The most commonly requested vitamins blood levels in the UK are vitamin B₁₂, folate (usually tested together) and lately vitamin D. Deficiencies of other vitamins are less common, usually associated with severe malnutrition and are reserved for specialist centres and services. Vitamin D requesting has particularly increased in the last few years resulting in a number of recent guidelines advising when to test and when and how to supplement or treat both children and adults.

Vitamins B₁₂ and folate
B₁₂ and folate are essential vitamins affecting all cell metabolism particularly DNA and energy production. B₁₂ and folate supplements/medication are cheap and although straightforward to assay, the blood tests are relatively expensive, over-requested and may need careful interpretation, resulting in various guidelines to limit their requesting to when useful without being too prescriptive.¹–⁶

Sources, causes and groups at risk
Vitamin B₁₂ is found in animal food products. Its absorption depends on availability of gastric pepsin, hydrochloric acid and intrinsic factor, and intact mucosa in the terminal ileum.¹⁻⁴⁻⁶ Deficiency (see Table 1) can arise through reduced dietary intake or malabsorption, with pernicious anaemia (PA) being the term classically used for autoimmune B₁₂ deficiency due to lack of intrinsic factor. The recommended intake is small (1–2µg per day) and because of extensive body stores (2000–5000µg), deficiency may take a long time to be manifest.⁴

Folic acid is present in small amounts in most foods with good sources from green leafy vegetables, legumes, liver, egg yolk and folate-fortified breakfast cereals. It is absorbed from the upper small intestinal tract.⁴ Body stores are limited to only several months thus deficiency can quickly occur with insufficient intake, which should be about 200µg per day.⁴ However, pregnant women, where folate deficiency is associated with neural tube defects, need 400µg per day and if there
is a family history of neural tube defects 5mg per day is recommended.\textsuperscript{5}

Unlike B\textsubscript{12} deficiency, where the main causes are PA or vegan diets, folic acid deficiency is found in a range of conditions including insufficient intake, malabsorption, increased utilisation and increased urinary loss.\textsuperscript{4}

**Prevalence, symptoms and signs**

PA has a frequency of 1 in 10 000 and tends to be more common in patients with a family or personal history of autoimmune disorders. It is also more common in women and in persons with blue eyes and premature grey hair.\textsuperscript{1,6,12} The prevalence of vitamin B\textsubscript{12} deficiency (except in strict vegans) is low in younger people, 5 per cent in those aged 65–74 and more than 10 per cent in those aged 75 years and older, with similar findings for folate deficiency; 10 per cent of those with low B\textsubscript{12} also have low folate levels.\textsuperscript{8}

Most patients diagnosed with B\textsubscript{12} and/or folate deficiency present with nonspecific symptoms of tiredness, depression, memory problems, muscle weakness, glossitis or are found incidentally to have red blood cell (RBC) macrocytosis/raised mean cell volume (MCV) with or without a mild anaemia. Severe psychiatric problems, frank anaemia or peripheral neuropathy (PN) associated with PA are now relatively rare due to earlier diagnosis. Patients with folate deficiency can also present with PN or depression but it tends to be milder.

**Diagnosis and recommended tests**

In Table 2 are included the first- and second-line investigations, associated tests and tests for differential diagnosis. Although macrocytosis is fundamental to B\textsubscript{12} and folate deficiency, it is also associated with other conditions (see Table 3) and it can be absent if there is concomitant iron deficiency (dimorphic RBC film). MCV is often >110fl in B\textsubscript{12} deficiency, while with other causes of macrocytosis it tends to be <110fl. Falsely low but not deficient B\textsubscript{12} levels may also occur (eg in folate deficiency, vitamin C excess or pregnancy) as can misleading 'normal' B\textsubscript{12} levels with impaired utilisation. At borderline low B\textsubscript{12} levels or if deficiency/impaired utilisation is suspected both plasma/serum methyalmalonic acid and homocysteine will be raised, while in suspected folate deficiency only plasma/serum homocysteine will be raised.\textsuperscript{1}

Intrinsic factor autoantibodies though highly specific for PA (>95 per cent) are less sensitive (60–70 per cent), while gastric parietal cell antibodies have very low specificity.\textsuperscript{1,2} The Shilling test...
is now rarely used but was useful in differentiating between autoimmune disease, malabsorption and bacterial overgrowth causes.

Associated diseases
Patients with PA are at increased risk of other autoimmune disorders (including primary hypothyroidism, Hashimoto’s thyroiditis, vitiligo, Addison’s disease and diabetes) and gastric cancer thus regular reviews are needed. Coeliac disease is frequently diagnosed following discovery of folic acid deficiency

Management
Recommendations for B<sub>12</sub> and folate treatment/supplementation in patients with different presentations are shown in Tables 4 and 5.1,2,6 Hydroxocobalamin rather than cyanocobalamin (Ozymet) is the intramuscular B<sub>12</sub> treatment of choice as it is retained in the body longer and may be safer. Before starting B<sub>12</sub> treatment, folate and iron status should be checked. If B<sub>12</sub> and folate deficiency co-exist, both should be treated; B<sub>12</sub> status should be checked before commencing folate supplementation because associated B<sub>12</sub> deficiency/insufficiency may lead to fulminant neurological problems if not also corrected (thus laboratories usually measure both).4 Potential underlying causes should be looked for and treated. In patients with possible dietary B<sub>12</sub> deficiency it is worth trying oral supplements for two to three months and then reviewing. Once the RBC indices, B<sub>12</sub> and folate levels have normalised, on-going blood monitoring, particularly with intramuscular B<sub>12</sub> replacement, is not necessary.2,6 Prophylactic B<sub>12</sub> and/or folate should also be given where deficiency is expected, eg B<sub>12</sub> following ileal resection and folate with methotrexate therapy or pregnancy.6

Who to refer
Patients with neurological involvement, severe anaemia, heart failure due to anaemia, unexplained B<sub>12</sub> and/or folate deficiency, continuing symptoms despite adequate replacement or with associated iron deficiency anaemia or gastrointestinal complaints should be referred to relevant specialists, with those with neurological involvement needing urgent haematology referral. Patients with folic acid deficiency with positive serum coeliac antibodies should be referred for duodenal biopsy for confirmation and further advice prior to starting a gluten free diet.2,6 Vegans may need dietitian advice.6

Vitamin D
Vitamin D is essential for bone growth and health, with recent studies suggesting that it may also be associated with long-term conditions such as osteoporosis, diabetes mellitus, cancer, multiple sclerosis, immunosuppression and cardiovascular disease. Vitamin D deficiency is, however, widespread and there is still much debate as to who and when to test and how to treat. In my own NHS Trust

<table>
<thead>
<tr>
<th>Vitamin B&lt;sub&gt;12&lt;/sub&gt;</th>
<th>Folate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
<td></td>
</tr>
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<tr>
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</tr>
<tr>
<td><strong>Second line</strong></td>
<td></td>
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<tr>
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<tr>
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<td>serum coeliac screen</td>
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<tr>
<td><strong>Additional tests</strong></td>
<td></td>
</tr>
<tr>
<td>liver function tests</td>
<td>as for B&lt;sub&gt;12&lt;/sub&gt; deficiency but also upper GI biopsy</td>
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<tr>
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<td></td>
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Table 2. First and second-line investigations for B<sub>12</sub> and folate deficiency

is now rarely used but was useful in differentiating between autoimmune disease, malabsorption and bacterial overgrowth causes.

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Maidstone and Tunbridge Wells, requests for testing have risen from less than 100 a year 10 years ago to now several hundred a month. The cost to the primary care for treatment of vitamin D deficiency has risen from £28 million in 2004 to £76 million in 2011.7

Synthesis, sources and daily requirements of vitamin D
Around 10–20 per cent of the body’s vitamin D is obtained from the diet, the rest produced internally in the skin as D$_3$ (cholecalciferol) through the action of UV light on 7-dehydrocholesterol derived from cholesterol. D$_2$ (ergocalciferol) is derived from plants but the contribution of that dietary source is limited except from mushrooms. However, ergocalciferol is an important source of vitamin D in vegans. In the liver vitamin D is hydroxylated to calcidiol, 25(OH)D, and in the kidney to the active metabolite calcitriol, 1,25(OH)$_2$D$_3$, although some hydroxylation also occurs in tissues such as the granulomas (thus increased ‘sensitivity’ to vitamin D in sarcoidosis and tuberculosis).11

Due to the limited availability of UV light, dietary vitamin D is important.7 It is plentiful in oily fish, egg yolk and mushrooms, but amounts in other foods are negligible (see Table 6).4,8,11 The recommended minimum daily vitamin D intake is not at risk populations is 400IU in under-one year olds, 600IU in 1–70 year olds and 800IU in those aged over 70, and double or triple these amounts in those at risk.9,10

What is measured when requesting serum vitamin D levels
When requesting vitamin D, laboratories measure either 25(OH)D$_3$ alone or with 25(OH)D$_2$ (D$_2$ contributing 80 per cent of the total) rather than 1,25(OH)$_2$D$_3$ because the half-life is longer (21–30 days compared to 4–15 hours), the levels less dependent on calcium and parathyroid hormone (PTH) level fluctuations, and is more representative of the overall vitamin D status. Replacements or supplements are usually 25(OH)D$_3$ (or D$_3$ in vegans). However, when monitoring patients treated with calcitriol, 1,25(OH)$_2$D$_3$ should be requested specifically.

Table 4. Management of B$_12$ deficiency; * only available on an NHS prescription for vegans or those with a proven vitamin B$_12$ deficiency of dietary origin, and the prescription must be Selected List Scheme endorsed

| Patients with probable malabsorption but non-neurological involvement | hydroxocobalamin 1mg im on alternate days for 2 weeks, followed up by 1mg im every 2–3 months for life |
| Patients with neurological involvement | hydroxocobalamin 1mg im every 2 days until no further improvement in symptoms, then every 2 months for life |
| Patients with suspected dietary deficiency | dietary advice and hydroxocobalamin 1mg im every 2 days for 2 weeks, then maintenance with cyanocobalamin* 50–150µg daily or hydroxocobalamin 1mg im twice yearly (particularly the elderly and vegans) |

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Deficiency and those where D₃ deficiency may affect treatment
D₃ deficiency, patients with disorders associated with vitamin D
gait, undue sweating, nonspecific itching, deteriorating memory
and concentration, depression and frequent colds; in children
at high risk, in those with symptoms potentially due to vitamin
simple at-risk populations such as pregnant/breastfeeding

Symptoms
Vitamin D deficiency is often asymptomatic or associated with
vague nonspecific symptoms. Common presentations include
nonspecific tiredness/lethargy, muscle and bone aches, waddling
gait, undue sweating, nonspecific itching, deteriorating memory
and concentration, depression and frequent colds; in children
also irritability, delayed growth, bone deformities and fits.

Laboratory tests
Hypocalcaemia only occurs with severe long-standing deficiency
because the ‘normal’ serum calcium levels are preserved through
the increased levels of PTH, but serum phosphate may be low.
Although often used as a biochemical marker of vitamin D defi-
ciency, serum alkaline phosphatase activity (ALP) is rarely raised
and then usually with severe deficiency and osteomalacia. If ALP
is raised another cause such as obstructive liver disease or bony
metastases should be excluded prior to attributing it to vitamin
D deficiency alone. The ‘normal’ PTH reference range is wide but
metastases should be excluded prior to attributing it to vitam in
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Vitamin D serum levels
The general consensus is that the lower limit of the optimal vita-
m in D level is 75nmol per litre with gradations from replete to
severely deficient (see Table 7). ¹⁰ In the UK about 50 per cent
of the population is thought to have inadequate levels, particularly
by spring, and 16 per cent to be severely deficient. ¹⁰

Testing for vitamin D deficiency should be reserved for those
at high risk, in those with symptoms potentially due to vitamin
D deficiency, patients with disorders associated with vitamin D
deficiency and those where D₂ deficiency may affect treatment
for osteoporosis. ⁹ ¹¹ ¹³ Present guidelines also suggest that for
simple at-risk populations such as pregnant/breastfeeding
women, elderly or dark skinned people simple supplementation
of 400IU daily should be encouraged and no vitamin D moni-
toring is required. ⁹ ¹¹

Treatment and monitoring of patients with low vitamin D lev-
els depends on the severity, cause and age of the patient (see
Table 8). While a large loading dose of vitamin D may be more
practical, smaller daily doses appear to be more effective. For
mild deficiency lifestyle advice alone may be sufficient – arms
and face exposure to sunlight at least 30 minutes per day and
at least one portion of oily fish per week.

Patients taking bisphosphonates for osteoporosis may require
stand-alone vitamin D in addition to the usual calcium/vitamin
D combinations, as simply increasing the dose of the combination
to treat the deficiency could result in hypercalcaemia. ¹¹

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**Table 5. Management of folate deficiency**

<table>
<thead>
<tr>
<th>Dietary deficiency</th>
<th>dietary advice and folic acid 5mg for 4 months check FBC if previous anaemia at 8 weeks, check folate level at completion of treatment; no further monitoring usually needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malabsorption</td>
<td>5mg daily long term or for life if underlying causes persists</td>
</tr>
<tr>
<td>Prophylaxis when planning for pregnancy</td>
<td>400µg/day</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>5mg/day in first trimester or 5mg/day throughout pregnancy if family history of neural tube defects</td>
</tr>
<tr>
<td>Prophylaxis eg dialysis, methotrexate therapy</td>
<td>5mg weekly</td>
</tr>
<tr>
<td>Chronic haematological conditions</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis pregnancy</td>
<td>400µg/day for 12 weeks or 5mg day if history of neural tube defects</td>
</tr>
</tbody>
</table>

before starting treatment check for deficiency of folate and iron status, potential causes for deficiency and other causes for macrocytosis if present

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**Table 6. Sources of vitamin D**

| UV exposure in fair skin 20 minutes on face and arms | 2000IU |
| egg yolk                                           | 500IU  |
| mushrooms 60g                                      | 600IU  |
| tablespoon of cod liver oil margarine 100g          | 1800IU |
| infant formula milk 100kcal supplemented breakfast cereal 100g | 2800IU |

In simple deficiencies once serum vitamin D levels reach
the optimal reference range usually no further vitamin D moni-
toring is needed. Serum calcium should be checked at least
once a month after starting vitamin D treatment in order to
unmask concomitant primary hyperparathyroidism and vitamin
D levels checked at three months from the start of a regimen
with larger doses and in children. ⁹ ¹¹

Renal disease
In chronic kidney Disease (CKD) vitamin D supplementation
should not be offered routinely. However, the prevalence of sec-
ondary hyperparathyroidism increases with decreasing glomeru-
lar filtration rate (GFR). Vitamin D deficiency in people with GFR
<30ml per min per 1.73m² is 73 per cent compared to 5.5 per

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**Table 7. Sources of vitamin D**

<table>
<thead>
<tr>
<th>Sources of vitamin D</th>
<th>Amounts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cod liver oil</td>
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</table>

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In the UK at risk populations include children, pregnant/breast-
feeding women, dark skinned people, those where custom or
religion result in little skin exposure, older people and vegans,
and those with malnourishment, obesity (BMI >30 mg/m²), mal-
absorption, thyrotoxicosis, liver or kidney disease or those taking
long-term enzyme-inducing medications, bile sequestrants
steroids or antiretrovirals. ¹¹
percent of those with eGFR >90ml per min 1.73m². Thus, vitamin D (and calcium, phosphate and PTH) should be monitored in all patients with CKD and treatment with vitamin D₃ (or calcitriol if there is no improvement in PTH and calcium with vitamin D₃) offered. As potential adverse effects are hypercalcaemia, extraskeletal (vascular) calcification and increased cardiovascular risk, serum calcium and phosphate should be regularly monitored. Although there is insufficient data on clinical outcomes to date, potential benefits of vitamin D therapy in people with CKD and deranged bone metabolism include increased bone mineral density and muscle strength, and reduced risk of falls and fractures.¹³

**Toxicity**

Vitamin D toxicity appears to be a significant problem only at levels >500nmol per litre and if in combination with supplemental rather than dietary calcium, liver or kidney disease, renal stones, a high normal or high serum calcium, sarcoidosis or tuberculosis.

**When to refer**

Referrals is usually unnecessary but should be considered for patients not responding to replacement, in those with no obvious cause for deficiency and particularly for patients with vitamin D deficiency in combination with malabsorption, liver or kidney disease, renal stones, a high normal or high serum calcium, sarcoidosis or tuberculosis.

**Conclusion**

Though testing for vitamin B₁₂, folate and vitamin D are frequently justified, there is insufficient evidence for screening asymptomatic individuals and populations at low risk. However, there is a case for increased awareness and the testing of populations and individuals at high risk, particularly in relation to vitamin D, due to the resurgence of rickets and osteomalacia in the UK. For all three vitamins, once replete, no further testing or monitoring is generally needed except in relevant vulnerable patients such as those with malabsorption, renal disease and similar.

**References**


**Declaration of interests**

None to declare.

*Dr Lolin is consultant in chemical pathology and metabolic medicine, Tunbridge wells and Maidstone Hospitals, Maidstone and Tunbridge Wells NHS Trust*