East Kent Hospitals University NHS Foundation Trust

VITAMIN D – GUIDANCE ON MEASUREMENT OF 25-HYDROXYVITAMIN D

Version:	1.4
Ratified by:	Clinical Biochemistry Senior Staff Group
Date ratified:	16th May 2013
Name of originator/author:	Dr Edmund Lamb
Director responsible for implementation:	Prof F Muhlschlegel
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Target audience:	Clinical staff (medical, nursing and scientific), Trust wide and primary care

Version Control

Version	Date	Author	Status	Comment
0.1	10th August 2012	Dr Edmund Lamb	draft	Circulated for comment
0.2	23rd March 2013	Dr Edmund Lamb	draft	Amended in light of KSS model guidance
1.0	2nd August 2013	Dr Edmund Lamb	Final	Amended to include multiple sclerosis
1.1	1st January 2015	Dr Edmund Lamb	Final	Amended to update guidance re: denosumab and zoledronic acid
1.2	22nd December 2015	Dr Edmund Lamb	Final	Amended to include melanoma as an indication for measurement

1.3	31st January 2018	Dr Edmund Lamb	Final	Amended to include mention of and link to East Kent Vitamin D Prescribing Recommendations for non–specialists
1.4	2nd June 2021	Dr Edmund Lamb	Final	Amended to include hypercalcaemia as an indication for measurement (endocrinology requests only). Under-recovery of D2 included. Use in advanced CKD and long-COVID discouraged. Use in cystic fibrosis described. Put into current (November 2020) Trust guideline template. Revised ROS 2018 guidance included.

Consultation Schedule

Name & Job Title of Individual / Meeting name	Date consulted
Initial consultation as described in section 6, with later revision details described in Q-Pulse as change requests	2013-2020
All clinical scientists in clinical biochemistry. Version 1.4	7th April 2021

Ratification Schedule

Name of Meeting / Committee	Date approved / authorised
Clinical Biochemistry Senior Staff Group	16th May 2013, version 1.0
Dr Sally Stock, Head of Service Clinical Biochemistry, through Q-pulse	2nd June 2021, version 1.4

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1. Introduction, Background and Purpose

Vitamin D is essential for good bone health. Vitamin D deficiency and insufficiency have also been linked to other health concerns. Awareness of vitamin D deficiency has increased significantly in recent years. The most reliable way to assess vitamin D status is by measurement of 25-hydroxyvitamin D. 'Routine' testing of vitamin D concentration in the general population is *not* recommended: a large proportion of the population are known to have insufficient levels but the significance of this in the absence of symptoms is uncertain. It is worthwhile encouraging all patients with risk factors – even those not exhibiting symptoms – to make lifestyle changes in order to achieve vitamin D adequacy but it is not necessary to measure their blood concentrations.

This guidance describes when and how to measure vitamin D, and when not to. The guidance is consistent with that initially developed by the Kent, Surrey and Sussex Health Policy Support Unit for application in primary care and has been modified to take secondary care needs into consideration. The purpose of this guidance is to ensure a consistent, rational and cost-effective approach to the investigation of vitamin D deficiency across the health service in East Kent ensuring best use of health service resources.

2. Definitions

The term vitamin D is used for a range of compounds including vitamin D2 (ergocalciferol, calciferol) and vitamin D3 (cholecalciferol), dihydrotachysterol, alfacalcidol (1-hydroxycholecalciferol) and calcitriol (1,25-dihydroxycholecalciferol).

The East Kent Hospitals laboratory measures total 25-hydroxyvitamin D (i.e. both 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3). However, the assay used (Abbott Diagnostics) significantly under-recovers vitamin D2 and the assay is unsuitable for monitoring patients receiving supplementation with vitamin D2 forms.

For the purposes of this document the following definitions of 25-hydroxyvitamin D status apply:
<25 nmol/L vitamin D deficiency
25-50 nmol/L vitamin D insufficiency (may be inadequate in some people)
>50 nmol/L vitamin D sufficiency (for the majority of the population)

3. Scope

All staff involved in requesting, measuring or interpreting blood vitamin D concentrations should adhere to this policy.

4. Guidance

When to measure vitamin D

Vitamin D deficiency should be considered and checked for *only* if:

1. A patient has one or more of the following clinical features:

- Insidious onset of widespread or localised bone pain and tenderness (especially lower back and hip pain, but may include rib, thigh or foot pain)
- In children, bone deformity, reluctance to weight bear, impaired growth
- Proximal muscle weakness i.e. in quadriceps and glutei. This may cause difficulty rising from a

chair and/or a waddling gait
- Swelling, tenderness and redness at pseudo-fracture sites
- Fractures, typically femoral neck, scapula, pubic rami, ribs or vertebrae
- Non-specific myalgia, especially with a raised creatinine kinase (CK)
- Myalgia on prescription of a statin

AND

2. The patient has one or more of the following risk factors:

- Black and ethnic minority patients with darker skin
- Elderly patients in residential care or housebound
- Intestinal malabsorption, for example cystic fibrosis, coeliac disease, inflammatory bowel disease, gastrectomy or bariatric surgery, radiation enteritis
- Routine covering of face or body, for example wearing a veil or habitual sunscreen use
- Vegan or vegetarian diet
- Liver or renal disease
- Medications including cholestyramine, rifampicin, glucocorticoids, antiretrovirals
- Pregnant and lactating women
- Obesity (BMI >30)

AND

3. Other causes for symptoms have been excluded, for example myeloma, rheumatoid arthritis, polymyalgia rheumatica and hypothyroidism.

Only test if both risk factors and symptoms are present and other causes have been excluded.

Other clinically appropriate indications for measuring vitamin D include:

- Older adults with a history of falls
- Patients with bone disease that may improve with vitamin D treatment or in whom correcting vitamin D deficiency would be appropriate
- Before commencing zoledronate, denosumab (Prolia) or teriparatide. Correction of vitamin D deficiency is required before starting osteoporosis treatment with these potent antiresorptive agents to avoid the development of hypocalcaemia. Zoledronate is administered in an annual dose and denosumab at 6-monthly intervals. Pharmacy will expect patients to have had a measured vitamin D concentration $\geq$25 nmol/L in the previous 13 months before prescribing these drugs. Otherwise testing should follow the guidance in the flowchart, except that patients who have previously had vitamin D deficiency (<25 nmol/L) may require retesting before drug administration, even if they have demonstrated an adequate response to high-dose replacement.
- Unexplained biochemical abnormality (e.g. raised alkaline phosphatase [ALP], raised parathyroid hormone [PTH], low calcium or persistently low fasting phosphate)
- Pre-surgery in patients undergoing parathyroidectomy (NICE NG132, published May 2019) and in the investigation of hypercalcaemia (endocrinology requests only)
- Patients receiving enzyme-inducing anticonvulsant treatment: vitamin D should be checked every 2-5 years as recommended by NICE
- At initial diagnosis in patients with multiple sclerosis
- At initial diagnosis in patients with melanoma (NICE NG14, published July 2015)

Situations in which, in the absence of typical risk factors and symptoms of deficiency, vitamin D measurement is generally <u>not</u> indicated include:

- Hypercalcaemia. It is extremely rare for hypercalcaemia to be due to vitamin D toxicity (unless patients are receiving activated vitamin D preparations): vitamin D should not be requested for the initial investigation of hypercalcaemia (but see indication re: endocrine requests above).
- Fibromyalgia, long-COVID. There is no good evidence confirming vitamin D deficiency as a cause of symptoms in these conditions and no evidence of a beneficial treatment effect
- Ibandronic acid treatment. Vitamin D measurement is not indicated in patients receiving ibandronic acid for breast cancer

N.B. the laboratory will not carry out vitamin D analysis when samples are received with either no or inappropriate clinical details. A report will be issued advising the requesting clinician of this and such samples will then be held for one month before being discarded.

How to assess vitamin D status

Where vitamin D measurement is considered necessary, assessment of vitamin D status should include:

- 25-hydroxyvitamin D
- serum calcium (to provide a baseline for monitoring and interpretation)
- albumin (to allow an adjusted calcium concentration to be reported)
- ALP
- phosphate
- electrolytes and creatinine (to check for concomitant kidney disease)
- liver function tests (to check for concomitant liver disease)
- full blood count (anaemia may be present if there is malabsorption)

Blood for vitamin D measurement may be taken into gel separator (gold top) or plain (red top) tubes. There are no special sampling requirements, but note that concomitant assessments of calcium and phosphate are ideally undertaken in the fasting state.

How to monitor patients receiving vitamin D treatment

- 25-hydroxyvitamin D should be re-checked >12 weeks after commencing high dose replacement treatment in order to assess response
- It is generally not necessary to monitor 25-hydroxyvitamin D in vitamin D insufficiency where low dose treatment is given. However, monitoring but may be appropriate in patients with symptomatic vitamin D deficiency or malabsorption and where poor compliance with medication is suspected
- Serum calcium should be checked one month after starting vitamin D treatment in case primary hyperparathyroidism has been unmasked
- Once vitamin D deficiency is corrected monitoring every 12 months may be advisable for patients still considered at risk

See Appendix for flowchart.

5. Limitations/exceptions/notes

In the setting of chronic kidney disease when the GFR is below 30 mL/min/1.73 m^2, renal 1-alpha hydroxylation of vitamin D may be impaired. Measuring circulating concentrations of 25-

hydroxvitamin D is therefore not a good measure of activated vitamin D deficiency in these patients, many of whom will be receiving treatment with 1-alpha hydroxylated forms.

Low dose treatment of vitamin D insufficiency typically involves doses of 1,000 to 2,000 IU/day in adults: lower doses are used in children. High dose treatment of vitamin D deficiency involves the use of much higher doses e.g. a loading regimen up to a total of approximately 300,000 IU given as weekly or daily split doses should be used in adults. For further details, refer to Vitamin D Prescribing Guidelines for Non-Specialists, East Kent Prescribing Group.

Note that a different target concentration and dosing regimen may apply in patients with cystic fibrosis. According to the Cystic Fibrosis Trust, anyone with a vitamin D concentration below 75 nmol/L should be treated with vitamin D replacement. Patients should be supplemented using colecalciferol, they should be treated for 3 months and then blood concentration rechecked. If ≥75 nmol/L then they should be maintained on a prophylaxis dose.

6. Consultation and Approval

East Kent Hospitals University NHS Foundation Trust is the key stakeholder for this policy. This document was originally prepared in consultation with Dr Michael Jenkinson, Lead Clinician Drug & Therapeutics, EKHUFT, Dr Shelagh O'Riordan Lead Clinician for Falls and Orthogeriatrics, EKHUFT, Dr Neil Munro Lead Clinician for Neurology, EKHUFT, Dr Charles Williams Lead Clinician for Endocrinology, EKHUFT Trust and Brigid Baxter, Prescribing Advisor, Medicines Information, NHS Kent and Medway.

The policy has been modified to be consistent with model guidance on the prevention, investigation and treatment of vitamin D deficiency and insufficiency prepared by the Kent, Surrey and Sussex Health Policy Support Unit and circulated to all PCTs and CCGs in our locality in February 2013. The policy is broadly in keeping with 2013 recommendations from the National Osteoporosis Society.

The guidance on vitamin D measurement in patients receiving potent antiresorptive agents was revised in consultation with Debbie Janaway (matron, falls and osteoporosis) and Michael Skerratt (pharmacist) in September 2014. It was agreed at the EKHUFT Falls and Osteoporosis Business Meeting on 17th October 2014. The guidance relating to melanoma was discussed with Dr Kurt Ayerst, consultant dermatologist in Summer 2015. Copies of correspondence may be found on the pathology shared drive.

In 2017 the East Kent Prescribing Group produced 'Vitamin D Prescribing Guidelines for Non-Specialists' which is in accord with this guidance. Correspondence with Trish César, Prescribing Support Systems Manager for East Kent, Canterbury and Coastal CCG may be found on the shared drive.

Details of subsequent consultations and discussions are recorded on Q-Pulse as change requests.

7. Review and Revision Arrangements

Two years from implementation date, by author.

8. Training

All clinical scientists involved in the review of vitamin D analyses should read this document and

acknowledge on Q-Pulse that they have read it.

9. Document Control including Archiving Arrangements

Archive of this document will be through Q-Pulse under the governance of the pathology quality management system. The current version of this guidance will be hosted on the EKHUFT Policy Centre and in app-friendly form on the pathology app.

10. Monitoring

Within the Trust, compliance with this policy rests with the requesting Care Groups/Departments. Compliance will be ensured by pre-analytical request vetting within the laboratory and assessed by retrospective audit.

11. References and Associated Documents

East Kent Prescribing Group. Vitamin D prescribing guidelines for non-specialists, available at: http://www.canterburycoastalccg.nhs.uk/about-us/prescribing-advice/?categoryesctl7576148=9822
Endocrine Society. Evaluation, Treatment, and Prevention of Vitamin D Deficiency: An Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology & Metabolism,* July 2011, 96(7): 1911–1930

Kings College Hospital. Child Health Drugs used in Cystic Fibrosis handbook, version 2, 2017.

Model guidance on the prevention, investigation and treatment of vitamin D deficiency and insufficiency. Kent, Surrey and Sussex Health Policy Support Unit, final version dated 15th February 2013, Available from: www.ksshealthpolicysupportunit.nhs.uk

National Institute for Health and Care Excellence (NICE). The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. Clinical guideline CG137, January 2012

National Institute for Health and Care Excellence (NICE). Melanoma: assessment and management. NG14 published July 2015

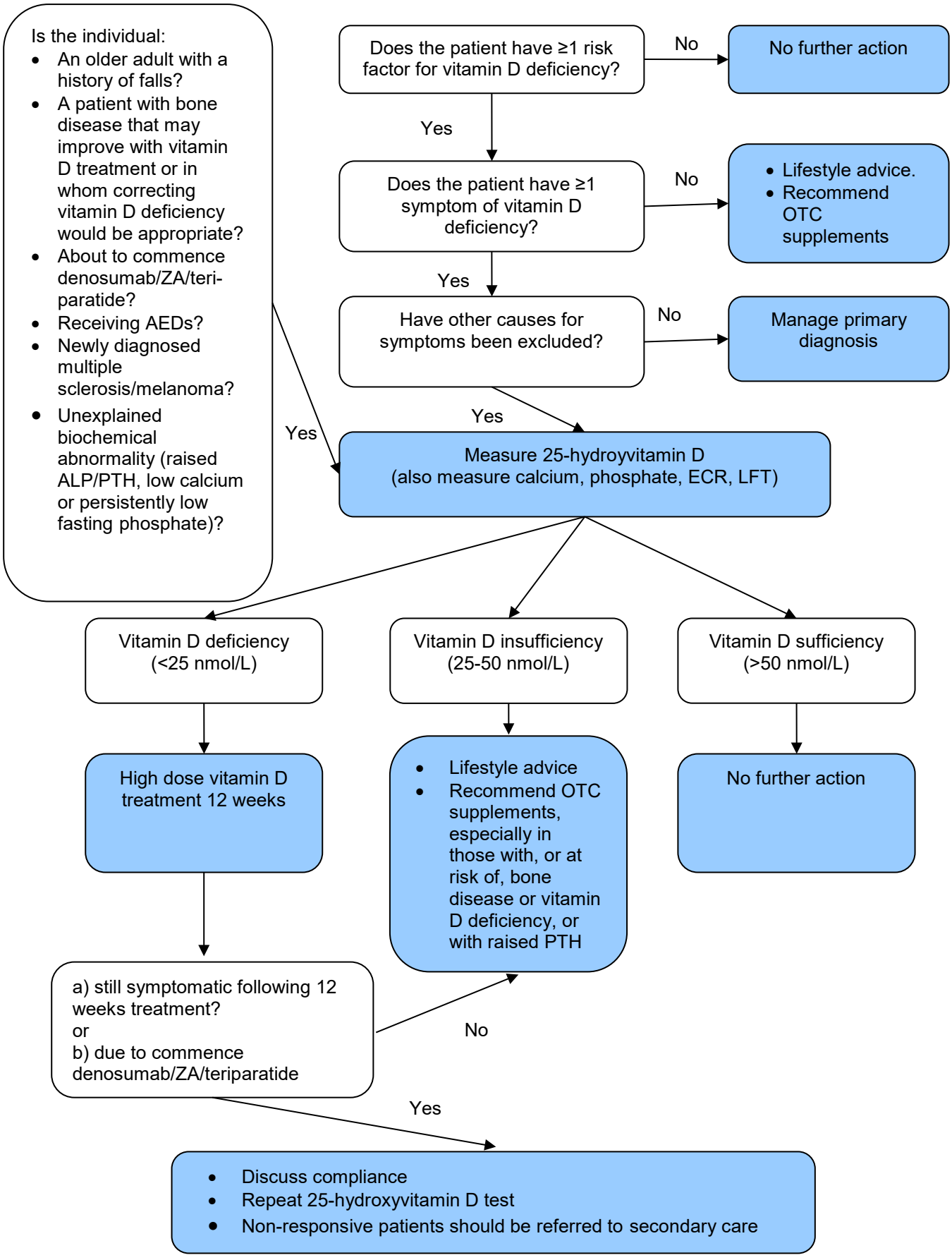
National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: managing the long-term effects of COVID-19. NG188 published December 2020. www.nice.org.uk/guidance/ng188/chapter/3-Investigations-and-referral.

National Institute for Health and Care Excellence (NICE). Hyperparathyroidism (primary): diagnosis, assessment and initial management. NG132 published May 2019

Royal Osteoporosis Society. Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management. December 2018, available at: https://theros.org.uk/clinical-publications-and-resources/

Sheffield Area Prescribing Group. Prescribing guidance for ibandronic acid 50 mg tablets in post menopausal women with breast cancer. July 2016

12. Appendix: Flow chart: Identification and monitoring of vitamin D deficiency and replacement treatment in adults (see next page)


Is the individual:
An older adult with a history of falls?
A patient with bone disease that may improve with vitamin D treatment or in whom correcting vitamin D deficiency would be appropriate?
About to commence denosumab/ZA/teri-paratide?
Receiving AEDs?
Newly diagnosed multiple sclerosis/melanoma?
Unexplained biochemical abnormality (raised ALP/PTH, low calcium or persistently low fasting phosphate)?
Yes
Does the patient have ≥1 risk factor for vitamin D deficiency?
No
No further action
Yes
Does the patient have ≥1 symptom of vitamin D deficiency?
No
Lifestyle advice.
Recommend OTC supplements
Yes
Have other causes for symptoms been excluded?
No
Manage primary diagnosis
Yes
Measure 25-hydroyvitamin D
(also measure calcium, phosphate, ECR, LFT)
Vitamin D deficiency (<25 nmol/L)
Vitamin D insufficiency (25-50 nmol/L)
Vitamin D sufficiency (>50 nmol/L)
High dose vitamin D treatment 12 weeks
Lifestyle advice
Recommend OTC supplements, especially in those with, or at risk of, bone disease or vitamin D deficiency, or with raised PTH
No further action
a) still symptomatic following 12 weeks treatment?
or
b) due to commence denosumab/ZA/teriparatide
No
Yes
Discuss compliance
Repeat 25-hydroxyvitamin D test
Non-responsive patients should be referred to secondary care