Adult Vitamin D guidelines

The Chief Medical Officers of the UK gave advice in February 2012 to GPs, practice nurses, health visitors and community pharmacists about supplementation with vitamin D to those at high risk. Principal recommendations of this communication included supplementation with 400 units of vitamin D daily to those over the age of 65 years, and to people who are not exposed to much sun. No mention of prior investigation or subsequent monitoring was made.

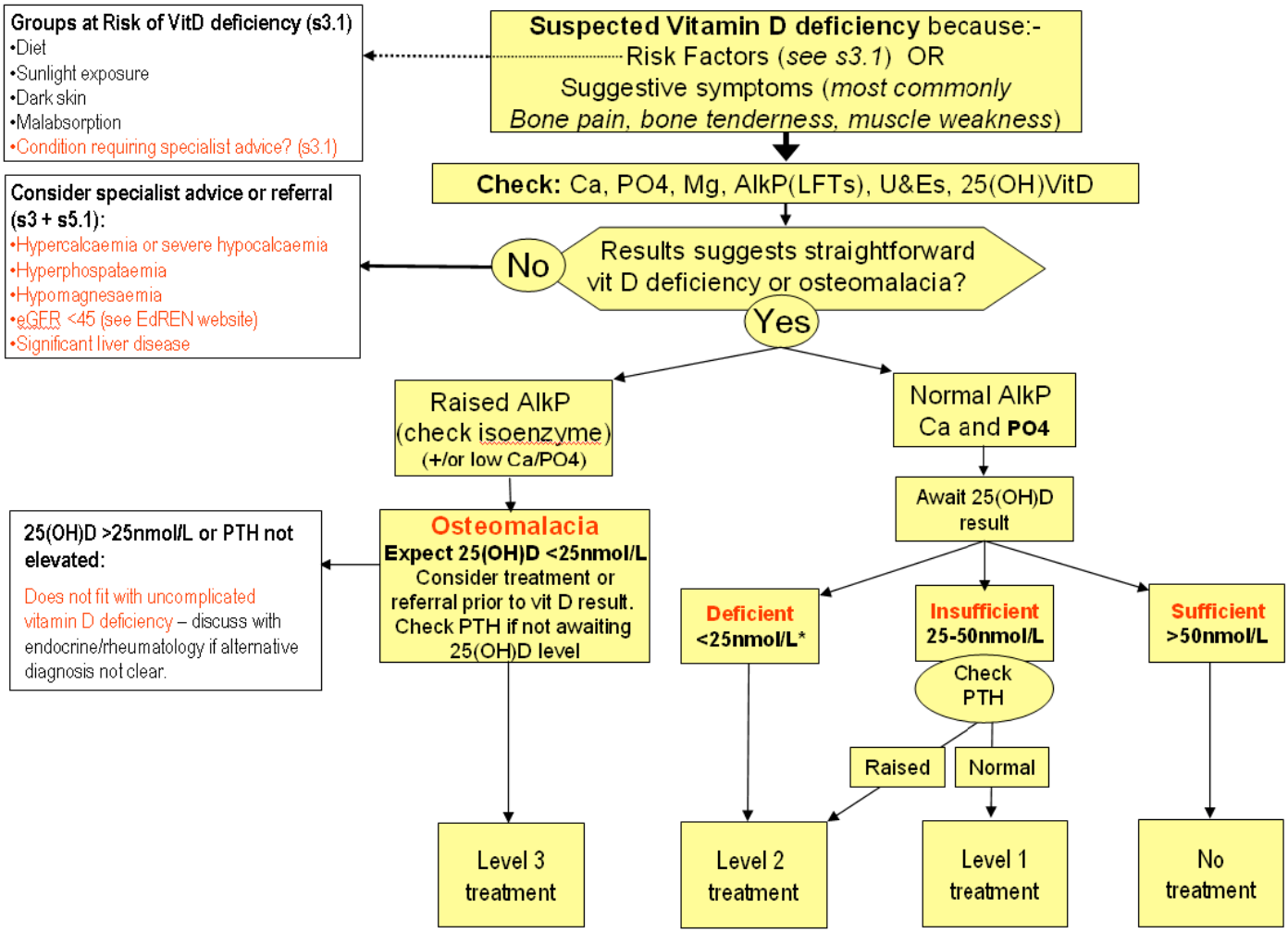
This current guideline should be used where the General Practitioner (or other medical staff determining management) feels a patient's clinical features warrant prior assessment relating to their Vitamin D status or are otherwise not satisfied that it is straightforward in a patient's case to apply the above advice (for potentially long term Vitamin D treatment) without investigation or monitoring lest it be unsafe or inadequate. Some reasons for this may include:

- The patient complains of symptoms requiring diagnosis and potentially high dose treatment with vitamin D where deficiency exists
- The patient may be at risk of complications from treatment with vitamin D due to a hypercalcaemic disorder, previous renal stones, renal impairment, granulomatous disorder etc
- The patient may be unwilling to take long term supplements without definite evidence of poor vitamin D status.

The current guideline is designed for use in symptomatic adults and/or those with abnormal biochemistry requiring investigation, diagnosis and treatment. The guideline also aims to highlight those with medical conditions which may put them at risk of vitamin D deficiency, or cause treatment with vitamin D to be complex or potentially risky. Paediatric subjects should be discussed with the paediatric team, who have developed a set of paediatric guidelines for use in secondary care.

Treatment Protocol for Vitamin D

Please see full referral guidelines in main body of text and/or discuss with endocrine registrar on-call if uncertain



*Level 2 treatment appears adequate[1]. In exceptional circumstances (eg 25(OH)D <14 nmol/L AND clearly symptomatic) level 3 treatment might be warranted to rapidly increase vit D level - would then require more active monitoring)

PTH – requires an extra EDTA sample to be sent.

Please note that second requests for the analysis of vitamin D within 1year of the first result are not currently being accepted unless special circumstances can be demonstrated. Samples are sent to Glasgow Royal Infirmary for testing.

[1] Ralston SH, Binkley N, Boonen S et al. Randomised trial of alendronate plus vitamin D3 versus standard care in osteoporotic postmenopausal women with vitamin D insufficiency. Calcif Tissue Int 2011;88:485-494

Table A -Recommended Treatment

Treatment	Indication	Dose	Follow up
Level 1	Vitamin D sufficient, but may be at risk of deficiency in future	Lifestyle advice (See section 1.1 and appendix)	Review as clinically indicated
Level 2	Biochemical insufficiency – benefit of treatment uncertain. See section 5.3 prior to commencing.	800units per day** OR 3200units twice weekly** OR 25000units monthly***	Repeat Ca, AlkP, PTH in 6 months and review clinical condition. Consider whether step down to level 1 treatment appropriate, or if long term treatment required.
Level 3	Osteomalacia – treatment of clear benefit	25,000units three times weekly for 4 weeks, THEN 25,000units per week for 8 weeks***	Repeat Ca weeks 2 and 4. Check Ca, AlkP, PTH every 12 weeks. Step down to level 2 treatment when PTH and AlkP normal.

** Fultium D3 (colecalciferol 800units capsules or tablets, 3200units capsules) is a licensed product approved by SMC and the Lothian Formulary Committee.

*** InVitaD3 25000units/ml solution single use ampules is a newly licensed product approved by SMC and the Lothian Formulary Committee.

1. Background

Recently there has been considerable interest in vitamin D, reflected in a large increase in the number of requests received by Glasgow Royal Infirmary clinical chemistry department over the past three years[2]. Vitamin D has been postulated to play a role in a diverse number of conditions including coronary heart disease, immunological disorders and malignancy. This guideline is designed to give practical advice on appropriate testing of vitamin D levels, investigation of vitamin D deficiency, and when and how to treat patients with low vitamin D.

1.1. Sources of Vitamin D

A major source of vitamin D comes from exposure of the skin to sunlight. Skin pigmentation, ageing and use of topical sun screen are factors which reduce the skin's production of vitamin D. From October to April, Scotland lies above the latitude that allows exposure to the UV-B wavelengths necessary for vitamin D synthesis[3]. For a fair-skinned person, 20 to 30 minutes of 'sub-erythematous' sunlight exposure at midday on the face and forearms two or three times weekly between April and October are sufficient to achieve healthy vitamin D levels in summer in the UK. However, for individuals with pigmented skin, and to a lesser extent the elderly, exposure time or frequency need to be increased two- to ten-fold to get the same vitamin D synthesis (depending upon skin pigmentation)[4]. The advice from the chief medical officer, Harry Burns, in the Scottish government CMO letter to health professionals August 2011 was: "In conveying a general message about sun exposure, 10-15 minutes of sun exposure each day in Scotland are thought to be safe for all skin types. However, it should be borne in mind that this is close to the exposure level which presents a risk for all skin cancers for those with fairer skins and, conversely, 10-15 minutes may not be sufficient for those with darker skins."

Dietary sources include oily fish such as trout, salmon, mackerel, herring, sardines, anchovies, pilchards or fresh tuna which should be consumed 2 to 3 times per week. Cod liver oil and egg yolks also contain vitamin D. Some breakfast cereals are supplemented, and in the UK margarine and infant formula milk have statutory supplementation. See appendix for a table of vitamin D content in selected foods.

1.2. Vitamin D metabolism and regulation

Vitamin D is made from a precursor (7-dehydrocholesterol) in the skin on exposure to ultraviolet irradiation and is also absorbed from dietary sources. Vitamin D2 (ergocalciferol) is provided by plant sources, and vitamin D3 (cholecalciferol) is synthesized in the skin and present in oil rich fish. Both these forms have equivalent biological potencies and are activated efficiently by hydroxylase enzymes in humans. In this guideline, the term vitamin D covers both cholecalciferol and ergocalciferol.

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[2] Sattar N, Welsh P, Panarelli M et al. Increasing requests for vitamin D measurement: costly, confusing and without credibility. Lancet 2012;379:95-6

[3] Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab 1988; 67:373-8.

[4] Ross W, Pearce S, Skinner J et al. Vitamin D guidelines: NHS Newcastle North Tyneside and Northumberland.

Vitamin D undergoes 25-hydroxylation in the liver to 25(OH)D, which has a half life of 2 to 3 weeks. This hydroxylation process is not tightly regulated and therefore the blood levels of 25(OH)D reflects the amount of vitamin D entering the circulation. 25(OH)D is then further hydroxylated in the kidney to the active form 1,25(OH)D, which has a half life of 6 to 8 hours. The renal hydroxylation is tightly regulated; PTH and hypophosphataemia induce the enzyme, while calcium, fibroblast growth factor 23 (FGF23) and 1,25(OH)D repress it. FGF23 is produced by bone cells, and its role in calcium and phosphate homeostasis is not yet fully understood[5].

1.3. Definition of insufficient vitamin D

There are a number of sources of variation in 25(OH)D levels between individuals; it is therefore difficult to assess the significance of vitamin D deficiency based on 25(OH)D concentrations alone. Furthermore, a number of factors such as duration of deficiency, race, age, responsiveness of vitamin D receptor, Ca intake, and Ca requirements are likely to modify the clinical consequences of vitamin D deficiency[6]. Genetic variation in proximity to the genes which influence metabolism of vitamin D and levels of its binding protein explains some of the inter-individual variability of 25(OH)D concentration[6].

A 25(OH)D level of 25nmol/L is generally recognized as the lower limit required for bone health, based on levels below this being found in patients with osteomalacia and rickets[7,8]. However, a cross-sectional study of iliac bone biopsy specimens obtained at autopsy revealed that even patients with very low levels did not consistently have evidence of osteomalacia; in fact the majority of patients with 25(OH)D levels below 25nmol/L had normal osteoid[9]. A minimum 25(OH)D level that is inevitably associated with manifest mineralization defects cannot therefore be established.

Several studies have tried to assess optimal levels for 25(OH)D, based on levels required for maximal intestinal absorption of calcium, and levels below which PTH begins to rise. Different studies have shown this value to be between 50 and 100nmol/L[10]. The paper looking at iliac bone biopsy specimens found no pathologic accumulation of osteoid in any patient with circulating 25(OH)D levels above 75nmol/L[9]. Unfortunately blood biochemistry such as PTH and alkaline phosphatase were not analysed, and information about medical history was not collected.

Provocative testing is another method which has been used to quantify optimal vitamin D levels; healthy adults with 25(OH)D levels above 50nmol/L demonstrated no change in PTH levels when challenged with high dose vitamin D[11]. There is therefore a feeling

[5] Chong WH, Molinolo AA, Chen CC et al. Tumour-induced osteomalacia. Endocrine-related cancer 2011;18:R53-R77
[6] Thacher TD, Clarke BL. Vitamin D insufficiency. Mayo Clin Proc. 2011;86(1):50-60.
[7] Holick, MF, Binkley NC, Bischoff-Ferrari, HA et al. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrin Metab 2011;96(7)
[8] Pearce SHS, Cheetham TD. Diagnosis and management of vitamin D deficiency. BMJ 2010;340:142-7.
[9] Priemel M, von Domarus C, Klatte TO et al. Bone mineralization defects and vitamin D deficiency: Histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. JBMR 2010;25(2):305-12
[10] Souberbeille J, Friedlander G, Kahan A et al. Evaluating vitamin D status. Implications for preventing and managing osteoporosis and other chronic diseases. Joint Bone Spine 2006;73:249-53
[11] Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. Lancet 1998;351:805-6

that these higher levels of vitamin D should be considered 'optimal' and used as a target for treatment.
However It remains unclear if low levels of vitamin D are causally related to adverse health outcomes[12] and at the present time, evidence that vitamin D supplementation is of benefit in people with "biochemical" deficiency is lacking.

1.3.1. Problems of widespread mildly reduced levels and seasonal variation

A study of 7437 white British adults aged 45 years looked at the prevalence of vitamin D deficiency and insufficiency[13]. They showed a clear circannual variation in 25(OH)D levels, which peaked in August to October, and troughed January to March. The percentage of subjects with levels below 25nmol/L was 15.5% in winter/spring and 3.2% summer and autumn. This rose to 21.4% and 4.5% respectively in obese individuals, and 23.5% and 8.3% for those living in Scotland. It is unknown whether seasonal low levels of vitamin D are harmful or not.

In the above study, further cut offs of <40nmol/L and <75nmol/L were also measured; 46% of the total had 25(OH)D values below 40nmol/L, and 87% below 75nmol/L during winter and spring. These percentages increased in obesity, female sex, and Scottish region of residence so that 92% of Scottish residents had values below 75nmol/L in winter and spring. These figures have huge implications in terms of patient numbers if a decision was taken to adopt higher cut off values for defining vitamin D deficiency.

1.3.2. Conclusions

While the clinical significance of cutoffs remain controversial, it has been suggested that people may be categorised into three groups based on their vitamin D levels:

a. 25(OH)D <25nmol/l is classified as vitamin D deficiency
b. 25(OH)D between 25 and 50nmol/l is classified as vitamin D "insufficiency"
c. 25(OH)D between > 50nmol is classified as vitamin D "sufficiency"

Factors increasing the significance of 25(OH)D <50nmol/l include clinical and biochemical features fitting with vitamin D deficiency (see sections 3 and 4), and reasons to feel that the vitamin D is usually lower than when measured (eg level was measured during seasonal or personal high point).

2. Actions of Vitamin D

The vitamin D receptor is expressed in most tissues and has been shown to regulate cellular differentiation and function in many cell types. A recent feature in the New England Journal of Medicine noted a number of significant associations with low levels of 25(OH)D in observational studies[14]. These included increased risk of metabolic, neoplastic, and immune disorders including type 1 diabetes mellitus and multiple

[12] Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JPA. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ 2014; 348:g2035
[13] Hypponen E and Power C. Hypovitaminosis D in British adults at age 45y:nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr 2007;85:860-8.
[14] Rosen CJ. Vitamin D Insufficiency. N Engl J Med 2011;364:248-54

sclerosis. A recent retrospective, observational study showed a J-shaped association between 25(OH)D levels and mortality[15].

The major physiologic effects of vitamin D involve regulation of intestinal calcium transport. Calcium absorption via the transcellular route and vesicular transport are dependent on 1,25(OH)D. Paracellular calcium absorption may also be enhanced by 1,25(OH)D. Under normal dietary conditions approximately 30% to 35% of the 700 to 900mg daily calcium intake is absorbed, this drops to 10% to 15% without vitamin D. 1,25(OH)D regulates cell proliferation in the parathyroid glands and decreases transcription of the PTH gene. In the kidney, 1,25(OH)D stimulates calcium reabsorption from the glomerular filtrate.

In the bone 1,25(OH)D has numerous effects: it represses synthesis of type 1 collagen, induces synthesis of osteocalcin, and increases osteoclastic bone resorption. However, in studies of 1,25(OH)D-deficient rats, the major osseous consequences of hormone deficiency can be reversed when mineral ion homeostasis is normalized. Also, parenteral calcium infusions have been shown to heal osteomalacic lesions in children with mutant vitamin D receptors. These findings would suggest that the major role of 1,25(OH)D in bone is to provide the appropriate micro-environment for bone mineralization through stimulation of calcium absorption in the intestine[16].

3. Presentation of Vitamin D Deficiency

Vitamin D deficiency in childhood, before epiphyseal closure, results in rickets with skeletal abnormality and muscle weakness. In adulthood the epiphyses are closed, and there is enough mineral in the skeleton to prevent skeletal deformity. The abnormal mineralization causes decreased bone mineral density, bone and muscle pains, and weakness; this is known as osteomalacia.

In a report of 17 patients with osteomalacia on biopsy, bone pain, bone tenderness and muscle weakness were the commonest symptoms present in 84% of the patients[17]. Bone pain was most pronounced in the lower spine, pelvis and lower extremities. The pain was characterised as dull and aching, and aggravated by activity and weight bearing. In the same series, fractures occurred in 76%, with little or no trauma and typically involving the ribs, vertebrae and long bones. Muscle weakness was proximal and may be associated with muscle wasting, hypotonia and discomfort with movement. Other symptoms were less common (<25% of patients) and included difficulty walking and waddling gait, muscle spasms, cramps, positive Chvostek's sign, tingling/numbness, inability to ambulate[17,18].

Adults may also be asymptomatic, and may be diagnosed on biochemistry findings of raised alkaline phosphatase, raised PTH, hypocalcaemia, and hypophosphataemia.

[15] Durup D, Jorgensen HL, Christensen J et al. A reverse J-shaped association of all cause mortality with serum 25-hydroxyvitamin D in general practice, the CopD study. J Clin Endocrinol Metab 2012;97(8):1-9
[16] Krononberg HM, Melmed S, Polonsky KS et al. Williams Textbook of Endocrinology 11th Edition. 2008; Chapter 27:1219 -21
[17]Basha B, Rao DS, Han ZH et al. Osteomalacia due to vitamin D depletion: a neglected consequence of intestinal malabsorption. Am J Med 2000;108:296-300
[18] Menkes CJ, Drezner MK, Mulder JE. Clinical manifestations, diagnosis, and treatment of osteomalacia. www.uptodate.com Updated 14/2/2011, viewed 1/11/2011.

Where a raised alkaline phospahatase is found, isoenzymes should be requested to confirm bone source prior to investigation for vitamin D deficiency.

3.1. People at risk

Vitamin D deficiency should be considered in those at risk, and appropriate investigation performed.

A. Those with reduced intake, absorption or synthesis of vitamin D:

- Dark skinned people
- People who cover up (eg muslim women, people with skin photosensitivity)
- Housebound, institutionalized and elderly people
- Non-fish eaters (eg vegetarian diets)
- People with fat malabsorption (including those on Orlistat), coeliac disease, small bowel disease and short bowel syndrome (due to reduced absorption of fat soluble vitamins)

B. Conditions with inadequate vitamin D action requiring specialist management:

- Hypoparathyroidism – most commonly following neck surgery
- Hypomagnesaemia which inhibits PTH release leading to hypoparathyroidism
- People with chronic renal impairment who have a reduced capacity to hydroxylate 25(OH)D into its active form. These people should be discussed with the renal team (see section 5.1)
- Tumour induced osteomalacia – tumour production of fibroblast growth factor 23 (FGF23) inhibits phosphate transport in the renal tubule, and 1-hydroxylation of vitamin D by the kidney[5].

C. Other causes:

- Obese people (probably due to reduced bioavailability)[19]
- People with nephrotic syndrome who lose 25(OH)D bound to vitamin D binding protein in the urine

Other conditions which may require assessment of vitamin D status and specialist input include people on a range of medications including anticonvulsants, rifampicin and medications to treat AIDS/ HIV because these drugs enhance the catabolism of 1,25(OH)2D[20]. These people are at risk of hypocalcaemia, and specialist advice should be considered. Hyperparathyroidism causes unregulated hydroxylation of 25(OH)D into the active form, and the resultant hypovitaminosis can worsen the PTH level[21]. These patients are hypercalcaemic by definition, and the low vitamin D and underlying hyperparathyroidism should be managed by a specialist to avoid exacerbating hypercalcaemia.

4. Investigation

Vitamin D deficiency should be considered in people complaining of bone pain, muscle pain or weakness, particularly those who are at risk (see above). It should also be considered in people who have indicative biochemistry performed for other reasons. The

[19] Wortsman J, Matsuoka LY, Chen TC et al. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000;72:690-3.
[20] Zhou C, Assem M, Tay JC et al. Steroid and xenobiotic receptor and vitamin D receptor crosstalk mediates CYP24 expression and drug-induced osteomalacia. J Clin Invest 2006;116:1703-12
[21] Grey A, Lucas J, Horne A et al. Vitamin D repletion in patients with primary hyperparathyroidism and coexistent vitamin D insufficiency J Clin. Endocrinol. Metabolism 2005; 90:2122-6

characteristic biochemical picture is of raised alkaline phosphatise (check isoenzymes to ensure bone), raised PTH, hypocalcaemia and hypophosphataemia. The key diagnostic test is decreased serum 25(OH)D, but it takes several weeks for a result to become available. The 1,25(OH)D may be normal in vitamin D deficiency, probably as a result of maximal stimulation of 1 alpha-hydroxylase due to low phosphate and raised PTH levels; this is therefore not routinely measured. In retrospective reviews of biopsy proven nutritional osteomalacia, the AlkP was elevated in 95 – 100%, 25(OH)D less than 37.5nmol/l in 100% and the PTH elevated in 100% of patients. Serum Ca and Phosphorus were reduced in far fewer patients (27 – 38%)[18].

The latest Glasgow 25(OH)D is an immunoassay which shows only 50% cross-reactivity with vitamin D2 (ergocalciferol). This means that patients on ergocalciferol could have their total 25(OH)D level underestimated (indeed, these patients should have 25(OH)D measured by tandem mass spectrometry). Accordingly, the guideline for Lothian encourages using vitamin D3 (cholecalciferol) preparations. Patients on vitamin D treatment do not generally require monitoring of vitamin D levels however, so this would only become an issue in special circumstances such as suspected poor compliance or malabsorption.

Reduced 1 alpha-hydroxylase activity due to renal insufficiency, tumour-induced osteomalacia or genetic abnormality (which usually present in childhood) will result in low 1,25(OH)D and raised levels of 25(OH)D. These forms of osteomalacia should be considered if the biochemistry is not typical. The possibility of tumour induced osteomalacia should be considered in those with typical features of vitamin D deficiency and hypophosphataemia who do not respond to vitamin D.

Hypoparathyroidism, commonly due to previous surgery but also secondary to low magnesium and other rare causes, can result in hypocalcaemia, hyperphosphataemia with low (or normal) PTH and should be referred to the endocrine team for management.

Consideration should be given to the reason for vitamin D deficiency, and celiac serology should be considered in cases where an underlying cause is not apparent.

25(OH)D should not be measured in those with conditions not linked to bone disease, such as cardiovascular disease or malignancy. There is insufficient evidence to recommend supplementation with vitamin D in this group, and testing is therefore not justified and may lead to harm[2].

5. Management and vitamin D replacement considerations

(See treatment protocol)

The general approach is as shown in the algorithm (page 1), and is centred on clinical features and biochemical investigation. Characteristic findings of vitamin D deficiency should be confirmed, whilst being alert to alternative causes and biochemical findings indicating different management or specialist referral is appropriate. If there is any doubt about how a patient should be managed, advice can be sought from the endocrine registrar on call (#6800) or from the rheumatology team (SpR phone 31807).

5.1. When should referral to secondary care be considered?

- Patients with severe pain or weakness
- Those with severe hypocalcaemia (Ca^{2+} usually <1.9mmol/l with muscle twitches, convulsions, Chvostek's sign, Trousseau's sign, carpal spasm, papilloedema, prolonged QT interval on ECG) or hypomagnesaemia, who may need iv replacement
- Any patient who does not respond to vitamin D replacement as expected
- Patients with renal failure (eGFR <45) who may need 'activated' vitamin D, or lower doses of vitamin D, should be discussed with the renal team; referral guidelines can be found here: http://www.edren.org/pages/gpinfo/when-to-refer-to-the-renal-unit.php For advice: rierenaladvice@luht.scot.nhs.uk
- Patients with nephrotic syndrome
- Patients with GI disorders who may require high doses or parenteral administration of vitamin D
- Patients with probable primary hyperparathyroidism (raised Ca and normal or high PTH) should be referred to endocrinology. This may become uncovered by vitamin D treatment causing Ca^{2+} levels to rise.
- Patients with hypoparathyroidism should be referred to endocrinology (Low PTH, low Ca, low/normal 25(OH)D, low 1,25(OH)D, high PO4, normal AlkP – particularly in patients with history of neck surgery).
- Patients with osteoporosis should be managed as per osteoporosis guidelines, consider referral to the osteoporosis clinic

5.2. General considerations

There is variable inter-individual response to treatment with oral vitamin D in terms of serum 25(OH)D levels[22,23]. It has been estimated that 1000IU daily of oral cholecalciferol will eventually raise serum 25(OH)D by 25nmol/l[23], however this was in vitamin D replete subjects. It has been suggested that in adults 10000IU daily, or 60000IU weekly, will lead to restoration of body stores in 8 to 12 weeks, although the evidence behind this was not cited[8]. These guidelines use a more conservative dosing regimen.

Vitamin D has a high therapeutic index, and most reports of toxicity involve serum levels of greater than 350nmol/L[24]. Vitamin D doses of 10000IU per day[22], and even 40000IU per day[25], have been shown to be safe in vitamin D replete populations. Despite high serum levels of vitamin D in these subjects, hypercalcaemia did not occur. This makes vitamin D a safe treatment with relatively few contra-indications; hypercalcaemic disorders being the main one.

[22] Heaney RP, Davies KM, Chen TC et al. Human serum 25-hydroxycholecalciferol response to extended dosing with cholecalciferol. Am J Clin Nutr 2003;77:204-10
[23] Aloia JF, Patel M, DiMaano R et al. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. Am J Clin Nutr 2008;87:1952-8.
[24] Catharine Ross, Christine L. Taylor, Ann L. Yaktine, and Heather B. Del Valle, Editors; Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Institute of Medicine; 2011
[25] Kimball SM, Ursell MR, O'Connor P et al. Safety of vitamin D3 with multiple sclerosis. Am J Clin Nutr. 2007;86:645-51

Normally as vitamin D levels rise, PTH levels fall and this in turn down regulates 1-alpha-hydroxylase activity. Any condition which causes the activity of 1-alpha-hydroxylase to remain inappropriately high (hyperparathyroidism, granulomatous disorders etc) require caution to avoid hypercalcaemia, and specialist referral is appropriate. Calcium should be monitored to ensure that hypercalcaemia does not occur, particularly in patients with renal dysfunction. Vitamin D levels need not be routinely rechecked.

Hydroxylated vitamin D such as alfa-calcidol (1(OH)D) or calcitriol (1,25(OH)D) can cause hypercalcaemia, and are not effective at replenishing vitamin D stores. These preparations may occasionally be used for vitamin D deficiency in secondary care to induce a rapid response, but should not be used long term. Their use is largely limited to patients with severe renal impairment leading to reduced renal hydroxylation of 25(OH)D and secondary hyperparathyroidism. These patients should be discussed with a renal physician (see section 5.1).

5.3 Treatment Recommendations

All patients should be given lifestyle and dietary advice in the first instance, as described in section 1.1.

Patients with symptoms of osteomalacia and typical biochemistry require treatment with high dose vitamin D. Treatment should be given with oral colecalciferol. For adults 25,000 to 75,000units per week should be given (see treatment protocol). Biochemistry should be monitored to ensure that it normalizes and that hypercalcaemia does not occur, and patients referred to a specialist if this is not the case.

Patients without these typical features should be assessed carefully with the aid of the treatment algorithm on page 1. The evidence supporting intervention in people with vitamin D values between 25-50nmol/L (even with raised PTH) is lacking. Assessment of the importance of the vitamin D level in the context of symptoms, biochemistry, risk factors and time of year is important when considering the most appropriate management strategy. These guidelines recommend measuring PTH in this group in order to help with risk stratification. This recommendation is based on the fact that the clinical significance of low levels of 25(OH)D in people with normal levels of PTH is uncertain and that PTH levels are inversely related to BMD, independent of vitamin D level[26,27]. PTH also correlates with markers of bone turnover[27]. A study of British Asians showed PTH to be the best underlying marker of histological osteomalacia[28]. However, other factors should also be considered including time of year, intercurrent illness, and fracture risk, in order to assess if vitamin D treatment is worthwhile. A trial of treatment may be undertaken, with a review at 6 months to consider whether there has been symptomatic benefit or biochemical improvement.

[26] Collins D, Jasani I, Fogelman I et al. Vitamin D and bone mineral density. Osteoporos Int. 1998;8:110-4

[27] Mezquita-Raya P, Munoz-Torres M, De Dios Luna J et al. Relation between vitamin D insufficiency, bone mineral density, and bone metabolism in healthy postmenopausal women. Journal of Bone and Mineral Research. 2001;16(8):1408-15

[28] Nisbet JA, Eastwood JB, Colston KW et al. Detection of osteomalacia in British Asians: a comparison of clinical score with biochemical measurements. Clin Sci 1990;78:383-9

Following a course of treatment, patients should always be reassessed in order to ensure that the treatment has had the desired effect, and to consider whether long term vitamin D replacement will be required. This should be done by reassessing their clinical condition for signs and symptoms of vitamin D deficiency. Also, any biochemical abnormality should be repeated following a course of treatment to ensure normalisation (eg raised PTH, AlkP). A repeat vitamin D level is generally not required, unless it is felt that the initial test did not reflect current vitamin D levels due to mitigating factors already discussed. In these cases, if a repeat vitamin D level is requested within 1 year, the request must be discussed with the biochemist in Glasgow or it will routinely be refused.

Long term treatment should be considered in those with ongoing, irreversible risk factors. If diet and sunlight exposure cannot be improved in this group, then low dose treatment with 800units of vitamin D daily may be required to prevent repeated episodes of osteomalacia. Evidence to support this is lacking.

5.4. Supplementation with low dose vitamin D

Recent endocrine society clinical practice guidelines[7] suggest that adults aged 19 – 70 years require at least 600IU/day of vitamin D to maximise bone health and muscle function. It is unknown whether this is enough to provide all the potential nonskeletal health benefits associated with vitamin D. Similarly adults over 70 years require at least 800IU/day of vitamin D. To raise blood level of 25(OH)D consistently above 75mmol/L may require at least 1500 – 2000IU/day. There is evidence that bone mineral density is higher in people with vitamin D levels greater than 50nmol/L. There is also meta-analysis evidence that supplementing elderly patients with vitamin D reduced non-vertebral fracture risk (>400units per day) and reduced falls risk (>700units per day and 25(OH)D levels >60nmol/L)[6]. However, the evidence is not consistent, and some recent trials show no benefit on fracture and falls with vitamin D supplementation in the elderly[14,29]

Calcium and vitamin D supplementation is recommended for certain elderly patients classed as being at risk of falls as part of the falls risk strategy (see the NHS Lothian Falls Policy). The Chief medical officers of the UK have also recommended routine supplementation with 400units of vitamin D per day in those over 65years, and those not exposed to much sun. This is a rapidly emerging field, and future trials may help to guide us on who might benefit most from vitamin D supplementation in due course.

5.5. Non musculoskeletal conditions and screening

There is observational evidence that low vitamin D levels are associated with increased mortality[15], cardiovascular mortality, type 2 diabetes, cancer, multiple sclerosis, and various other conditions. As these studies are observational however, they cannot prove causality. There is no interventional evidence to support treatment with vitamin D for these conditions[2]. There is no evidence for screening for vitamin D deficiency in the general population[6,7]

[29] Aloia, JF. The 2011 report on dietary reference intake for vitamin D: Where do we go from here? J Clin Endocrin Metab. 2011;96(10):2987-96

Appendix

Table B: Selected food sources of vitamin D[30]

Food	**vitamin D per serving (IU)**
Cod liver oil, 1 tablespoon	1,360
Salmon, cooked, 3.5 ounces	360
Mackerel, cooked, 3.5 ounces	345
Tuna fish, canned in oil, 3 ounces	200
Sardines, canned in oil, drained, 1.75 ounces	250
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	98
Margarine, fortified, 1 tablespoon	60
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75-1 cup (more heavily fortified cereals might provide more of the DV)	40
Egg, 1 whole (vitamin D is found in yolk)	20
Liver, beef, cooked, 3.5 ounces	15
Cheese, Swiss, 1 ounce	12

[30] National institute of health office of dietary supplements 'Dietary supplement factsheet Vitamin D' Downloaded Feb 2013 from http://ods.od.nih.gov/factsheets/VitaminD_pf.asp. 7/30/2009, reviewed 6/24/2011.