strategies to address this. Supplements are most commonly available as 400 IU vitamin D3 (cholecalciferol)—usually with calcium at this dose—or higher doses (2000–5000 IU, either tablet or spray) without calcium. General practitioners are often unwilling to prescribe vitamin D outside of bone health recommendations; we therefore advise patients that they may have to purchase supplements, and that this can be both easier and cheaper for them. Calcitriol (1,25(OH)vD) is also available, but is prescription-only in the UK, with specific indications. Patients taking calcitriol may still have low serum concentrations of 25(OH)vD, as the oral supplement bypasses this precursor.

Does the advice differ from standard recommendations for some groups, and how do I approach these patients?

The approach towards vitamin D supplementation differs between patients with multiple sclerosis and those with epilepsy, mainly because of differing evidence around the role of vitamin D in neurological disease development and pathogenesis versus downstream co-morbidity risk.

3. Patients with multiple sclerosis

Multiple sclerosis has been linked to vitamin D deficiency, both as a risk factor for disease development and following diagnosis [14]; many people with MS are aware of this association. People with MS also have an increased risk of fracture. It therefore seems sensible that patients with MS should

be taking some form of vitamin D supplementation. Patients commonly take high doses of vitamin D, risking supra-physiological levels, which could be associated with harm, especially when supplements also contain calcium [2,3, 15]. We recommend that people with MS should have their serum 25(OH)D concentration tested at least once when established on supplements for several weeks (and clinicians should know the supplement status in the weeks before such testing) in order to make recommendations regarding safe supplementation.

Our experience is that (almost) all patients who are not supplementing with vitamin D have levels in the range suggesting insufficiency, if not the deficiency. Given the lack of evidence of harm associated with high dose vitamin D supplementation in the majority of patients, and the potential benefits (in terms of both fracture risk and MS pathogenesis), in the absence of contraindications, we advocate empirical replacement with 4000 IU (100 µg) vitamin D per day, which can be taken daily or as a bolus on alternate days or weekly—this dose should not be taken with calcium, and standard preparations of high dose vitamin D do not contain additional calcium. In patients who are supplementing at this level, is there is limited benefit to repeated testing once supplementing levels are known.

4. Patients with epilepsy

Epilepsy has been associated with both hypovitaminosis D and a doubling of overall fracture risk [16]. Although vitamin D deficiency is probably only a contributory factor to the increased fracture risk, it is an easily modifiable one [17]. There is a dose-responsive increase in the fracture risk in epilepsy patients associated with the use of older antiepileptic medications, both enzyme inducers and inhibitors [18]. Each year of antiepileptic medication use is associated with a 9% increase in fracture risk [19] and whilst some have suggested newer agents may carry less of a risk, this has not been demonstrated. In the epilepsy population, vitamin D supplementation remains the only easily modifiable determinant of

fracture risk, and has been recommended for some time, at least for people taking the older antiepileptic medications [17].

In line with the approach of the UK Scientific Advisory Committee on Nutrition, we recommend advising all patients starting antiepileptic medication to consider a supplement of at least a 400 IU vitamin D per day, typically with 1000 mg calcium in standard preparations, with a target serum concentration of >50 nmol/L.

Patients who are very deficient (<30 nmol/L) may need doses of up to 4000 IU/day for at least a few weeks to achieve normal serum concentrations, later transferring to a standard supplement. Similarly, they may need high doses to improve bone mineralisation, particularly in combination with enzyme inducers [20]. We therefore test serum concentrations early, and use these to guide treatment, alongside assessment of fracture risk in adults using a validated tool such as QFracture (www.qfracture.org).

5. Patients planning pregnancy

A significant proportion of neurological patients will become pregnant; concerns may arise around high dose supplementation during pregnancy. The Royal College of Obstetricians and Gynaecologists and the UK Scientific Advisory Committee on Nutrition each recommend standard supplementation during pregnancy. Low maternal serum 25(OH)D has been associated with adverse pregnancy-related outcomes, including pre-eclampsia, altered placental vascular pathology, impaired glucose tolerance and adverse birth outcomes [21].

Vitamin D metabolism alters substantially during pregnancy. The conversion of 25(OH)D to 1,25(OH)D—the active form—increases substantially during the early weeks of pregnancy. By 12 weeks gestation, serum 1,25(OH)D concentrations have more than doubled [22], and are closely related to baseline 25(OH)D concentrations (figure 2). However, pregnant women do not develop the hypercalcaemia and hypercalciuria usually associated with such serum concentrations. The fact that this occurs so early in pregnancy suggests that fetal skeletal development is not the sole driver of this physiological change [21].

Several studies have examined beneficial and adverse outcomes associated with high dose vitamin D supplementation during pregnancy. A large randomised controlled trial in 2004 examined maternal and fetal outcomes associated with high dose vitamin D supplementation (4000 IU/day) during pregnancy, with supplementation starting before 16 weeks gestation. There were no supplementation-associated adverse events at this dose, either in the mother or the fetus [22]. There appear to be fewer pregnancy-associated comorbidities with serum vitamin D concentrations >80 nmol/L [23], highlighting the importance achieving adequate serum concentrations of vitamin D.

As the biological effects of pregnancy on vitamin D metabolism are fully apparent by 12 weeks gestation, with possibly important implications for placental development, vitamin D supplementation should begin before pregnancy. Vitamin D concentrations in the newborn have been associated with the risk of subsequent MS [24] (although these data have not been replicated [25]); given the absence of any proven negative consequences of vitamin D supplementation, it seems prudent to advise strongly that women with MS trying to conceive should take high dose supplementation. The Royal College of Obstetricians and Gynaecologists suggests universal supplementation of 400 IU for all pregnant females, increasing to 800 IU for those at risk of eclampsia and 1000 IU for those at high risk of deficiency. Doses of up to 4000 IU/day have been shown to be safe in pregnancy [22], and we would recommend not

reducing the dose of vitamin D supplementation during pregnancy in those taking this dose (e.g. MS patients). In addition, it seems prudent that those with epilepsy or other neurological conditions who might be at additional risk of deficiency should receive adequate supplementation before trying to conceive.

Conclusions

Public awareness about vitamin D has increased exponentially and patients increasingly ask their neurologists about this. We need a thorough understanding of the meaning of serum concentrations, together with an appreciation of the risks and benefits of both testing and supplementing to enable good communication with both patients and primary care physicians. Figure 3 summarises the discussion above. In line with advice of the UK Scientific Advisory Committee on Nutrition, the UK population should have a daily intake of at least 400 IU vitamin D, which is frequently not achievable by natural sources alone. The safest and cheapest solution is to recommend a standard supplement to all patients, without the need for serological testing. Those at additional risk of deficiency, specifically including patients with MS and epilepsy, may well need higher doses, which can only be guided by serum concentrations at some point.

Key points:

- Vitamin D deficiency and insufficiency is widespread in the UK; the UK Scientific Advisory Committee on Nutrition recommends supplementation in the general population of 400 IU/day with no need for serum concentration testing

- In people with multiple sclerosis, high dose supplementation up to 5000–10,000 IU/day is not associated with harm and may be of benefit in terms of both fracture risk and MS pathogenesis – we advise supplementation with 4000 IU/day in those without contraindications pending formal evidence supporting (or not) the use of higher dose supplementation.
- In people with epilepsy who are taking antiepileptic medication, we recommend standard supplementation with 400 IU/day with testing of serum levels to guide treatment– higher levels of supplementation may be needed to achieve normal serum concentrations in some
- Advice regarding vitamin D supplementation should be part of pre-pregnancy counselling in those with neurological diseases; many patients should consider taking higher levels of vitamin D before and during pregnancy – 1000–4000 IU/day in many patients

Figure legends:

Figure 1: Absorption and metabolism of vitamin D in humans (taken from reference 18)

Figure 2: Alterations to vitamin D metabolism during pregnancy – these changes are established by the end of the first trimester, and at no other time in life are concentrations of 25(OH) vD so closely linked to those of 1,25(OH)vD. Figure adapted from reference 18.

Figure 3: Infographic detailing a suggested approach to vitamin D testing and supplementation in the neurology clinic

Further reading:

UK Scientific Advisory Committee on Nutrition (*SACN) report on vitamin D in the UK*: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/537616/SACN_Vitamin_D_and_Health_report.pdf

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Bone health in MS and Parkinson's disease: Dobson R, Yarnall A, Noyce AJ, Giovannoni G. Bone health in chronic neurological diseases: a focus on multiple sclerosis and parkinsonian syndromes. Pract Neurol. 2013;13: 70–79.

Bone health in epilepsy: Sheth RD. Bone health in epilepsy. Lancet Neurol. 2004;3: 516.

Competing interests:

RD has received sponsorship to attend conferences from Biogen Idec, Novartis, Teva and Sanofi Genzyme. She has received speaking honoraria from Teva.

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GG has received consultation and speaking fees from Biogen-Idec, GSK, Merck-Serono, Novartis, Genzyme-Sanofi and Synthon BV. He is on the steering committee for studies sponsored by AbbVie, Biogen-Idec, Novartis, Teva and Roche.

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