National Osteoporosis Society

Vitamin D and Bone Health:

A Practical Clinical Guideline for Patient Management in Children and Young People

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There continues to be considerable clinical and academic interest in vitamin D in children and young people. This partly relates to recognition of a resurgence of symptomatic vitamin D deficiency with reports of children presenting with rickets or hypocalcaemic symptoms. An additional development has been the recognition that vitamin D may have a physiological extraskeletal role beyond its traditional function as a key regulator of calcium and bone metabolism. There has been a large increase in requests for measurement of vitamin D with evidence that many individuals have suboptimal vitamin D status, often without symptoms.

These guidelines have therefore been produced to guide clinicians in the appropriate investigation and management of vitamin D deficiency in children and young people. Since the production of the last guidelines in 2015, there have been some key evidence-based publications including the *"Global Consensus Recommendations on Prevention and Management of Nutritional Rickets"*[1] and the latest recommendations from the UK Scientific Advisory Committee on Nutrition (SACN)[2]. The authors have sought to reflect recent literature whilst also acknowledging other developments in clinical practice over the last few years including responses to the ever-broadening range of vitamin D preparations on the market. Nonetheless, the key messages regarding the importance of prevention, vigilance and effective treatment remain the same.

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OTS ossibus animisque coniunctis

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Glossary and abbreviations

Vitamin D	**calciferol (either D_2 or D_3)**
Vitamin D_3	**cholecalciferol**
Vitamin D_2	**ergocalciferol**
25-hydroxy vitamin D	**25(OH)D** **calcidiol** **calcifediol**
Parathyroid Hormone	**PTH**
Vitamin D Binding Protein	**VDBP**
High-Performance Liquid Chromatography (linked to either fluorescence or MS (Tandem MS))	**HPLC**
Mass Spectrometry	**MS**
3-epi-25(OH)D	**C_3 epimer**
British National Formulary for Children	**BNFC**
Scientific Advisory Committee on Nutrition	**SACN**
International Unit	**IU**

Conversion factors

10µg (micrograms) vitamin D = 400IU vitamin D

2.5 nmol/L plasma 25(OH)D = 1 ng/mL plasma 25(OH)D

Note

25(OH)D may be measured in plasma or serum

Key recommendations

- Measurement of plasma 25(OH)D is the best way to estimate vitamin D status.
- Routine testing of plasma 25(OH)D levels is not recommended and it is advised to be restricted to children and young people with a clear indication for measurement.
- Primary prevention with advice regarding dietary sources of vitamin D and multivitamin supplements as recommended for age.
- Treatment is recommended to consist of oral preparations of vitamin D_3 given daily for eight to 12 weeks.
- Many children with vitamin D deficiency have a poor dietary calcium intake and therefore may need to increase their dietary calcium intake or take calcium supplementation.

The role of vitamin D in paediatric bone health

Nutritional vitamin D deficiency can lead to health problems in children including rickets, impaired growth, muscle weakness, cardiomyopathy and seizures due to hypocalcaemia.

There is no universal consensus on the biochemical definition of vitamin D deficiency. It is current paediatric practice to use a threshold of plasma 25-hydroxyvitamin D (25(OH)D) of less than 25 nmol/L to define vitamin D deficiency. This is based on the fact that symptomatic vitamin D deficiency in children (e.g. rickets, hypocalcaemia) will usually only occur with a plasma 25(OH)D level below 25 nmol/L. This is consistent with current UK guidelines.

- plasma 25(OH)D < 25 nmol/L is deficient
- plasma 25(OH)D of 25–50 nmol/L may be inadequate in some people.
- plasma 25(OH)D > 50 nmol/L is sufficient for almost the whole population.

How should we assess vitamin D status?

Measurement of plasma 25(OH)D is the best way to assess vitamin D status. The assay used should have the ability to recognise all forms of 25(OH)D (D_2 or D_3) equally. In practice this means that it should use either High-Performance Liquid Chromatography (HPLC) or, more likely, tandem MS. Tandem MS assays can be subject to interference from metabolites such as the C_3 epimer, which is synthesised by babies and young children but has also been detected in adult populations. The role of vitamin D binding protein (VDBP) and the impact on free 25(OH)D concentrations currently remains unclear.

Who should be tested for vitamin D deficiency?

Low levels of vitamin D are common in the UK. It is therefore important to consider whether the child's symptoms or signs could be related to vitamin D deficiency before requesting the measurement of vitamin D.

Routine screening is not recommended.

Indications for testing vitamin D status

1. Symptoms and signs of rickets:
   - progressive bowing of legs (bowing of legs can be a normal finding in toddlers)
   - progressive knock knees
   - wrist swelling
   - rachitic rosary (swelling of the costochondral junctions)
   - craniotabes (skull softening with frontal bossing and delayed fontanelle closure)
   - delayed tooth eruption and enamel hypoplasia.

2. Other symptoms or conditions associated with vitamin D deficiency:
   - long-standing (> three months), unexplained bone pain
   - muscular weakness (e.g. difficulty climbing stairs, waddling gait, difficulty rising from a chair or delayed walking)
   - tetany due to low plasma calcium
   - seizures due to low plasma calcium (usually in infancy)
   - infantile cardiomyopathy.

3. Abnormal investigations:
   - low plasma calcium or phosphate, high alkaline phosphatase (greater than the local age-appropriate reference range)
   - radiographs – showing osteopenia, rickets or pathological fractures revealed by radiographs.

4. Chronic disease that may increase risk of vitamin D deficiency:
   - chronic renal disease, chronic liver disease
   - malabsorption syndromes (e.g. coeliac disease, Crohn's disease, cystic fibrosis).

5. Treatment with bone-targeted drugs that require vitamin D sufficiency such as bisphosphonates (used in conditions affecting bones such as osteoporosis due to steroids, immobility or inflammatory disorders).

In the absence of the above indicators, measurement of vitamin D is not indicated.

Primary prevention

It is advised that primary preventative measures (at minimum) be undertaken in patients at high risk. These include advice about dietary intake of vitamin D and multivitamin supplements.

Indications for vitamin D supplements

Public Health England recommends daily vitamin D supplements as follows:

- all babies from birth to one year should consume 8.5 to 10µg per day
- babies receiving infant formula do not require supplements if receiving more than 500ml per day
- children from one to four years should consume 10µg per day

The provision of Healthy Start multivitamin drops through primary health care services and Children's Centres remains key to the delivery of vitamin D supplementation to children. Whilst Healthy Start multivitamins currently provide only 7.5µg (300IU per day), it is the understanding of the authors that this is under review.

Other indications for vitamin D supplements:

- children and young people previously shown to be vitamin D deficient or with a plasma 25(OH)D of 25–50 nmol/L should take a supplement containing vitamin D. This should be continued unless there is a significant lifestyle change to improve vitamin D status.
- vitamin D supplements should be considered in other groups at high risk of vitamin D deficiency (see below), especially if they do not adhere to lifestyle advice.

Groups at high risk of vitamin D deficiency

Children and young people in the following groups are at high risk of vitamin D deficiency. Primary prevention is therefore particularly important for them.

- children and young people with diets insufficient in calcium (e.g. vegan or low dairy intake) (see Appendix 1) or with generally poor diets
- children and young people with limited sun exposure (e.g. veiled and photosensitive patients and patients who are advised to apply high factor sun block due to malignancy risk e.g. cancer survivors)
- children and young people who spend very little time outdoors (e.g. those with limited mobility)
- children and young people who have dark skin, for example people of African, African-Caribbean or South Asian origin, as they may not get enough vitamin D from sunlight[3].
- children and young people taking anticonvulsants that induce liver enzymes such as phenytoin, carbamazepine, primidone or phenobarbitone
- children and young people with family members with proven vitamin D deficiency.

Season

There is a seasonal variation in vitamin D status in the UK, with lower circulating concentrations seen in the population in winter and late spring, compared to summer and autumn. It may be helpful to take into consideration the likely decline in vitamin D status when determining what to do with a child with a low 25(OH)D concentration in autumn or winter.

Having a low 25(OH)D concentration in late summer may reflect a lifestyle that places the individual at risk of vitamin D deficiency. It is important to state that the physiological significance of a given 25(OH)D concentration at a given moment is the same whatever the time of year.

Dietary vitamin D

Consumption of vitamin D rich foods can contribute to improving vitamin D status. Foods rich in vitamin D include:

- oily fish such as sardines, pilchards and mackerel
- eggs, meat and milk (in small and varying amounts)
- margarine, some breakfast cereal, some yoghurt and infant formula, which are fortified with vitamin D.

Who will benefit from treatment?

It is advised that in those patients where 25(OH)D is tested (discussed in the previous section) the results be acted upon as follows:

- plasma 25(OH)D < 25 nmol/L: treatment recommended.
- plasma 25(OH)D 25–50 nmol/L:
  - give advice on dietary sources of vitamin D
  - advise oral preparations containing vitamin D 400–600 IU per day for patients aged one month to 18 years. Continue unless there is a significant lifestyle change to improve vitamin D status
  - ensure dietary calcium intake is adequate
  - retesting is not normally required if the individual is asymptomatic and compliant with multivitamin supplements
- plasma 25(OH)D > 50 nmol/L: provide reassurance and give advice on maintaining adequate vitamin D status through diet and supplements

Indications for referral to secondary care

The following circumstances indicate that referral to secondary care is warranted:

- repeated low plasma calcium concentration with or without symptoms (irritability, brisk reflexes, tetany, seizures or other neurological abnormalities)
  - symptomatic: requires immediate referral to A&E if outpatient
  - asymptomatic: discuss treatment with paediatrician
- underlying complex medical disorders (e.g. liver disease, intestinal malabsorption)
- in children, deformities or abnormalities probably related to rickets
- poor response to treatment despite good adherence (defined as a level of 25(OH)D < 50 nmol/L after eight to 12 weeks of adherent therapy)
- persisting low plasma phosphate or low/high alkaline phosphatase.

How should vitamin D deficiency be treated?

Vitamin D_3 or vitamin D_2?

As there is data to show that vitamin D_3 is more bioavailable than vitamin D_2[1], we would recommend vitamin D_3 as the preferred treatment although treatment with vitamin D_2 is effective.

The doses of vitamin D below are based on what are currently recommended in the *British National Formulary for Children* (BNFC)[4]. However, these may need to be changed dependent on the availability of other vitamin D preparations and evidence of alternative dosing regimens.

- one–five months: 3,000 IU orally daily for eight–12 weeks
- six months to 11 years: 6,000 IU orally daily for eight–12 weeks
- 12–17 years: 10,000 IU orally daily for eight–12 weeks; a single or divided oral dose totalling 300,000 units can be considered if there is concern about compliance.

It is recognised that equivalent weekly or fortnightly dosing is likely to be effective in treating vitamin D deficiency.

Calcium supplementation

Many children with vitamin D deficiency rickets have a poor dietary calcium intake[5]. As their bones are growing, there is a greater risk of negative calcium balance. Therefore, in children consider the need for calcium supplementation. Many children with vitamin D deficiency will have a depleted calcium status and/or a poor calcium intake and may therefore benefit from advice about dietary calcium intake.

In some cases calcium supplementation may be worthwhile over the period of vitamin D treatment (see Appendix 1). These recommendations represent a represent a recommended calcium intake to prevent rickets[1].

- birth – six months: 200mg per day
- six – 12 months: 260mg per day
- over 12 months: >500mg per day

Dietary intake can be achieved through a combination of diet and supplementation as required. The dose of any supplements also needs to take into account dietary calcium intake and the size of the child.

There is no place for the use of 1α hydroxylated preparations (e.g. alfacalcidol or calcitriol) in the routine management of vitamin D deficiency. Their use is limited to treating significant hypocalcaemia, disorders of malabsorption, renal disease and rare diseases of calcium and phosphate regulation.

Monitoring

Bone profile and vitamin D tests (and a PTH test if the patient has rickets or hypocalcaemia) are recommended to be repeated at the end of the course of treatment.

If the 25(OH)D level is greater than 50 nmol/L and the bone profile is normal:

- advise multivitamins containing vitamin D 400– 600 IU per day. Continue unless there is a significant lifestyle change to improve vitamin D status.

If 25(OH)D is below 50 nmol/L:

- consider poor compliance, drug interactions and underlying disease such as renal disease, liver disease and malabsorption.
- if poor compliance is suspected, a high-dose treatment may be considered if the patient is aged 12–18 years (e.g. 300,000 IU as a single or divided dose).

Note: If a child's symptoms/signs have not improved despite a satisfactory 25(OH)D concentration, they are unlikely to be related to vitamin D deficiency.

Vitamin D toxicity

The *"Global Consensus Recommendations on Prevention and Management of Nutritional Rickets"* define toxicity as hypercalcemia and a plasma 25(OH)D > 250 nmol/L with hypercalciuria and suppressed PTH. Whilst recommending a concentration of 250 nmol/L as the upper limit of 25(OH)D the paper's authors acknowledge that this allowed a "large safety margin" and that symptomatic toxicity from randomised control trials had only been reported at levels >500 nmol/L[1].

There is no widespread agreement on the threshold concentration or amount of vitamin D that results in toxicity. This is, in part, a reflection of the paucity of studies that address the safety of vitamin D supplementation. In adults, prolonged daily intake of vitamin D up to 10,000 IU or plasma concentrations of 25(OH)D of up to 240 nmol/L appear to be safe. Although described, acute vitamin D intoxication is rare and usually results from vitamin D doses much higher than 10,000 IU per day.

However, the long-term effects of supplementation with high doses of vitamin D are not known. Risks such as nephrolithiasis cannot be excluded. Caution is required in any child or young person with a granulomatous disease (e.g. tuberculosis or sarcoidosis).

Reference List

1. Munns CF, Shaw N, Kiely M, et al. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. *J Clin Endocrinol Metab*. 2016;101(2):394-415.
2. *Scientific Advisory Committee on Nutrition. Vitamin D and Health 2016.*; 2016. Available from: https://www.gov.uk/government/groups/scientific-advisory-committee-on-nutrition. Accessed July 26, 2018.
3. Updated Public Health England advice – updated in March 2017 following SACN recommendations. Available from: www.nhs.uk/conditions/vitamins-and-minerals/vitamin-d/.
4. *British National Formulary for Children* 2017–2018 London: BMJ Group, 2018. Section 9.7 Vitamin Deficiency.
5. Aggarwal V, Seth A, Aneja S, et al. Role of calcium deficiency in development of nutritional rickets in Indian children: a case control study. *J Clin Endocrinol Metab* 2012;97(10): 3461–3466.
6. Nordblad M, Graham F, Mughal MZ et al. Rapid assessment of dietary calcium intake. *Arch Dis Child* 2016; 101:634-636.

Appendix 1: Guideline on assessing dietary calcium intake

Dietary reference values for calcium [a]

Age	Reference nutrient intake for calcium mg/day (mmol/day)
0–12 months	525 (13.1)
1–3 years	350 (8.8)
4–6 years	450 (11.3)
7–10 years	550 (13.8)
11–14 years, male	1000 (25.0)
11–14 years , female	800 (20.0)
15–18 years, male	1000 (25.0)
15–18 years, female	800 (20.0)

Note: 1 mmol calcium = 40 mg calcium.

[a] *Department of Health, Dietary Reference Values for Food, Energy and Nutrients for United Kingdom (Report 41), London: TSO, 1991.*

Calcium-rich foods

Find calcium-rich foods from this list for a bone-healthy diet[b]. Serving sizes are based on average portions[c]. The details below provide a general guide – precise calcium content can vary depending on source of food stuffs. Consider also the use of a validated food frequency questionnaire to rapidly assess dietary calcium intake in children such as that published by *Nordblad et al.,*[6].

Food	Serving size (average)	Calcium (mg)
Milk		
Milk, semi-skimmed	glass, 200 ml	240
Milk skimmed	glass, 200 ml	244
Milk whole	glass, 200 ml	236
Milkshake	takeaway, 300 ml	387
Soy drink, calcium enriched	glass, 200 ml	178
Yoghurt and cream		
Yoghurt, low-fat, fruit	pot, 150 g	210
Yoghurt, low-fat, plain	pot, 150 g	243
Cream, double, whipped	portion, 45 g	26
Cream single	tablespoon, 15 g	13
Cheeses		
Danish blue	portion, 40 g	195
Edam	portion, 40 g	318
Feta	portion, 40 g	144
Camembert	portion, 40 g	94
Cheddar	medium chunk, 40 g	296
Cheese spread	portion, 30 g	149
Cottage	small pot, 112 g	142
Mozzarella, fresh	portion, 56 g	203
Parmesan, fresh	portion, 30 g	308
Vegetables		
Broccoli, boiled	serving, 85 g	34
Watercress, raw	small bunch, 20 g	34
Curly kale	serving, 95 g	143
Okra, stir fried	8 medium, 40 g	88
Red kidney beans, canned	3 tablespoons, 105 g	75
Chick peas, boiled	3 tablespoons, 90 g	41
Green/French beans	serving, 90 g	50
Baked beans	serving, 135 g	72
Nuts		
Almonds	12 whole, 26 g	62
Brazil nuts	6 whole, 20 g	34
Hazelnuts	20 whole, 20 g	28
Sesame seeds	1 tablespoon, 12 g	80
Walnuts	12 halves, 40 g	38
Tahini paste	1 heaped teaspoon, 19 g	129
Desserts		
Cheesecake, fruit	slice, 120 g	94
Custard made with milk	portion, 120 g	166
Rice pudding, canned	portion, 200 g	176
Ice cream, dairy, vanilla	serving, 75 g	75
Fromage frais, fruit	small pot, 60 g	52
Fish		
Sardines in oil, tinned	portion, 100 g	500
Whitebait, fried	portion, 80 g	688
Salmon, tinned	portion, 100 g	91
Fish paste	small jar, 35 g	98
Breads and grains		
Pasta, plain, cooked	portion, 230 g	85
Rice, white, boiled	portion, 180 g	32
White bread	slice, 30 g	53
Wholemeal bread	slice, 30 g	32
Muesli, Swiss style	portion, 50 g	55
Fruits		
Apricots, raw, no stone	4 fruit, 160 g	117
Figs, ready to eat	4 fruit, 220 g	506
Currants	2 tablespoons, 50 g	47
Orange	peeled, 160 g	75
Other foods		
Tofu, soy bean, steamed	100 g	510
Omelette, cheese	2 eggs, 120 g	344
Quiche, cheese and egg	slice, 140 g	367
Macaroni cheese	portion, 220 g	374
Pizza, cheese and tomato	9"–10" pizza, 410 g	873
Lasagne	portion, 420 g	420

[b] *Food Standards Agency. McCance and Widdowson's The Composition of Foods, Sixth Summary Edition. Cambridge: Royal Society of Chemistry, 2002.*

[c] *Food Standards Agency. Food Portion Sizes 2002.*

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About us

The National Osteoporosis Society is the only UK-wide charity dedicated to ending the pain and suffering caused by osteoporosis. The Charity works tirelessly to help and support people with the condition as well as promoting good bone health to prevent osteoporosis. We do this by:

- Providing a range of information resources covering all aspects of osteoporosis for health professionals and the public.
- Providing a free helpline staffed by nurses with specialist knowledge of osteoporosis and bone health.
- Investing in research to ensure future generations are freed from the burden of osteoporosis.
- Influencing government and campaigning to improve and maintain essential services.
- Educating Health Professionals to ensure they are kept up to date about osteoporosis – through events, accredited training courses and our leading conference on osteoporosis and bone health.
- Working in partnership with the NHS to set up and improve Fracture Liaison Services which can reduce the number of fractures caused by osteoporosis.

To find out more about our information, support and services, visit our website: www.nos.org.uk

Professional Membership

Professional membership of the National Osteoporosis Society will ensure you become better informed and able to deliver the best care possible to people with osteoporosis or fractures.

As a professional member, you'll have all the information you need at your fingertips and will stay up to date on best practice, care, delivery, new treatments and the latest news on osteoporosis research findings.

You'll also feel proud to be part of an organisation working hard to help those affected by osteoporosis.

To join a growing network of professional members like you, call our membership team on 01761 473287 or visit www.nos.org.uk/professionals

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