

A Literature Review of the Potential Impact of Medication on Vitamin D Status

Michael Wakeman 

Faculty of Health and Wellbeing,
University of Sunderland, Sunderland,
SRI 3SD, UK

Abstract: In recent years, there has been a significant increase in media coverage of the putative actions of vitamin D as well as the possible health benefits that supplementation might deliver. However, the potential effect that medications may have on the vitamin D status is rarely taken into consideration. This literature review was undertaken to assess the degree to which vitamin D status may be affected by medication. Electronic databases were searched to identify literature relating to this subject, and study characteristics and conclusions were scrutinized for evidence of potential associations. The following groups of drugs were identified in one or more studies to affect vitamin D status in some way: anti-epileptics, laxatives, metformin, loop diuretics, angiotensin-converting enzyme inhibitors, thiazide diuretics, statins, calcium channel blockers, antagonists of vitamin K, platelet aggregation inhibitors, digoxin, potassium-sparing diuretics, benzodiazepines, antidepressants, proton pump inhibitors, histamine H₂-receptor antagonists, bile acid sequestrants, corticosteroids, antimicrobials, sulphonamides and urea derivatives, lipase inhibitors, hydroxychloroquine, highly active antiretroviral agents, and certain chemotherapeutic agents. Given that the quality of the data is heterogeneous, newer, more robustly designed studies are required to better define likely interactions between vitamin D and medications. This is especially so for cytochrome P450 3A4 enzyme (CYP3A4)-metabolized medications. Nevertheless, this review suggests that providers of health care ought to be alert to the potential of vitamin D depletions induced by medications, especially in elderly people exposed to multiple-drug therapy, and to provide supplementation if required.

Keywords: ergocalciferol, cholecalciferol, vitamin D, medication interactions, drug interactions

Introduction

Classically, the function of fat-soluble vitamin D is considered to be regulating the absorption of calcium and management of its homeostasis, and hence its role in musculoskeletal health is well recognized. However, in recent years evidence has begun to appear that suggests that certain non-skeletal conditions, such as cardiovascular and coronary heart disease, diabetes, some cancers, multiple sclerosis, Parkinson's disease, age-related cognitive decline, and arthritis, may be associated with suboptimal concentrations of 25-hydroxyvitamin D (25(OH)D) in the serum. But it remains unclear whether inadequate vitamin D could be the result or the cause of these disorders.¹ Nevertheless, it is commonly understood that the vitamin facilitates absorption of calcium from the gastrointestinal tract, promotes mineralization of osteoid tissue in newly formed bone, and also performs a significant role in the function of muscle.² A chronic deficiency in the vitamin is well

Correspondence: Michael Wakeman
Faculty of Health and Wellbeing,
University of Sunderland, Chester Road,
Sunderland, SRI 3SD, UK
Tel +44 1335 350935
Email mikepwakeman@gmail.com

recognized to be damaging to skeletal health, which can result in osteomalacia in adults or rickets in children.³ In these conditions, 25(OH)D serum concentrations are typically <20 nmol/L.⁴ Insufficiency of vitamin D – a situation where the deficiency is deemed to be less severe – has been shown to result in secondary hyperparathyroidism, along with higher levels of bone loss, and in older people, increased muscle weakness leading to falls and subsequent fragility fractures.²

The European Foods Standards Agency (EFSA) has approved health claims for vitamin D relating to

contribution to the normal function of the immune system; contribution to the maintenance of normal bones and teeth; normal growth and development of bone in children; normal absorption/utilisation of calcium and phosphorus; normal blood calcium concentrations and maintenance of normal muscle function.^{5–7}

However, despite there being a number of ongoing debates relating to specific requirements for the vitamin, its status, and subsequent effects on health, there is a consensus that the prevention of vitamin D deficiency is an important public health issue, especially since low levels appear to be prevalent in certain demographics, such as the institutionalized elderly, various ethnic groups, pregnant women, and young children.^{8,9}

Vitamin D is manufactured as a supplement, as either vitamin D₂ (ergocalciferol) or vitamin D₃ (cholecalciferol). Cholecalciferol is endogenously formed in the skin following exposure to ultraviolet (UV) radiation. It is also present in liver, fish, and eggs. In the liver, hepatic 25-hydroxylases (including cytochrome P450 (CYP) enzymes 3A4, 2R1, and 27A1) convert both ergocalciferol and cholecalciferol to the main circulating form, 25-hydroxycholecalciferol (25(OH)D₃). In turn, the active species, 1,25-dihydroxycholecalciferol (1,25(OH)₂D), is converted via 1 α -hydroxylase (CYP27B1) both in the kidney and at a local tissue level. The 24-hydroxylase enzyme (CYP24A1) is responsible for catabolism of vitamin D metabolites.

1,25-Dihydroxycholecalciferol (1,25(OH)₂D) affects intracellular signalling, and can induce either rapid or slower genomic responses. In the former case, it can initiate membrane-associated signal transduction, and in the latter, it can affect expression of those genes that contain a response element for vitamin D through initiation or inhibition of transcription.¹⁰ Studies show that 1,25(OH)₂D can induce the transcription of specific enzymes involved in both phase 1¹¹ and phase 2

biotransformations,¹² and multidrug-resistant protein 1, p-glycoprotein,¹³ as well as enzymes that control the bioavailability and metabolism of certain drugs.

Because 1,25(OH)₂D is more metabolically active, its presence in tissues is tightly regulated, and it is present in only picomolar concentrations in the circulation; hence, in terms of assessing clinical vitamin D status, 25(OH)D₃ is typically used as the chosen appropriate marker. However, the definition of sufficiency is still open to debate. Hence, some institutions propose concentrations of ≥ 20 ng/mL of 25(OH)D in the serum as providing sufficiency, based specifically on levels thought to be required for the prevention of osteoporosis,¹⁴ whereas others suggest a status of ≥ 30 –32 ng/mL (75–80 nmol/L) to be optimal for populations of healthy individuals.^{15–17} There are also interindividual issues which need to be taken into consideration in the interpretation of serum concentrations. For example, obese individuals are commonly reported to exhibit lower levels of 25(OH)D than subjects of normal weight. This has been suggested to be due to sequestration in adipose tissue, which is known to be a significant site for storage of the vitamin.¹⁸ During the winter months, UV intensity is not sufficient at latitudes >40° N to effect skin synthesis of cholecalciferol, leading to seasonal variation in vitamin D status in some individuals¹⁹ and one study suggests that higher concentrations of 25(OH)D occur in men, although reasons for this remain unknown.²⁰ Other factors impacting on vitamin D status include supplementation, dark skin, and increasing age.^{21,22}

In vitro studies suggest that while around 50% of all medications are metabolized by the phase I biotransformation enzyme 25-hydroxylase CYP3A4, which also transforms both supplemental forms of vitamin D to 25(OH)D, many other therapeutic entities may also inhibit or induce its activity.^{22,23} Given that CYP3A4 is active in both intestinal mucosal enterocytes and hepatocytes,^{24,25} it is likely that interactions with oral vitamin D consumption are of greater significance than those of intravenously administered drugs. Because the CYP3A4 gene has an element responsive to vitamin D, the presence of 1,25(OH)₂D may up-regulate its expression, which, in turn, could affect the metabolism of medications that depend on CYP3A4 for activation.^{13,26,27} Other potential interactions may result in an increased risk of hypercalcaemia when used together with calcium-sparing drugs, and/or limited absorption of vitamin D supplements if consumed alongside medications which either enhance the elimination of dietary fat or inhibit its absorption.

That suboptimal vitamin D levels are a common issue, even in prosperous countries, is typified by an analysis in the UK that reported the lowest mean concentrations of 25 (OH)D between January and March and the highest during July to September.²⁸ The study also reveals that 24% of females aged 11–18, males aged 19–64, and females aged 65 years and over have a year-round concentration below 25 nmol/L plasma 25(OH)D, which is the World Health Organization (WHO) threshold for vitamin D deficiency, as do 22% of females aged between 19 and 64 and 17% of males aged 65 years and over. This increases to around 40% in males aged 11–64 during January to March, and 29% of males aged 65 years and over.

This paper aims to summarize the published literature on the potential effects of medication on vitamin D status and to consider the implications that these could have a further impact on populations that are likely to be already deficient or depleted, and where chronic exposure to poly-pharmacy may further compromise this situation.

Methods

Studies published in peer-reviewed journals were considered for inclusion in the current review. The methods used and results obtained from the included papers were required to be well described, with appropriate data collection and analysis performed. The following electronic databases – MEDLINE via PubMed, Embase, Scopus, and CINAHL – were searched through to January 2021. Initially, this strategy was employed using keywords and the Medical Subject Headings (MeSH) “ergocalciferol”, “cholecalciferol”, “vitamin D”, “medication interactions”, and “drug interactions”. As a result of references identified in this primary search, additional terms including “statin”, “hydroxymethylglutaryl-CoA reductase inhibitors”, “colestyramine”, “cimetidine”, “antibiotics”, “glucocorticoids”, “anticonvulsants”, “laxatives”, “diuretics”, “cyclosporins”, “thiazides”, “HIV protease inhibitors”, “histamine H2 antagonists”, “antidepressants”, “ACE inhibitors”, “calcium channel blockers”, “polypharmacy”, and “immunosuppressive agents” were added and subsequently searched. Study quality and findings were abstracted according to relevance. Additional references and/or review articles revealed as a result of the primary research were also reviewed. In total, 576 titles were identified and 204 reports met the inclusion criteria.

Results

Medications Impacting on Vitamin D Status

A summary of the findings of key studies are presented in Table 1.

Anti-Epileptic Drugs (AEDs)

It has been recognized since the 1960s that there appears to be an association between metabolic bone abnormalities, such as osteomalacia, and the use of antiepileptic drugs (AEDs). Subsequently, a number of prospective and cohort studies have demonstrated an association between their use and reduced bone mineral density (BMD), together with an elevated risk of fracture.

Enzyme-Inducing Anti-Epileptic Drugs (EIAEDs)

Carbamazepine, phenobarbital, and phenytoin all increase the hepatic catabolism of vitamin D to inactive metabolites, thereby negatively affecting the absorption of calcium.^{29–31} This has been observed to result in hypocalcaemia and osteomalacia, especially as a result of prolonged use, such as in patients taking carbamazepine for 6 months or more, or where other enzyme-inducing anticonvulsants are co-prescribed, or when additional vitamin D deficiency risk factors occur, and these patients are likely to require calcium and vitamin D supplements as a result.^{29,31} The daily dose of vitamin D required to correct these deficits may differ, depending on the individual, from 10 µg (400 units) to 100 µg (4000 units), which necessitates that in high-risk patients, serum vitamin D and calcium status be monitored on a regular basis.³² However, unfortunately, many studies combine data for a variety of patients using either different individual or multiple AEDs, and fail to adjust for either duration of treatment or dose.^{33–54}

In the healthy kidney, CYP24A1 activity likely dominates 1,25(OH)₂D and 25(OH)D catabolism, whereas CYP3A4 activity is predominant in this metabolic process in the liver and small intestine. Between 10% and 30% of patients using phenobarbitone or phenytoin show radiological or biochemical evidence of decreased vitamin D levels.⁵⁵ Evidence of osteomalacia may occur within several months after initiation of anticonvulsant therapy and it is likely that concurrent use of different anticonvulsants will result in additive effects induced by these enzymes in the liver. Here, the modifying effects of degree of sunlight

Table I Summary of the Findings of Key Studies

Medication	Outcomes from Key Studies	References
Antidiabetic Medications		
Metformin	<p>Users of oral antidiabetics were observed in a cohort study to have on average lower mean 25(OH)D serum concentrations of 7.3 nmol/L compared with diabetics not using these drugs.</p> <p>In two similarly designed studies, with a total of over 11,500 patients, a negative association between vitamin D status and oral antidiabetic use was observed, and a further cross-sectional study identified a specific effect due to metformin only.</p>	[76,78–80]
Thiazolidinediones (TZDs)	<p>The decrease in bone mineral density (BMD) and the increase in risk of fracture in type 2 diabetes (T2D) have been shown to be exacerbated as a result of prescription of TZDs to improve insulin sensitivity.</p> <p>A systematic review and meta-analysis suggests that TZD use may result in bone loss that may be specific and moderate in women.</p> <p>Chronic TZD treatment has been reported to elevate the risk of bone fracture more in those women already at a greater risk for bone loss, osteoporosis, and bone fracture, than in men.</p> <p>T2D patients on antidiabetic therapies are likely to have a reduced intake of nutrients essential for bone health, such as vitamin D, calcium, and magnesium.</p>	[83–85,88–90]
Diuretics		
Thiazide Diuretics	<p>Associations with vitamin D levels appear mixed.</p> <p>The combination of supplementation with vitamin D (which enhances absorption of intestinal calcium) and thiazide diuretics (which decrease calcium excretion in the urine) and may theoretically result in hypercalcaemia, or exacerbate it. None of four additional studies reported that thiazide treatment resulted in significant alterations in concentrations of 25(OH)D.</p>	[91–96]
Loop Diuretics	<p>The use of loop diuretics resulted in associations with 25(OH)D being either negative or not present, whilst those with 1,25(OH)₂D were similarly mixed.</p> <p>A randomized clinical trial comparing placebo with loop diuretic use showed elevation of both 1,25(OH)₂D and serum parathyroid hormone (PTH) levels, together with an increased renal calcium excretion that may induce hyperparathyroidism, which, in turn, increases hydroxylation of 25(OH)D, resulting in increased concentrations of 1,25(OH)₂D.</p>	[76,91,97]
Potassium-Sparing Diuretics	<p>van Ortein-Luiten et al highlighted an inverse association between potassium-sparing diuretics and vitamin D in the elderly.</p> <p>Another cross-sectional study in patients of a similar demographic failed to replicate these findings.</p>	[76,80]
Medications Used in Cardiovascular Disease		
Calcium Channel Blockers	<p>In a cohort study of elderly individuals, the use of calcium channel blockers (such as verapamil and diltiazem) resulted in a reduction of 7.7 nmol/L in levels of 25(OH)D in serum in contrast to non-use.</p> <p>As verapamil and diltiazem are known to inhibit CYP3A4, the anabolism of 25(OH)D precursors in the skin through exposure to UV radiation may be decreased as a consequence, thus resulting in lower serum 25(OH)D.</p> <p>Drugs, such as nifedipine, which are ligands for the nuclear pregnane X receptor (PXR) can induce an increase in vitamin D catabolism.</p>	[23,75,76,98–101]

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Table I (Continued).

Medication	Outcomes from Key Studies	References
Angiotensin-Converting Enzyme (ACE) Inhibitors	<p>ACE inhibitor use in a cohort of elderly patients resulted in a 7.6 nmol/L reduction in 25(OH)D serum levels compared with those not prescribed this type of medication. German and Dutch cross-sectional studies also reported lower levels of 25(OH)D in those using these drugs.</p> <p>A further examination of the cohort in the Dutch study and two quasi-experimental studies showed no relationship.</p> <p>Another study identified higher concentrations in those prescribed quinapril, but reported no change in enalapril users.</p>	[76,102–106]
Statins	<p>Statins exert their cholesterol-lowering effects by inhibiting the hydroxymethylglutaryl-coenzyme A reductase (HMG CoA reductase) enzyme, which is rate limiting in cholesterol synthesis; hence, it is thought that statins could also reduce the synthesis of vitamin D.</p> <p>Since simvastatin, lovastatin, and atorvastatin are primarily metabolized by CYP3A4, competition for this enzyme may present another route for drug–vitamin interactions.</p> <p>CYP2C9 primarily metabolizes rosuvastatin and fluvastatin, whereas pravastatin and pitavastatin interact minimally with hepatic enzymes, instead being degraded in the stomach.</p> <p>Reports from several groups have indicated that atorvastatin administration may increase circulating 25(OH)D concentrations.</p> <p>Two studies investigating the effects of pravastatin therapy on vitamin D status identified no significant differences in 25(OH)D levels.</p> <p>Rosuvastatin has been demonstrated to robustly increase levels of vitamin D.</p> <p>In a prospective cohort study in hyperlipidaemic patients, compared with baseline levels, statistically significant increases were observed in both 25-hydroxyvitamin D and 1,25-hydroxyvitamin D.</p> <p>The same authors later reported that 25-hydroxyvitamin D levels increased with rosuvastatin treatment compared to fluvastatin.</p> <p>Well-designed larger multicentre trials are required to resolve the issue.</p>	[105,108–119,122,123]
Bile Acid Sequestrants	<p>Bile acid sequestrants may also bind with vitamin D, and since its metabolites are also present in bile, an elevated excretion of bile acids may also reduce levels of this and other fat-soluble vitamins.</p> <p>One trial in children with familial hypercholesterolaemia reported a significant decrease in vitamin D status in those taking 8 g colestyramine daily over the period of a year.</p> <p>The reduction in absorption of vitamin D induced by colestyramine can occasionally lead to osteomalacia in patients receiving daily doses of colestyramine of >32 g for prolonged periods of over 2 years.</p> <p>Three other studies on the same class of medications reported the opposite findings.</p>	[116,128–135]
Vitamin K Antagonists	<p>Two cross-sectional studies from the Netherlands indicate that patients prescribed vitamin K antagonists experienced more greatly reduced concentrations of 25(OH)D than non-users.</p> <p>This was confirmed in a cross-sectional study from Germany of 7553 males.</p> <p>Four other studies did not report this effect.</p>	[76,79,80,136–139]
Platelet Aggregation Inhibitors	<p>Two cross-sectional studies failed to report an inverse relationship between the use of platelet aggregation inhibitors and vitamin D status.</p> <p>However, three other studies have found to the contrary.</p>	[76,79,80,140,141]

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Table I (Continued).

Medication	Outcomes from Key Studies	References
Heparin	When used for 3 months or more, at a dose of $\geq 15,000$ IU, unfractionated heparin has been demonstrated to be associated with osteoporotic fractures and reduced bone density, and vitamin D metabolism is also negatively affected. Low molecular weight heparins are unlikely to reduce bone density to the same extent as unfractionated heparin, but there is the possibility that these compounds may adversely affect vitamin D metabolism.	[206–214]
Digoxin	In one Dutch cross-sectional study of geriatric patients, a negative, tending towards a statistically significant inverse relationship between digoxin and vitamin D was identified. Statistical significance was not confirmed in other studies.	[76,79,80]
CNS Medications		
Benzodiazepines	A lack of a significant effect of benzodiazepines has been reported in three cross-sectional studies. Sohl et al, in a subsequent subgroup analysis of participants in their study, did observe a significant inverse association between this category of drug and vitamin D.	[76,80,142]
Antidepressants	The finding of an inverse relationship between the use of selective serotonin reuptake inhibitors (SSRIs) and 25(OH)D levels was reported in two cross-sectional studies.	[80,142]
Enzyme-Inducing Antiepileptic Drugs (AEDs)	A systematic review suggests that in adult patients treated with AEDs, vitamin D deficiency is commonly observed, with consequently reduced levels and frequency of deficiency differing according to the medication used.	[61]
Newer Antiepileptic Drugs	A large retrospective cohort study of over 15,000 patients reported an elevated risk of bone fracture for gabapentin but none with lamotrigine, levetiracetam, or oxcarbazepine. However, a smaller, similarly retrospective, study of 560 patients concluded that there was no association between newer AEDs and lower BMD. Other studies are conflicting.	[63–70]
Gastrointestinal Medications		
Proton Pump Inhibitors (PPIs)	Theoretically, the hypochlorhydria induced by this class of medication could result in malabsorption of calcium, with the suggestion that prolonged exposure to acid suppression might be a clinically relevant consequence contributing to increased osteoporosis risk. Vitamin D and calcium for the elderly where high-dose PPI therapy, especially over a long-term period, is being employed, is recommended.	[144–146]
Histamine H₂-Receptor Antagonists	Preclinical studies demonstrate that cimetidine inhibits 25-hydroxylases. A small study of nine patients with cimetidine-treated gastric ulcers identified no significant decrease in 25(OH)D serum concentrations from baseline while patients were receiving the medication; however, levels rose significantly once cimetidine was discontinued. Preclinical models fail to identify the same interaction with ranitidine.	[147–150]

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Medication	Outcomes from Key Studies	References
Lipase Inhibitors	<p>Orlistat binds within the gastrointestinal tract to the active sites of pancreatic and gastric lipases and thereby blocks absorption of fats in the diet, thus limiting calorie intake; hence, vitamin D uptake and absorption from the diet and supplements may be inhibited.</p> <p>Three studies reported decreased concentrations of 25(OH)D in those receiving orlistat. However, decreases were similarly reported in the control groups, which may be attributable to a reduction in total fat intake.</p>	[194–198]
Laxatives	<p>A reduction in absorption of vitamin D and calcium from food as a result of high doses and prolonged use of stimulant laxatives can lead to hypocalcaemia and osteomalacia.</p>	[73]
Anti-Inflammatory Medications		
Corticosteroids	<p>A commonly observed complication of corticosteroid therapy is osteoporosis, and the impact of this class of medication on vitamin D metabolism as a potential contributory factor has been the subject of a number of studies.</p> <p>The majority identified no significant differences in levels of 25(OH)D in comparison to pretreatment or in controls.</p> <p>Lems et al identified that treatment of healthy controls with low-dose prednisone reduced 25(OH)D levels.</p> <p>Lund et al similarly reported 25(OH)D concentrations to be significantly reduced in a study of patients with rheumatoid arthritis taking low-dose prednisone, but none was considered to be deficient.</p> <p>Two other centres reported a lack of significant differences in pre- versus post-treatment 25(OH)D concentrations with prednisolone.</p> <p>In the USA, those taking prednisolone ≥ 7.5 mg/day (or corresponding doses of other corticosteroids) for ≥ 6 months are advised to take a daily vitamin D supplement of 800 IU and to maintain a calcium intake of 1500 mg each day.</p>	[151–163,181]
Inhaled Corticosteroids (ICS)	<p>One study failed to identify any effect of inhaled glucocorticosteroids (ICS) on serum 25(OH)D</p> <p>Sohl et al, in a cohort study, reported a significant negative association with lower 25(OH)D in serum in men treated with this class of medication.</p> <p>One systematic review concluded that ICS use may affect markers of BMD and bone metabolism in asthmatic patients and those with COPD, as well as healthy adults.</p> <p>Another meta-analysis identified a significant relationship between greater doses of ICS and elevated turnover of bone in mild COPD as well as asthmatic patients, but this failed to reach significance at lower doses of ICS.</p> <p>A third meta-analysis reported no difference in BMD between asthma patients receiving long-term ICS treatment and healthy controls.</p> <p>A later systematic review and meta-analysis found no significant associations between BMD and fracture risk in asthmatic children and adults receiving long-term ICS treatment.</p> <p>Meta-analyses assessing the association between fracture risk in COPD patients and long-term ICS use have established a modest but significant, dose-dependent increase.</p> <p>In summary, the effect of long-term ICS use may negatively influence bone metabolism and BMD in certain patients, especially those with COPD.</p>	[76,170,173–176,178–180]

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Table 1 (Continued).

Medication	Outcomes from Key Studies	References
Bronchodilators	In one case–control study, a greater risk of femur and hip fractures was reported for larger doses, but this was attenuated after adjusting for underlying disease and oral glucocorticoid use. This finding is supported by a 2-year randomized trial assessing BMD in patients receiving ICS compared to a non-corticosteroid group taking beta2-agonists.	[182,183]
Hydroxychloroquine	One study assessing the predictors and prevalence of deficiency of vitamin D found it to be common in systemic lupus erythematosus patients. Those prescribed hydroxychloroquine had elevated concentrations of 25(OH)D in comparison with non-users.	[199]
Anti-infectives/Antivirals		
Antimicrobials	Six small studies investigated the possibility of an association between the use of rifampicin and/or isoniazid and vitamin D status. Of these, four reported a decrease in 25(OH)D, one identified no change, and one demonstrated an increase. Osteomalacia has been reported after therapy prolonged for >1 year, especially when accompanied by low intake of vitamin D.	[184,185,189–193]
Sulphonamides and Urea Derivatives	A cross-sectional study of 892 community-living outpatients in the Netherlands identified a statistically significant negative effect of these medications on vitamin D status.	[80]
Highly Active Antiretroviral Therapy (HAART)	Of three clinical studies, two reported lower concentrations of 25(OH)D in serum in patients prescribed HAART compared with non-users, but this was only statistically significant in one study. Reduction of plasma levels of vitamin D has been reported within 6 months of initiation of therapy with favirenz-based antiretroviral therapy, but not after longer term use.	[202–205]
Medications Used in Malignancy		
Chemotherapeutic Agents	Many of these medications are metabolized by CYP3A4 and hence may interact with vitamin D. These include tamoxifen, docetaxel, paclitaxel, ifosfamide, etoposide, vinblastine, vincristine, cyclophosphamide, imatinib, and irinotecan. The effect of the use of docetaxel and anthracycline-based adjuvant chemotherapy on vitamin D plasma levels was investigated in a longitudinal evaluation of breast cancer patients with an early-stage diagnosis, and it was identified that 30–50% were vitamin D deficient at the initial diagnosis of their breast cancer. Two other studies of the same chemotherapy regimens failed to report a significant change in 25(OH)D concentrations; however, in both, patients received vitamin D supplements. Another study in a similar group of patients found that nearly all patients had insufficiency of vitamin D by the completion of neoadjuvant chemotherapy, accompanied by associated alterations in the calcium/ RANKL/OPG axis, which suggests a disruption of regulatory mechanisms at a functional level. Three other studies assessed vitamin D status during chemotherapy. These studies examined patients diagnosed with colorectal, breast, uterine, and ovarian cancers treated with a variety of chemotherapeutic drugs (5-fluorouracil, cisplatin, capecitabine, epirubicin, oxaliplatin, irinotecan, as well as a number of monoclonal antibodies) and reported a lack of significant changes in concentrations of 25(OH)D during treatment.	[215,216,218–223]

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Table I (Continued).

Medication	Outcomes from Key Studies	References
Others		
Sunscreens	Reduction of synthesis of vitamin D in the skin, and hence plasma levels, can occur as a result of extensive or frequent use of sunscreens, and there is concern that excessive use or overuse may result in deficiency.	[224–228]

exposure and dietary intake are also important to take into consideration.⁵⁶ Supplementation with vitamin D has been demonstrated to result in improvements in the biochemical and radiological changes reported above.^{57–59}

One study reported that irrespective of which antiepileptic medication of this type is prescribed, subjects with concentrations of 25(OH)D considered to be within a “normal” range went into insufficiency and deficiency states upon initiation of treatment, and that this occurred even at subtherapeutic levels of the drug in serum.⁶⁰ The authors therefore suggested that it is worthwhile to recommend vitamin D and calcium supplementation prior to the commencement of any antiepileptic therapy of this type.

The primary finding in a previous systematic review is that in adult patients treated with these AEDs, vitamin D deficiency is commonly observed, with consequent levels and frequency of deficiency differing according to the medication used.⁶¹ However, the authors question whether the inherently suboptimal levels of vitamin D commonly observed in these patients might act as a confounder. One randomized trial identified that using higher dose vitamin D supplementation could help to stabilize the total hip and spine BMD compared with a lower dose of vitamin D in patients on these AEDs.⁶²

Newer AEDs

Data are limited on newer AEDs and the specific effects on bone. A large retrospective cohort study of over 15,000 patients reported an elevated risk of bone fracture for gabapentin, but not with lamotrigine, levetiracetam, or oxcarbazepine.⁶³ However, a smaller, similarly retrospective, study of 560 patients concluded that there was no association between newer AEDs and lower BMD.⁶⁴ Likewise, other studies are conflicting.^{65–70} However, a preclinical study of levetiracetam suggests although bone density was not impaired, there was a negative effect on bone quality, which indicates that traditionally used measures of BMD may not necessarily identify all changes in bone health.⁷¹ Wu et al also demonstrated that patients

with osteoporosis were more likely to have epilepsy and to have received EIAED or non-CYP450-inducing antiepileptic drug (NEIAED) treatment.⁷² However, a later retrospective study of BMD and some of the more recently introduced anticonvulsants (topiramate, gabapentin, levetiracetam) failed to identify any detrimental effects.⁶⁴

Laxatives

Laxatives accelerate the movement of foods and liquids through the digestive tract, and this potentially reduced transit time may induce a negative impact on vitamin absorption, especially those that are fat soluble, such as vitamins A, D, E, and K, as well as minerals such as calcium, sodium, magnesium, and potassium. This reduction in absorption of vitamin D and calcium from food as a result of high doses and prolonged use of stimulant laxatives can lead to hypocalcaemia and osteomalacia.⁷³

Diabetes Medications

Metformin

Deficiency of vitamin D is associated with decreased insulin secretion and increased resistance to insulin.^{74,75} Users of oral antidiabetics were observed in a cohort study to have, on average, lower mean 25(OH)D serum concentrations of 7.3 nmol/L compared with diabetics not using these drugs.⁷⁶ One group has suggested an intrinsic limitation of this study to be that any potential effect of metformin on lowering levels of vitamin D may have been confounded as a result of the use of supplements when deficiency was diagnosed.⁷⁷ However, in two other similarly designed studies, with a total of over 11,500 patients, a negative association between vitamin D status and oral antidiabetic use was observed, and a further cross-sectional study identified a specific effect due to metformin only.^{78–80}

Thiazolidinediones

It is well established that patients with type 2 diabetes (T2D) have a higher incidence of bone fractures in

comparison to their non-diabetic counterparts, despite there being no significant differences in BMD between the two populations.^{81,82} The decrease in BMD and the increase in risk of fracture in T2D have also been shown to be exacerbated as a result of prescription of thiazolidinediones (TZDs) to improve insulin sensitivity.^{83–85} TZDs appear to affect mesenchymal stem cells, resulting in an increase in adipogenesis and a decrease in osteoblast formation.^{86,87}

A systematic review and meta-analysis suggests that TZD use may result in bone loss that may be specific and moderate in women.⁸⁸ Likewise, chronic TZD treatment has been reported to elevate the risk of bone fracture more in those women already at a greater risk for bone loss, osteoporosis, and bone fracture, than men.⁸⁹ This situation is exacerbated by reports that T2D patients on antidiabetic therapies are likely to have a reduced intake of nutrients essential for bone health, such as vitamin D, calcium, and magnesium.⁹⁰

Diuretics

Thiazide Diuretics

Associations between vitamin D levels and thiazide diuretics appear mixed.⁹¹ The combination of supplementation with vitamin D (which enhances the absorption of intestinal calcium) and thiazide diuretics (which decrease calcium excretion in the urine) may theoretically result in hypercalcaemia, or exacerbate it.⁹² This is especially likely in those individuals considered to be at risk in these situations, such as those, typically elderly patients, with hyperparathyroidism or compromised renal function. None of four additional studies reported that thiazide treatment resulted in significant alterations in concentrations of 25(OH)D.^{93–96}

Loop Diuretics

The use of loop diuretics resulted in associations with 25(OH)D being either negative or not present, whilst those with 1,25(OH)₂D were similarly mixed.⁹¹ A randomized clinical trial comparing placebo with loop diuretic use showed elevation of both 1,25(OH)₂D and serum parathyroid hormone (PTH) levels, together with an increased renal calcium excretion that might induce hyperparathyroidism, which, in turn, increases hydroxylation of 25(OH)D, resulting in increased concentrations of 1,25(OH)₂D.^{76,97}

Potassium-Sparing Diuretics

van Orstein-Luiten et al highlighted an inverse association between these medications and vitamin D in the elderly,⁸⁰ but another cross-sectional study in patients of a similar demographic failed to replicate these findings.⁷⁶

Medications Used in Cardiovascular Disease

Calcium Channel Blockers

In a cohort study of elderly individuals, the use of calcium channel blockers (such as verapamil and diltiazem) resulted in a reduction of 7.7 nmol/L in levels of 25(OH)D in serum, in contrast to non-use.⁹⁸ As verapamil and diltiazem are known to inhibit CYP3A4, the anabolism of 25(OH)D precursors in the skin through exposure to UV radiation may be decreased as a consequence, thus resulting in lower serum 25(OH)D.^{23,75,99–101} It also appears that drugs, such as nifedipine, which are ligands for the nuclear pregnane X receptor (PXR) can induce an increase in vitamin D catabolism.⁷⁶

Angiotensin-Converting Enzyme (ACE) Inhibitors

ACE inhibitor use in a cohort of elderly patients resulted in a 7.6 nmol/L reduction in 25(OH)D serum levels compared with those not prescribed this type of medication.⁷⁶ However, the potential of polymorphisms in CYP enzymes metabolizing these drugs has also been suggested as a possible confounder.¹⁰² German and Dutch cross-sectional studies also reported lower levels of 25(OH)D in those using these drugs,^{103,104} whereas a further examination of the cohort in a Dutch study⁷⁶ and in two quasi-experimental studies^{102,105} showed no relationship. Although another study identified higher concentrations in those prescribed quinapril, it reported no change in enalapril users.¹⁰⁶ However, as other authors point out,

it cannot be excluded that an inverse association reflects the inverse relationship between low 25(OH)D level and the indication for prescription: high blood pressure and associated comorbidities of diabetes.¹⁰⁷

Statins

Statins exert their cholesterol-lowering effects by inhibiting the hydroxymethylglutaryl-coenzyme A reductase (HMG CoA reductase) enzyme, which is rate-limiting in cholesterol synthesis.¹⁰⁸ Since cholesterol is a precursor of vitamin D, it is thought that statins could also reduce the synthesis of this vitamin.^{109,110} Because simvastatin,

lovastatin, and atorvastatin are primarily metabolized by CYP3A4, competition for this enzyme may also present another route for drug–vitamin interactions.^{111,112} In contrast, CYP2C9 primarily metabolizes rosuvastatin and fluvastatin, whereas pravastatin and pitavastatin interact minimally with hepatic enzymes, instead being degraded in the stomach.^{112,113}

Despite these potentially detrimental effects on vitamin D status, reports from several groups have indicated that atorvastatin administration may increase circulating 25 (OH)D concentrations.^{105,114–116} In one study, researchers identified that patients consuming a daily supplement containing 800 IU of a vitamin D over 6 weeks had levels of atorvastatin or metabolites that were statistically significantly lower than in subjects who were not receiving supplements ($P < 0.05$).¹¹⁴ Nevertheless, cholesterol scores were reduced in the supplementation group, despite these lower atorvastatin concentrations. Both studies investigating the effects of pravastatin therapy on vitamin D status^{110,116} identified no significant differences in 25(OH)D levels. Rosuvastatin has been demonstrated to robustly increase levels of vitamin D, leading to the suggestion that the beneficial effects of this medication, as identified in the “Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)” study, were partly related to this effect in a population that was vitamin D insufficient.¹¹⁷

These observations were supported in a prospective cohort study in hyperlipidaemic patients. Of the 91 patients, 19% were diabetic and 47% were diagnosed with systemic hypertension, all of whom were statin treatment naïve and were treated for 8 weeks with rosuvastatin.¹¹⁸ Compared with baseline levels, statistically significant increases were observed in both 25-hydroxyvitamin D and 1,25-hydroxyvitamin D. In a further trial of hyperlipidaemic patients, the same authors later reported that 25-hydroxyvitamin D levels increased with rosuvastatin treatment compared to fluvastatin.¹¹⁹ Their findings generated a great deal of controversy, with a number of authors highlighting potential issues,^{120,121} thereby resulting in a consensus that well-designed larger multicentre trials are required to resolve the issue.^{122,123}

It is clear that a complex and poorly elucidated relationship exists between statins and vitamin D. However, it is known that both affect the function and metabolism of skeletal muscle, with myalgia linked specifically with vitamin D deficiency.¹²⁴ Certain authors suggest vitamin D deficiency is associated with increased intolerance to

statins as a result of myopathy.¹²⁵ This is supported by one study of 150 patients with hypercholesterolaemia, which identified that individuals who were intolerant to one statin as a result of myalgia also had low serum vitamin D.¹²⁶ These patients were subsequently supplemented with vitamin D and then recommenced on statin therapy for 8 months. Subsequently, 87% were reported to be free of myalgia and able to tolerate reinitiation of the statin.

Seven studies with 2420 patients were the subject of a systematic review and meta-analysis, which indicates that low vitamin D levels are indeed associated with myalgia in those receiving statins.¹²⁷ It is suggested that a reversible relationship between deficiency of vitamin D and patients taking statins who experience skeletal muscle myopathy exists, which may be resolved as a result of correcting any underlying deficiency. Alternatively, in certain patients, statin myopathy or drug-unrelated myalgias may be potentiated by deficiency of vitamin D. However, there is not sufficient evidence to support extensive vitamin D status testing in patients with myalgia thought to be the result of statin treatment. Nevertheless, where a patient is known to be deficient in vitamin D and where a history of intolerance to a statin has been established, a rechallenge with a statin would appear to be a reasonable strategy once levels of vitamin D are confirmed to be replete.

Bile Acid Sequestrants

These drugs bind with bile acids in the gastrointestinal tract to prevent cholesterol reabsorption and thereby reduce its circulating levels. However, they may also bind with vitamin D, and since its metabolites are also present in bile, an elevated excretion of bile acids may also reduce levels of this and other fat-soluble vitamins.^{128–133} One trial in children with familial hypercholesterolaemia reported a significant decrease in vitamin D status in those taking 8 g colestyramine daily over the period of a year.¹²⁸ The reduction in absorption of vitamin D induced by colestyramine can occasionally lead to osteomalacia in patients receiving daily doses of colestyramine of >32 g for prolonged periods of over 2 years.¹³³ However, three other studies on the same class of medications reported opposite findings.^{116,134,135}

Vitamin K Antagonists

Two cross-sectional studies from the Netherlands indicate that patients prescribed vitamin K antagonists experienced greater reductions in concentrations of 25(OH)D than non-users,^{76,80} an effect confirmed in a cross-sectional study

from Germany of 7553 males.⁷⁹ However, four other studies did not report this effect.^{136–139}

Platelet Aggregation Inhibitors

Whereas two cross-sectional studies^{76,80} failed to report an inverse relationship between the use of these drugs and vitamin D status, three others have done so.^{79,140,141} However, it is suggested that confounding by indication may be a factor.¹³³

Digoxin

In one Dutch cross-sectional study of geriatric patients, a negative, tending towards a statistically significant inverse relationship between digoxin use and vitamin D.⁸⁰ However, statistical significance was not confirmed in other studies.^{76,79}

CNS Medications

Benzodiazepines

Whereas a lack of a significant effect of benzodiazepines on vitamin D status has been reported in three cross-sectional studies,^{76,80,142} Sohl et al, in a subsequent subgroup analysis of participants in their study, did observe a significant inverse association.⁷⁶

Antidepressants

The finding of an inverse relationship between the use of selective serotonin reuptake inhibitors (SSRIs) and 25(OH)D levels was reported in two cross-sectional studies.^{80,142} This may be the result of a negative impact on synthesis of 25(OH)D, as the antidepressant drugs fluvoxamine and fluoxetine are both reported to inhibit the metabolism of CYP enzymes involved in this process.⁹² However, the authors of the two above cross-sectional studies also acknowledged the association that has been reported to exist between depression and vitamin D levels,^{80,142} and this is confirmed by a prospective cohort study,¹⁴³ which suggests that this indication might be considered as a confounding issue.

Disorders of Gastric Acid and Ulceration Medications

Proton Pump Inhibitors (PPIs)

Theoretically, the hypochlorhydria induced by this class of medication could result in malabsorption of calcium, with the suggestion that prolonged exposure to acid suppression may be a clinically relevant consequence contributing to increased osteoporosis risk.^{144,145} One review suggests that it may be advisable to consider supplementation

with vitamin D and calcium for the elderly, where high-dose PPI therapy, especially over a long-term period, is being employed.¹⁴⁶

Histamine H₂-Receptor Antagonists (H₂RAs)

H₂RAs, such as cimetidine, inhibit the secretion of gastric acid by limiting the ability of gastric parietal cells to produce histamine. Preclinical studies demonstrate that cimetidine also inhibits 25-hydroxylases.^{147,148} A small study of nine patients with cimetidine-treated gastric ulcers identified no significant decrease in 25(OH)D serum concentrations from baseline while patients were receiving the medication; however, levels rose significantly once cimetidine was discontinued.¹⁴⁹ In contrast, preclinical models failed to identify the same interaction with ranitidine.¹⁵⁰

Corticosteroids

A commonly observed complication of corticosteroid therapy is osteoporosis, and the impact of this class of medication on vitamin D metabolism as a potential contributory factor has been the subject of a number of studies.^{151–161} Here, the majority identified no significant differences in levels of 25(OH)D in comparison to those measured pre-treatment, or in controls.^{152–154,157,158,160} However, Lems et al¹⁵⁵ identified that treatment of healthy controls with low-dose prednisone reduced 25(OH)D levels, but since the study was undertaken in the autumn, the authors attributed this observation to seasonal effects. Lund et al¹⁵⁹ similarly reported 25(OH)D concentrations to be significantly reduced in a study of patients with rheumatoid arthritis taking low-dose prednisone, but none was considered to be deficient. Two other centres reported a lack of significant differences in pre- versus post-treatment 25(OH)D concentrations with prednisolone.^{162,163}

However, while some investigations reviewing this issue identify precisely the specific glucocorticoid that the patients were prescribed, this is not the case in many of the studies, making the conclusions unclear.^{164–167} In one study where this did occur, in adult rheumatoid arthritis patients on daily doses of between 2.5 and 10 mg of prednisone equivalents over at least three months, it was identified that 25(OH)D concentrations were significantly reduced in corticosteroid users compared to those of healthy controls.¹⁶⁵ Likewise, two studies in young adults and children identified that those with the most significantly reduced levels of 25(OH)D were the ones with the highest cumulative exposure to glucocorticoids.^{168,169} A

limitation to most of these studies is the lack of reporting of any potential confounders, such as differences in body composition, supplemental or dietary vitamin D intake, and exposure to UV sunlight.

Whereas previous studies had not identified any effect of inhaled glucocorticosteroids (ICS) on serum 25(OH)D,¹⁷⁰ Sohl et al, in a cohort study, reported a significant negative association with lower 25(OH)D in serum in men treated with this class of medication.⁷⁶ Inhaled corticosteroids are also commonly used in chronic obstructive pulmonary disease (COPD), where deficiency of vitamin D has a high prevalence and where serum concentrations seem to correlate directly with the severity of the condition. Hence, confounding by this indication may contribute to any observed associations between reduced 25(OH)D serum concentrations and inhaled corticosteroid use in this disease.^{171,172}

The effects of long-term (>12 months) inhaled corticosteroid (ICS) use on bone are currently unclear.¹⁷⁰ One systematic review concluded that ICS use may affect markers of BMD and bone metabolism in asthmatic patients and those with COPD, as well as healthy adults.¹⁷³ This is supported by another meta-analysis, where a significant relationship between greater doses of ICS and elevated turnover of bone in mild COPD, as well as asthmatic patients, was observed.¹⁷⁴ This failed to reach significance at lower doses of ICS. However, a third meta-analysis reported no difference in BMD between asthma patients receiving long-term ICS treatment and healthy controls.¹⁷⁵ Furthermore, a later systematic review and meta-analysis found no significant associations between BMD and fracture risk in asthmatic children and adults receiving long-term ICS treatment.¹⁷⁶

In COPD patients, the high prevalence of factors such as smoking, cachexia, and low-grade systemic inflammation^{176,177} is likely to negatively impact bone formation and would possibly have an effect on BMD. Nevertheless, meta-analyses assessing the association between fracture risk in COPD patients and long-term ICS use have established a modest but significant, dose-dependent increase.^{178,179} In summary, long-term ICS use may negatively influence bone metabolism and BMD in certain patients, especially those with COPD.¹⁸⁰

In the USA, those taking prednisolone ≥ 7.5 mg/day (or corresponding doses of other corticosteroids) for 6 months or more are advised to take a daily vitamin D supplement of 800 IU and to maintain a calcium intake of 1500 mg each day.¹⁸¹

Bronchodilators

There are limited human studies investigating the effects of beta2-agonists on bone health. In one case-control study, a greater risk of femur and hip fractures was reported for larger doses, but this was attenuated after adjusting for underlying disease and oral glucocorticoid use.¹⁸² This finding is supported by a 2-year randomized trial assessing BMD in patients receiving ICS compared to a non-corticosteroid group taking beta2-agonists.¹⁸³

Antimicrobials

The relationship between tuberculosis (TB) and vitamin D is complex but well established. Historically, exposure to sunshine and supplementation with vitamin D were the mainstays of treatment, prior to the introduction of effective antibiotic therapy. Vitamin D modulates the activity of macrophages and also increases production of cathelicidin, a protein with antimicrobial activity. Enhanced susceptibility to infection with TB has been reported to be associated with deficiency of vitamin D, as has reactivation of latent infections. As CYP3A4 is inhibited by isoniazid and induced by rifampicin, these drugs may affect vitamin D status.¹⁸⁴⁻¹⁸⁷

Six small studies investigated the possibility of an association between the use of rifampicin and/or isoniazid and vitamin D status.^{184,188-192} Of these, four reported a decrease in 25(OH)D,^{184,191,192} one identified no change, and one demonstrated an increase. Two of these studies reported that the patients had below-normal pretreatment concentrations of 25(OH)D,^{184,191} but confounders such as season of vitamin D status assessment, supplemental or dietary intake of vitamin D, and stratification by skin tone/race, or UV exposure were poorly reported. Osteomalacia has been reported after prolonged therapy for more than one year, especially when accompanied by low intake of vitamin D.^{185,193}

Sulphonamides and Urea Derivatives

A cross-sectional study of 892 community-living outpatients in the Netherlands identified a statistically significant negative effect of these medications on vitamin D status.⁸⁰

Lipase Inhibitors

The weight-loss medication orlistat binds within the gastrointestinal tract to the active sites of pancreatic and gastric lipases and thereby blocks the absorption of fats in the diet, thus limiting calorie intake.¹⁹⁴ Because it is fat soluble, vitamin D uptake and absorption from the diet and supplements may be inhibited by orlistat.¹⁹⁵ Three studies

reported decreased concentrations of 25(OH)D in those receiving orlistat.^{196–198} However, decreases were similarly reported in the control groups, which may be the result of a reduced total intake of dietary fat.

Hydroxychloroquine

Because patients with autoimmune conditions often experience photosensitivity, they commonly avoid exposure to sunshine, leading to a concern that a deficiency of vitamin D might be prevalent in this cohort. One study with a comparison group assessed the predictors and prevalence of deficiency of vitamin D in 92 adults with systemic lupus erythematosus (SLE).¹⁹⁹ Deficiency was found to be common in this cohort, being present in around 75% of patients, and those prescribed hydroxychloroquine had elevated concentrations of 25(OH)D in comparison with non-users. The authors suggest that this may be a result of a limited conversion rate of 25(OH)D to 1,25(OH)₂D.

Highly Active Antiretroviral Agents

Highly active antiretroviral therapy (HAART) consists of several classes of antiretroviral medications that variously act by inhibiting different stages of the life cycle of the human immunodeficiency virus (HIV). They include protease inhibitors (PIs), nucleotide reverse transcriptase inhibitors (NtRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and entry inhibitors.²⁰⁰ Reports indicate that these medications are metabolized by CYP3A4, either inducing or inhibiting its activity,⁹² and hence these effects could affect the rate of synthesis and degradation of 25(OH)D. This observation was confirmed by Cozzolino et al and others.^{201–203} Of four clinical studies,^{202–205} two reported lower concentrations of 25(OH)D in serum in patients prescribed HAART compared with non-users,^{202,204} but this was only statistically significant in one study.²⁰² A reduction in plasma levels of vitamin D has been reported within 6 months of initiation of therapy with efavirenz-based antiretroviral therapy, but not after longer term use.²⁰⁵

Heparin

When used for 3 months or more at a dose of $\geq 15,000$ IU, unfractionated heparin has been demonstrated to be associated with osteoporotic fractures and reduced bone density.^{206–209} This is mainly the result of the direct effects of heparin reducing bone formation and increasing resorption, but vitamin D metabolism is also negatively

affected,^{206,210,211} suggesting that patients on long-term therapy should consider supplements containing calcium and vitamin D. Although low molecular weight heparins are unlikely to reduce bone density to the same extent as unfractionated heparin, there is the possibility that these compounds may adversely affect vitamin D metabolism.^{212–214}

Chemotherapeutic Agents

Many of these medications are metabolized by CYP3A4 and hence may interact with vitamin D. These include tamoxifen, docetaxel, paclitaxel, ifosfamide etoposide, vinblastine, vincristine, cyclophosphamide, imatinib, and irinotecan.²¹⁵

The effect of the use of docetaxel and anthracycline-based adjuvant chemotherapy on vitamin D plasma levels was investigated in a longitudinal evaluation of breast cancer patients with an early-stage diagnosis. It was identified that 30–50% were vitamin D deficient at the initial diagnosis of their breast cancer.²¹⁶ Furthermore, a prospective cohort study identified an inverse association between breast cancer prognosis and serum levels of 25(OH)D.²¹⁷ However, since lower circulating levels of 25(OH)D can be attributed to increased storage in adipose tissue, it may be that the apparent reduction in plasma vitamin D levels is associated with increases in body mass index, which often occur in early-stage breast cancer patients receiving adjuvant chemotherapy.¹⁸ Two other studies of the same chemotherapy regimens failed to report a significant change in 25(OH)D concentrations; however, in both, patients received vitamin D supplements.^{218,219} Another study in a similar group of patients found that nearly all had insufficiency of vitamin D by the completion of neoadjuvant chemotherapy, accompanied by associated alterations in the calcium/RANKL/OPG axis, which suggests a disruption of regulatory mechanisms at a functional level.²²⁰

Given that as they age, female breast cancer patients and survivors, in particular, experience elevated rates of bone loss, with a 15% increased fracture risk compared to their healthy counterparts, the preservation of bone health in breast cancer survivors is a key issue. Here, in a large cohort study of patients with early-stage breast cancer, univariate analyses identified that reduced levels of vitamin D were significantly associated with elevated risks of both recurrence and death. Together, these findings suggest that supplementation with vitamin D appears advisable

both during chemotherapy and when treatment has been completed, unless specifically contraindicated.²¹⁸

Three other studies^{221–223} assessed the vitamin D status during chemotherapy. These studies examined patients diagnosed with colorectal, breast, uterine, and ovarian cancers, treated with a variety of chemotherapeutic drugs (5-fluorouracil, cisplatin, capecitabine, epirubicin, oxaliplatin, irinotecan, as well as a number of monoclonal antibodies) and reported a lack of significant changes in concentrations of 25(OH)D during treatment. However, baseline vitamin D deficiency was common, especially in colorectal cancer patients, and more particularly in rectal cancer patients.

Sunscreens

Reduction of synthesis of vitamin D in the skin, and hence plasma levels, can occur as a result of the extensive or frequent use of sunscreens,^{224–226} and there is concern that excessive use or overuse may result in deficiency.^{227,228}

Discussion

Interpretation of the Data

Most of the early research in this area consisted of case studies of adverse outcomes or investigated medications commonly associated with osteoporosis, as this evidence suggested that this may be the result of imbalances in the metabolism of vitamin D. However, more recent advances in the understanding of drug metabolism mediated by CYP3A4, and awareness of the role of vitamin D in gene expression of this enzyme, and of drugs metabolized by CYP2R1, CYP24, CYP27A, and CYP27B, have led to a more structured and systematic approach. Nevertheless, this review indicates that increased research is needed to better identify the impact of medications that affect the activity of CYP enzymes involved in the metabolism and regulation of vitamin D. For example, *in vitro* studies which demonstrate that classes of medications, such as the proton pump inhibitor omeprazole and the antimicrobial agent ketoconazole, which inhibit both CYP3A4^{229,230} and CYP24,²³¹ require evaluation in a clinical setting to establish their effect, if any, on vitamin D status in humans.

As discussed above, there are limitations in a number of the cited studies. Many are either individual case studies or observational in nature, involving small numbers of patients, or analyses of data collected for reasons other than originally intended, and some were hospital based, without a relevant comparison group. Evaluation of

supplemental or additional dietary vitamin D intakes and sun exposure was limited in many, and the lack of consideration of potential confounders, such as body composition and weight, as contributory to either vitamin D status or medication concentrations and drug response, makes it difficult to assess whether the reported impact on levels of vitamin D is the result of a lack of vitamin intake or actually caused by the medication in its own right.

Although not strictly within the remit of this review, the reported effect of smoking on vitamin D status also needs to be considered as an additional possible confounder. Two studies found that smokers had concentrations of serum 25(OH)D which were reduced compared to non-smokers.^{232,233} Moreover, a large population study identified odds ratios of severe deficiency of vitamin D (25(OH)D <10 ng/mL) associated with daily smoking to be 1.47, and 1.36 for vitamin D deficiency (25(OH)D <20 ng/mL).²³⁴ In contrast, other studies in men found that smoking was not correlated with levels of 25(OH)D.^{235–237} However, it may be that these inconsistencies are attributable to differences in the way in which smoking was characterized, and/or smoking intensity, as well as due to inconsistencies in the methodologies used to measure 25(OH)D in serum. For example, one of the latter studies used electrochemiluminescence, which, it is suggested, delivers falsely high levels of 25(OH)D compared to liquid chromatography–tandem mass spectrometry.²³⁸

This highlights a very important issue, since determinations of serum vitamin D from a technological perspective are challenging because it is highly hydrophobic and has a number of metabolites. Because methodologies for assessing vitamin D status have improved significantly in recent years, it is possible that some of the data appearing in a number of the older studies reviewed above may be less accurate or difficult to interpret alongside more recent data. Clearly, in the future, larger and more robustly designed studies addressing this limitation are required to provide clarification about potential interactions between medications and vitamin D. These studies should also use assay methodologies that are standardized to current best practice and carried out in centres which participate in externally validated assessments of the technology specific to vitamin D.

COVID-19 and Vitamin D

Recently, there has been a significant number of studies from around the world examining the possible association

between vitamin D status and susceptibility to coronavirus disease 2019 (COVID-19) and its consequences. Many are retrospective cohort analyses, and some are prospective studies involving sufficiently different patient populations, with different degrees of severity of symptoms and prognoses, and indeed varying definitions of the state of vitamin D sufficiency, to make meaningful systematic reviews and/or meta-analyses a difficult process. However, at least six systematic review and meta-analysis studies and two systematic reviews from around the world have appeared within the past 6 months, with a general consensus that it does appear that a higher vitamin D status is generally associated with a lower susceptibility to COVID-19, and better morbidity and mortality outcomes.^{239–246} Nonetheless, the definitive degree of correlation, if any, remains to be established, as does the likely efficacy of vitamin D supplementation as an intervention. However, it is important to recognize that patients experiencing the worst outcomes from the COVID-19 virus tend to be overweight, and experiencing comorbidities such as diabetes and hypertension.²⁴⁷ Given that these conditions are typically treated with many of the medications discussed above, often using them concurrently, their potential impact on vitamin D status is likely to be additive. Indeed, many of these medications can also compromise other vitamins and minerals recognized to maintain and support a healthy immune system, which is clearly of benefit in the current pandemic,²⁴⁸ but this consequence does not appear to have been taken into consideration in any supplementation guidelines issued to overcome potential suboptimal levels or deficiencies in these patients.

Vitamin D Status and Supplementation

While experts and consumers strive to establish the validity of the conflicting reviews on vitamin D and COVID-19, it is important not to forget that still today, even in prosperous countries such as the UK, almost one in five adults aged 19–65 years is reported to have a low concentration of serum vitamin D (<25 nmol/L, which is considered sufficiency by the UK Scientific Advisory Committee for Nutrition [SACN] in the National Diet and Nutrition Survey [NDNS]).²⁴⁹ This places them at a higher risk of the outcomes of a deficiency of vitamin D and conditions such as osteomalacia, rickets, falls, and possibly reduced muscle function and strength in those over 50 years of age.

It is also worth remembering the seasonality of this issue, as SACN reports that on average,^{250,251} around 30–40% of individuals have vitamin D levels below 25

nmol/L in winter and 2–13% below this level in summer. Moreover, even in summer, a significant proportion of certain cohorts failed to achieve a concentration ≥ 25 nmol/L in plasma (16% adults in London, 17% adults in Scotland, 53% of females living in the south of England of South Asian origin, and 29% of pregnant women in London).

This demonstrates the real need to establish the optimal level of vitamin D supplementation in specific groups, as typified by the vulnerable elderly, who may require a more personalized dosage regimen, over and above the universally recommended dose of 10 μg in the UK, as a result of the effects of medication on the status of the vitamin, or who are not free-living individuals. For example, in this population, one UK trial assessed the effects of daily vitamin D supplementation compared to placebo over one year using serum measures of vitamin D to assess status.²⁵² This randomized placebo-controlled trial was conducted in 305 community-dwelling subjects, 65 years of age or older. The results highlighted that 4000 IU (100 μg) vitamin D₃ taken on a daily basis is necessary to achieve serum concentrations associated with the lowest risks of disease. However, despite this situation, SACN has set the lowest level for establishing sufficiency (10 ng/mL or 25 nmol/L) of any scientific society or national advisory body, and as a result recommends a daily supplementation dose of 10 μg (400 IU). Here, a paper published by UK researchers in 2021 highlighted that a search for published evidence to support this recommendation was completely unsuccessful.²⁵³ They argue that

there is considerable evidence to support the higher level for sufficiency (20 ng/mL or 50 nmol/L) recommended by the European Food Safety Authority and the American Institute of Medicine and hence greater supplementation (20 micrograms or 800 IU per day)

As already highlighted, given that in the UK serum levels of 25(OH)D typically diminish by around 50% during winter, these authors believe “that governments should urgently recommend supplementation with 20–25 micrograms (800–1,000 IU) per day”.

Although these higher recommendations, if adopted, should help to meet people’s needs on a population basis, there are arguments to suggest that without them, and even possibly with them, supplementation needs to be considered on a more personalized basis in order to achieve optimal status for certain individuals. Carlberg and Haq identified significant interindividual responses to

supplementation, which suggest that higher than currently recommended reference intakes may be needed, but which can only be identified as a result of monitoring status, which many observers consider unnecessary from a cost perspective.²⁵⁴ Without this, it is unlikely that these individuals will benefit as they might from the correct dose of vitamin D supplementation, thereby raising the question of the cost/benefit validity of vitamin status evaluations.

Polypharmacy and Vitamin D

Finally, in this context, it is highly relevant to note that the incidence of patients taking five or more prescription medications and/or over-the-counter products has risen significantly in recent years. For example, in the UK in the past two decades, the percentage of elderly people aged 65 and over taking five or more items increased four-fold, from 12% to 49%, while those not taking any medication decreased in the same period, to around one in 13 from one in five²⁵⁵. This pattern also appears to be reflected in similar populations in the USA and Europe.^{256–259} Given that many of the medications listed above are extensively used, particularly in the elderly (where a high incidence of low vitamin D status seems to be prevalent), any likely incremental negative outcomes of polypharmacy on levels of vitamin D in this age group are of notable relevance and require special attention from health professionals. This view is supported by two studies performed in the elderly and examining precisely this issue, and cited in this current review.^{76,80} The latter, entitled “Vitamin D deficiency as adverse drug reaction”, identified an overall prevalence of polypharmacy (five or more medications used concomitantly) of 65% and a level of severe polypharmacy (10 or more medications) of 22% in a population of almost 1000 community-dwelling Dutch citizens. It identified a 49% level of vitamin D deficiency (<50 nmol/L), or 77% (<75 nmol/L) depending on the cut-off value used to determine insufficiency. If patients were using a vitamin D supplement, these figures fell to 17% and 49%, respectively. However, in non-users of vitamin D supplements, after adjustment for age and gender, the other main factor identified as being negatively associated with levels of the vitamin was the use of multiple medications. This was especially highly significant in male patients who had been prescribed severe polypharmacy.⁸⁰ A similar conclusion was reached in the study by Sohl et al, who examined these effects in two different cohorts of over 2000 elderly Dutch patients.⁷⁶ Again, the study data showed that patients prescribed more than one

medication had lower concentrations of 25(OH)D in serum than non-users, leading the authors to recommend that vitamin D supplementation ought to be considered in patients prescribed long-term medication regimens.

Conclusion

This review has highlighted both significant classes of medications that have the potential to impact on vitamin D status and the need for further research into this important subject. However, until these data are available, all health-care professionals need to be cognizant of the potential for medication-induced effects on vitamin D status. Where appropriate, concentrations of 25(OH)D in serum should be monitored and, when necessary, vitamin D dietary supplements recommended, with the objective of achieving adequate levels of vitamin D while also optimizing the efficacy of treatment and limiting drug side-effects and toxicity.

Disclosure

The author reports no conflicts of interest in this work.

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