Vitamin D and bone health: adults

At last... some national guidance on whom we should be testing and treating for vitamin D deficiency. For those of us working in areas of high minority ethnic populations, vitamin D deficiency is a big issue.

What is the GPN's role?

After years of confusion and controversy, the situation is becoming clearer. There are four tasks with vitamin D:

- To encourage high risk groups to take adequate vitamin D supplements.
- To test and treat symptomatic high risk individuals.
- To assess vitamin D status in those with bone disease likely to benefit from treatment.
- To reassure and give lifestyle advice to the worried well!

The new guidance covers all of these groups. Before looking specifically at the guidance on who should be tested and treated, first a quick reminder about vitamin D physiology and why individuals become deficient; taken from a BMJ review (BMJ 2010;340:b5664).

Vitamin D physiology

Here comes the science bit!

Vitamin D comprises a group of fat-soluble pro-hormones. It is important in maintaining calcium and phosphate homeostasis and bone and muscle integrity. Humans acquire vitamin D from two sources:

- 90% of our requirement is synthesised in the skin – this is vitamin D3 (cholecalciferol):

  7-dehydrocholesterol → Vitamin D3

  UVB light

- 10% comes from ingestion of vitamin D2 (ergocalciferol) in foods.
- Together, these are pro-hormones and need to be activated by two hydroxylation steps in the liver and kidneys respectively:

  Vitamin D2 from diet → Liver → 25(OH) vitamin D → Kidney → 1,25(OH)2 Vitamin D (Calcitriol) ACTIVE

- Once activated, calcitriol acts on intranuclear receptors which are present on most body cells.

Why do people become vitamin D deficient?

In short, because we don’t get enough sunlight exposure and would need to eat large quantities of relatively expensive and relatively unpopular foods to make up for this!

- UVB sunlight should provide 90% of human vitamin D requirements, but for 6m of the year the UK lies too far north of the equator for adequate UVB to synthesise vitamin D.
- SPF 15+ blocks 99% of vitamin D synthesis.
- A fair skinned young person needs 20–30min of sunlight exposure at midday to face and forearms, 3x per week for adequate vitamin D synthesis (2000IU per exposure).
- Elderly people and those with pigmented skin need substantially more.

Which foods contain vitamin D?

- Recommended daily intake is 400IU (2800IU per week).

<table>
<thead>
<tr>
<th>Food source</th>
<th>Vitamin D content</th>
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<tbody>
<tr>
<td>Oily fish (mackerel/sardine/trout/salmon/fresh tuna/pilchards/herring) etc.</td>
<td>160–600IU per portion (raw &gt; cooked)</td>
</tr>
</tbody>
</table>
Small amounts can also be found in wild mushrooms, full fat margarine, fortified breakfast cereals and infant formula. So, we have identified why there is a problem but what should we do?

What are the symptoms of vitamin D deficiency?

Unfortunately, particularly in adults, the symptoms can be rather vague:

<table>
<thead>
<tr>
<th>Symptoms in children (rickets)</th>
<th>Symptoms in adults (osteomalacia)</th>
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</thead>
<tbody>
<tr>
<td>Tetany</td>
<td>Bone pain or tenderness or myalgia</td>
</tr>
<tr>
<td>Irritability</td>
<td>Proximal muscle weakness</td>
</tr>
<tr>
<td>Leg bowing or knock knees</td>
<td>Tenderness over bones</td>
</tr>
<tr>
<td>Impaired growth</td>
<td>Insufficiency fractures</td>
</tr>
<tr>
<td>Skeletal deformity</td>
<td>AND no other plausible explanation</td>
</tr>
<tr>
<td>Muscle pain/weakness</td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td></td>
</tr>
<tr>
<td>Proximal myopathy</td>
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Vitamin D and Bone Health: a practical guideline - National Osteoporosis Society 2013

This guideline covers the assessment and treatment of vitamin D deficiency in adults. It does not include pregnant women or children.

Who needs a vitamin D level testing?

The guidance recommends considering vitamin D testing in the following groups:

- Patients with bone disease that may be improved with vitamin D treatment, e.g. osteomalacia or osteoporosis.
- Patients with bone disease who are starting treatment that requires correction of vitamin D levels (e.g. zolendronate or denosumab but not oral bisphosphonates).
- Patients with musculoskeletal symptoms that may be attributable to vitamin D deficiency.
- It is not ALWAYS necessary to check levels in individuals starting treatment for osteoporosis with oral bisphosphonates who are going to be prescribed vitamin D as part of their treatment anyway. BUT do consider if vitamin D deficiency could be the cause of their fractures.

DO NOT test:

- Asymptomatic high risk individuals. They should be offered supplements as per DH guidance as discussed below.
- Asymptomatic population risk individuals requesting tests should be offered lifestyle advice about sun exposure, diet and over the counter supplements.

The following groups may be at higher risk of vitamin D deficiency:

- People with naturally dark skin: melanin impedes UV penetration, so dark-skinned people may require longer sun exposure to produce adequate vitamin D.
- People with little or no sun exposure including:
  - adults in residential care, or who are hospitalised or housebound, where it can be difficult to get enough sun exposure
  - people who wear concealing clothing for religious or cultural purposes, which may impair exposure of adequate skin
  - people who deliberately avoid sun exposure for cosmetic or health reasons
  - people at high risk of skin cancers and who avoid exposure to the sun

<table>
<thead>
<tr>
<th>Cod liver oil</th>
<th>1360IU per 15ml</th>
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<tbody>
<tr>
<td>Egg yolk</td>
<td>20IU per yolk</td>
</tr>
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</table>
people in night-shift occupations with limited sun exposure throughout the day.

The test of choice is a 25OH vitamin D level. This is one of the pricier blood tests, costing around £25.00 per test, even if included with other tests. It should therefore only be used if there is a sound clinical reason to do so.

The guideline argues that whilst a raised alkaline phosphatase (ALP) is a surrogate marker for significant vitamin D deficiency, it tends to occur late and therefore is not a substitute.

How do we interpret and act on results?

This guideline proposes the following cut-off values for action:

- People with some chronic diseases and conditions (obesity, end-stage liver disease, renal disease and fat malabsorption syndromes such as cystic fibrosis, coeliac disease, inflammatory bowel disease), or
- People taking medications that affect vitamin D metabolism.

What are the high strength replacement (loading) options?

- Oral vitamin D3 is the replacement and maintenance treatment of choice.
- If urgent replacement is required, e.g. in very symptomatic patients or those starting strong anti-resorptive medications such as zolendronate or denosumab: give 300 000IU total dose over 6–12w. Regimen can vary depending on local availabilities and most cost-effective preparation, e.g.:
  - 50 000IU capsule once weekly for 6w
  - 20 000IU capsule two per week for 7w
  - 800IU capsules five per day for 10w.

 **Do not use combined vit D/calcium tablets for the above regimens as this will overdose on calcium.**
- If there is no need for urgent replacement, a maintenance regimen of 800–2000IU per day can be started and continued long term.
Annual high dose IM vitamin D injections are not recommended due to variable bioavailability and concerns about toxicity.

Whilst not mentioned in the guideline, the best option now is to prescribe generic colecalciferol at the dose you require and let the pharmacist source the most cost-effective preparation. However, local policy may vary.

What are the maintenance options?
- Maintenance treatment should start 1m after loading treatment.
- Doses equivalent to 800–2000IU per day are recommended. You can buy 1000IU tablets over the counter for <3p/day.
- This can be given as a daily or monthly dose based on patient preference.
- For patients with osteoporosis if calcium supplementation is also required, a combined preparation can be used for maintenance treatment.

What monitoring is required?
- Check corrected calcium levels 1m after high dose replacement to check for unmasked primary hyperparathyroidism.
- If calcium level is raised stop any further vitamin D supplementation until this has been investigated (see Online handbook for more details on evaluating hypercalcemia).
- Routine monitoring of 25OH vitamin D levels is not required or recommended.

What about high risk asymptomatic groups?
- Follow the Department of Health guidance and promote vitamin D supplements in the following groups:

<table>
<thead>
<tr>
<th>Population groups</th>
<th>Recommended vitamin D supplementation in µg/day (IU)</th>
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<tbody>
<tr>
<td>5y – 65y (normal sun exposure)</td>
<td>None</td>
</tr>
<tr>
<td>&gt;65y</td>
<td>10 (400)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>10 (400)</td>
</tr>
<tr>
<td>Lactation</td>
<td>10 (400)</td>
</tr>
<tr>
<td>Adults with poor sun exposure</td>
<td>10 (400)</td>
</tr>
</tbody>
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FAQs not covered by this guideline

Here are the things we are frequently asked, which are not yet covered by the national guidelines.

Which preparations are available to prevent deficiency?

For pregnant/breast-feeding women
- Should not take a standard multivitamin because they contain vitamin A (harmful to fetus). Healthy start if eligible
Pregnacare or similar pregnancy multivitamins from chemist (not FP10) – check 400IU. OTC colecalciferol 400IU (£2 to £3.30 for a 3m supply).

- Generic colecalciferol on FP10 (currently Pro-D3 400IU caps are best buy for NHS).

**For vulnerable adults and the elderly**

- OTC vitamin D (as above – 400IU).
- Prescribed generic colecalciferol (currently Pro-D3 400IU caps are best buy for NHS).

*The majority of patients should be encouraged to take responsibility for vitamin D as part of their nutrition, but for some, where concordance or socio-economic factors are an issue, a prescription is preferable – follow your guidelines for now, if you have them.*

**Which adults need referral?**

When you decide to refer will depend on your own expertise, local guidelines and availability of treatment in your local area. These guidelines recommend referral of adults with (NHS North Central London 2012):

- Focal bony pain.
- Skeletal deformity.
- Atypical clinical presentation.
- Unexplained weight loss.
- Renal stones.
- Secondary causes e.g. renal/liver disease, sarcoid, parathyroid disorders, TB, lymphoma or metastatic cancer.

They suggest discussing the following cases before starting treatment:

- Pregnant and breast feeding women.
- Failure to respond to course of treatment.
- History of renal stones.
- Atypical biochemistry.

**Vitamin D binding protein**

We may see a change in the coming years in how vitamin D levels are tested....

It has been a long unexplained conundrum in the USA why low vitamin D levels were much more common in black African Americans and yet at the same time they tended to have higher bone mineral densities than their white counterparts with similar vitamin D levels. This study is the first of its type to look at levels of vitamin D binding protein and bioavailability of vitamin D (NEJM 2013;369:1991).

Within the context of a large cohort study, they compared vitamin D, parathyroid hormone, vitamin D binding protein and bone density between black and white community dwelling adults aged 30–64y at enrolment.

- Black Americans had low levels of vitamin D and its binding protein compared with white Americans. This is felt to be due to a genetic polymorphism.
- This meant that bioavailability of vitamin D was similar between the two groups.
- 77–96% of black participants would have been classed as vitamin D deficient based on traditional lab cut-offs despite having higher bone density and similar calcium and PTH levels to their white counterparts.

The authors conclude that in the future, laboratory cut-offs to define vitamin D deficiency may need to be racially stratified and take account of levels of vitamin D binding protein. It is not known how these results impact on black and Asian patients from other ethnic backgrounds.

**Vitamin D, mortality and chronic diseases**

There has been debate about whether vitamin D deficiency may be implicated in the development of chronic diseases and may increase the risk of mortality.

There have been three meta-analyses published in the BMJ in the past 12m which have looked at available data from three different angles (BMJ 2014;348:g2035, BMJ 2014;348:g1903, BMJ 2014;348:g3656). I am not going to dwell on each in turn because I don't think they change our practice yet! But, ....

*The bottom line!* (BMJ Editorial 2014;348:g2280)

- There are a lot of observational data which demonstrate that low vitamin D levels are associated with chronic diseases, including heart disease, cancer, bronchiectasis and mortality.
- What we do not know is whether this is cause or effect, e.g. if I am unwell, live in poverty and am unfit, I am less likely to get sunlight exposure – vitamin D level could just be a surrogate marker for poor health.
- We do not know that supplementing vitamin D in patients without musculoskeletal symptoms will reduce risk of chronic diseases or death.
We should stop re-analysing the same data and wait for the three large RCTs looking at vitamin D and prevention of cardiovascular disease, cancer and type 2 diabetes currently in progress which should report in the next 5–6y.

We should not measure vitamin D levels in asymptomatic individuals – we can give lifestyle advice and if they choose to take an OTC supplement, for now, that is fine!

Of interest to GPNs, the MRC have been working on a proof-of-concept study linking asthma and vitamin D deficiency, based on the theory that vitamin D may down-regulate allergen sensitivity and enhance steroid responsiveness; this may be helpful for patients with severe asthma for whom conventional medicines don’t work.

In a pilot study involving just 23 people with severe asthma, all identified as being steroid resistant, one group received a placebo tablet for 4w, the other group were given vitamin D. Two weeks into the trial both groups were also given a 2w course of oral steroids in order to test improvement in response to the vitamin. Improvements were measured primarily using lung function tests to see how well the lungs were working.

The study showed, albeit in a small group, that treatment with a short course of vitamin D may modestly improve responsiveness to asthma medicines, even in those participants classified as clinically steroid resistant.

Time will tell…!

Vitamin D and obstetric outcomes

In the UK, the government recommend that all pregnant and breast-feeding women should take vitamin D supplements at 400IU per day. It is well evidenced that adequate maternal vitamin D levels reduce the risk of osteomalacia in the mother and rickets in the infant. However, it has also been proposed that low vitamin D levels may have other adverse obstetric outcomes.

This imperfect meta-analysis combined available observational studies looking at this issue and identified an association between low vitamin D levels and small for gestational age, gestational diabetes, bacterial vaginosis, low birth weight and pre-eclampsia (BMJ 2013;346:f1169). Clearly this is an association rather than causative link and could be a surrogate marker for other factors – adjustment for confounding was poor in the included studies. They were not able to establish the optimal dose for supplementation, though they acknowledge that other countries recommend significantly higher doses than the UK (600–2000IU per day). Nor were they able to demonstrate a dose–response relationship between vitamin D levels and adverse outcomes.

A large UK-based prospective cohort study looked at the relationship between vitamin D status in pregnancy and bone mineral density in children in late childhood (mean age 9.9y) (Lancet 2013;381:2176). They found no association at all between maternal levels of vitamin D in pregnancy and their offspring’s bone mineral density at this time. Previous studies have demonstrated a relationship between maternal levels and bone mineral density in infancy. One much smaller study showed an impact on bone density in late childhood and has been cited as one of the reasons to recommend universal antenatal supplementation (Lancet 2006;367:36).
Vitamin D deficiency

- As a primary care team, remember to recommend supplements to high risk groups to prevent deficiency.
- Test vitamin D levels only in individuals who are in high risk groups AND have symptoms or who are starting denosumab or zolendronate for osteoporosis.
- For everyone else, offer lifestyle advice (sunshine, cod liver oil) and OTC supplements.
- Patients with deficiency (<30nmol/L) need high dose replacement of 300 000IU divided over 8–12w and then maintenance treatment.
- Check calcium levels 1m after completing high dose replacement -- if high investigate.
- Refer all children with vitamin D deficiency (<30nmol/L), who are aged <1y, have bony deformity or short stature.

Professional development

- Patients are encouraged to take responsibility for vitamin D as part of their nutrition and source vitamin D supplements over the counter. What is the cheapest way for patients to do this locally to you, or by buying online?
- Do you work in an area with large high risk populations for vitamin D deficiency? Find out what your local PCT guidance is with respect to testing and prescribing vitamin D supplementation.

Practical tools

- Vitamin D Food Factsheet, produced by the British Dietetic Association: www.bda.uk.com/foodfacts/VitaminD.pdf

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