Vitamin D deficiency: a diagnosis often missed

Vitamin D deficiency causes rickets in children and osteomalacia in adults. These are common today but often not recognized. This article summarizes the clinical features, investigation and treatment of these disorders and examines the factors contributing to failures of diagnosis.

Rickets has been recognized as a distinct disorder for over 300 years. The ability of fish liver oil to cure rickets has been known since the 1820s. The association of rickets with lack of sunlight was recognized in 1890, and since 1920 the role of vitamin D or ultraviolet radiation in treating or preventing rickets has been well understood. Osteomalacia in adults was thought to be the same disorder as rickets by Trousseau in the 1820s (Fourman and Royer, 1968). While the importance of vitamin D to bone health has long been recognized, rickets and osteomalacia remain widespread in the UK and in many other countries.

Apart from bone disease, there is growing evidence that vitamin D subnutrition may contribute to the risk of a wide range of disorders, particularly multiple sclerosis in which it is suggested that a lack of vitamin D may underlie the increased risk at higher latitudes (Pierrot-Deseilligny and Souberbielle, 2010). Other conditions in which there is some evidence of an association with low vitamin D status include rheumatoid arthritis, inflammatory bowel disease, both types of diabetes mellitus, cardiovascular disease, some winter illnesses and certain forms of cancer (Holick, 2007; Gillie, 2008; Pearce and Cheetham, 2010). The evidence for these associations is largely epidemiological and confounding factors cannot be excluded.

Sources of vitamin D

One source of vitamin D is the diet but the number of foodstuffs containing vitamin D is very limited. The best source is from oily fish including salmon, sardines and herring. Eggs are sometimes a valuable source of vitamin D but the vitamin D content of eggs depends on the diet of the hens and their exposure to sunlight. In the UK margarine is supplemented with vitamin D and this played a part in reducing the incidence of rickets during the second world war. Milk is supplemented with vitamin D in some countries but not in the UK. Infant formulae contain vitamin D.

Despite the limitations of our climate, most people in the UK obtain most of their vitamin D from exposure to the ultraviolet B component of sunlight (280–315 nm). This converts a precursor in the skin, 7-dehydrocholesterol, to colecalciferol (vitamin D_3). While overall in the UK population it is estimated that some 80% of the vitamin D obtained by the individual is derived from sunlight this hides substantial differences between individuals. Pigmentation in dark skin limits the effectiveness of sunlight. Clothing worn for cultural reasons may have the same effect. The use of sunscreens has been implicated in the pathogenesis of rickets in sunny parts of the UK; even factor 8 causes a substantial reduction in vitamin D formation (Matsuoka et al, 1987). Atmospheric pollution filters out the ultraviolet B (Agarwal et al, 2002). Similarly ultraviolet B is attenuated by the obliquity of the sun's rays in winter. For this reason, the incidence of vitamin D deficiency is greater in northern parts of the UK than in the south. Even in the south there is little effective ultraviolet B radiation between November and February (Gillie, 2008).

It is important to recognize that vitamin D is stored in adipose tissue for considerable periods. A vitamin D-replete person may have sufficient vitamin D to last for 2 or more years and is unlikely to develop subnutrition during the winter. Most of us obtain enough vitamin D during the summer to last at least the following winter (Devgun et al, 1981). However, those whose vitamin D intake and sunlight exposure are inadequate during the summer are much more at risk of significant deficiency in the winter and spring. Understanding vitamin D storage is important in devising strategies for treatment.

The vitamin D status of a newborn infant depends on that of the mother. Rickets is well recognized in newborn infants whose mothers are deficient. Indeed, overt radiological evidence of rickets has been described in the unborn child of a vitamin D-deficient mother (Russell and Hill, 1974). Studies in India, Pakistan, Iran and the United States have demonstrated vitamin D deficiency in infants and their mothers (Bodnar et al, 2007; Agarwal et al, 2010). In early childhood, rickets is well recognized particularly in breast-fed infants. Breast milk contains little vitamin D, particularly if the mother is herself deficient. The discovery of rickets in a child should lead to the investigation of the mother.

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Metabolism of vitamin D

Vitamin D_2 and vitamin D_3 undergo similar metabolic transformations. They are first hydroxylated in the liver to 25-hydroxyvitamin D, which is the principal form of vitamin D in the blood. The second hydroxylation step, in the kidney, leads to the production of 1,25-dihydroxyvitamin D (calcitriol). This is a hormone whose principal effect is on active calcium absorption in the gut. This step is controlled by parathyroid hormone and is affected by hypoparathyroidism, by various rare inborn metabolic disorders and in renal failure. Fuller details of vitamin D metabolism can be obtained from reviews by Holick (2007) and Rosen (2011).

Vitamin D requirements

In the UK there is no reference nutrient intake for healthy adults; it is assumed that outdoor exposure is adequate for most. For those with limited outdoor exposure 400 iu (10 μg) daily is advised (Macdonald et al, 2011). It is difficult to specify minimal sunlight exposure to provide an adequate vitamin D intake because much depends on skin colour, areas exposed, latitude and time of day. However, one estimate is that, for a fair-skinned person in the UK, 20–30 minutes of sunlight on the face and forearms at midday in summer would provide about 2000 iu of vitamin D. Two or three such exposures each week in summer would be adequate (Pearce and Cheetham, 2010).

In the USA, despite the lower latitude and greater sunshine, reliance on sunlight exposure is not now advised. Dietary intakes of 400 iu (10 μg) up to the age of 1 year, 600 iu (15 μg) between the ages of 1 and 70 years and 800 iu (20 μg) over 70 years of age are advised (Institute of Medicine, 2011).

Who is at risk of vitamin D deficiency in the UK?

Until recently it was widely thought that vitamin D deficiency was uncommon except in immigrant families and in elderly women living on their own. The major factor in these groups was the lack of sunlight exposure. These groups remain at risk (Iqbal et al, 1994) and elderly institutionalized adults are particularly prone to fractures as a result of vitamin D deficiency (Hirani and Primatesta, 2005; Gillie, 2008). With the increasing availability of appropriate investigations for vitamin D deficiency, it has become clear that subnutrition and frank deficiency are not uncommon in the general population (Hyppönen and Power, 2007; Macdonald et al, 2011). Factors contributing to vitamin D subnutrition include indoor working during daylight hours. In a small survey in a general practice in London, white male bankers were often found to be severely deficient (Livingstone, 2010).

Vitamin D deficiency worldwide

Numerous surveys have demonstrated a substantial prevalence of vitamin D deficiency in many countries. While there was a wide variation in the level of serum 25-hydroxyvitamin D used in the definition of vitamin D deficiency, it is clear from all the studies that substantial numbers of individuals were deficient by any standards. As in the UK, immigrants in western Europe and Australia are particularly at risk but, in the countries from which they come, vitamin D deficiency is also widespread despite substantial availability of sunshine. In several countries including Turkey veiling for cultural reasons has been shown to contribute to deficiency (Guzel et al, 2001). As in the UK, institutionalized elderly people have often been found to be deficient. Vitamin D deficiency rickets has been described in many countries including the United States and Canada (Weisberg et al, 2004; Ward et al, 2007; Keller and Barnes, 2008).

Malabsorption

All causes of malabsorption may contribute to vitamin D deficiency including Crohn's disease, coeliac disease, cystic fibrosis and primary biliary cirrhosis. Osteomalacia is well recognized as a sequel to partial gastrectomy and to jejunoileal bypass surgery (Bikle, 2007). Osteomalacia may be the first presentation of an adult with coeliac disease. Rickets is well recognized in children with biliary atresia.

Anticonvulsant therapy

For many years, it has been suggested that anticonvulsant therapy contributes to vitamin D deficiency by inducing enzymes that degrade active metabolites to inactive products. The evidence for this is limited and individuals on anticonvulsant therapy may develop vitamin D deficiency for 'ordinary' reasons.

Factors contributing to failures to diagnose vitamin D deficiency

Patients with rheumatoid arthritis and osteoarthritis may develop vitamin D deficiency; the increase in pain may be wrongly ascribed to a worsening of the underlying condition and treated inappropriately. In one study by Ralston et al (1988) in the west of Scotland, the authors commented that osteomalacia is 'a common, easily overlooked and treatable cause of morbidity in elderly patients with rheumatoid arthritis'. Similarly, an appreciable number of patients formally diagnosed as having fibromyalgia had evidence of vitamin D deficiency (Al-Allaf et al, 2003).

A diagnosis of malignancy may also cause difficulty. A particularly striking case report by Sievenpiper et al (2008) concerned a woman of Pakistani origin who was thought to have widespread secondary malignancy because of her symptoms and isotope bone scan appearances. Her symptoms and scan abnormalities resolved completely after a visit to Pakistan. Khokhar et al (2009) have described similar patients initially thought to have secondary malignancy.

The widespread availability of bone densitometry has often led to assumptions that a low bone density inevitably represents osteoporosis and requires treatment with antiresorptive drugs. In one study in North America, a substantial proportion of patients already taking anti-osteoporosis therapy were found, on investigation, to have vitamin D deficiency; the treatment being given was inappropriate (Holick et al, 2005).

In infants with fractures or pseudofractures a confident diagnosis of non-accidental injury is sometimes made when the cause is, in reality, vitamin D deficiency rickets (Keller and Barnes, 2008; Paterson, 2009).

Presentations of vitamin D deficiency

The classical presentations of osteomalacia in adults are bone pain and muscle weakness. In some patients, the dominant symptom is muscle weakness affecting particularly the proximal muscles so that patients have difficulty in rising from a chair and in going up and down stairs. In severe cases a waddling gait is sometimes observed or even complete loss of the ability to walk.

Fractures represent a frequent presentation of osteomalacia (Bours et al, 2011), and any type of fracture can occur, including the fractures thought classically to represent osteoporosis (hip, distal forearm and vertebrae). Fractures may take place with little or no recognized trauma (*Figure 1*). Delay in fracture healing or non-union may be the first indication of vitamin D deficiency (Brinker et al, 2007).

Today, many patients are recognized to have vitamin D deficiency following the finding of a low bone density after densitometry but some patients with undoubted osteomalacia have bone density figures within reference ranges. A few patients are identified following the finding of unexpected biochemical abnormalities, particularly a low serum calcium level or a raised serum alkaline phosphatase level.

Osteomalacia or previous osteomalacia is a common cause of cranio-pelvic disproportion, obstructed labour and a need for caesarean section in some parts of the world (Herm et al, 2005).

In children with rickets, bone pain is not always present but muscle weakness is frequently seen. Some patients present with the classical deformities associated with rickets in the past, and some patients present with fractures. As with osteogenesis imperfecta and other bone disorders, the parents may be unable to provide an explanation for the fractures and the child may be thought to have been abused (Keller and Barnes, 2008; Paterson, 2009). The extent to which rickets underlies unexplained fractures generally is controversial.

Physical signs in osteomalacia and rickets

In adults with osteomalacia one useful clinical sign is the presence of bone tenderness elicited either by gentle springing of the ribs or by springing the radius and ulna together. The physical signs of children with rickets are well recognized and include deformities such as genu varus and genu valgus, expansion of the costochondral joints giving a palpable 'rachitic rosary', frontal bossing of the skull and enlargement of the anterior fontanelle.

Biochemistry

About two thirds of patients with osteomalacia have hypocalcaemia; hypophosphataemia is found in a similar proportion. The majority of patients have raised serum alkaline phosphatase values. However, it should be noted that serum alkaline phosphatase levels may be raised for other reasons, particularly obstructive liver disease, pregnancy (placental alkaline phosphatase) and other bone disorders, such as Paget's disease.

Results of biochemical investigations may be difficult to interpret in childhood since serum alkaline phosphatase levels are higher in normal growing children

Figure 1. Fracture of the distal right femur in a 74-year-old woman. This occurred while she was being lifted onto an operating table for the repair of a fracture of the upper left femur. She was later found to have osteomalacia (serum 25-hydroxyvitamin D 4 nmol/litre) and a review of her records indicated that she probably had undiagnosed osteomalacia for the preceding 8 years.

than in adults. Reference ranges for children are often inadequate but figures higher than 2.5 times the upper reference limit for adults should be regarded as abnormal for a child (Kovar and Mayne, 1981). The serum alkaline phosphatase level is often inappropriately normal in children with rickets who are not growing (Nagi, 1972). A normal growing child has a higher serum inorganic phosphate level than an adult. Biochemical findings need to be interpreted in light of these facts.

The most useful biochemical investigations are the serum 25-hydroxyvitamin D and serum parathyroid hormone levels. The difficulty with the assessment of serum 25-hydroxyvitamin D is uncertainty about the appropriate reference range. Preparation of a range in the conventional way as 95% of an apparently normal population is meaningless since much depends on the season, the habitual diets and the habitual exposure to sunlight within that population. Furthermore the distribution of results is not normal, partly because of the inclusion of asymptomatic individuals who are, in fact, deficient.

The clearest way to define normal values for serum 25-hydroxyvitamin D is by reference to the level below which serum parathyroid hormone is increased. In one study this was 37 nmol/litre (Thomas et al, 1998). Other authors found that some patients with figures up to 50 nmol/litre still had responses in serum parathyroid hormone to the administration of vitamin D (Malabanan et al, 1998). There is no good evidence that figures higher than 50 nmol/litre should be regarded with concern. A similar conclusion can be drawn from studies of fracture risk. For example in women there was little evidence of benefit from vitamin D supplements unless the baseline serum 25-hydroxyvitamin D was less than 42 nmol/litre (Holick, 2007). In older men serum 25-hydroxyvitamin D levels lower than 40 nmol/litre were associated with an increased risk of fracture (Rosen, 2011). Most patients with symptomatic osteomalacia and rickets have figures for serum 25-hydroxyvitamin D of less than 20 nmol/litre but there is growing evidence that figures between 20 and 50 nmol/litre may be detrimental in other ways.

Radiology of osteomalacia

Patients with osteomalacia may have no radiological abnormality. Overt osteopenia on ordinary X-rays is uncommon. A few patients have pseudofractures (Looser's zones, Milkman's fractures) (*Figure 2*). Pseudofractures can be distinguished from undisplaced true fractures in two ways. While the skeleton may be generally tender there are no localized signs that might have been expected with a true fracture. Second, the appearance of a pseudofracture in serial X-rays does not change unless the patient is treated with vitamin D. While the appearance of pseudofractures may be striking and helpful diagnostically extensive radiology to search for pseudofractures cannot now be justified.

Radiology of rickets

The classical radiological signs of rickets, particularly in the wrists and knees, are well recognized. It is important, however, to be aware of the limitations of radiology in that only a minority of infants with significant vitamin D deficiency have any radiological abnormalities (Root et al, 1980; Ahmed et al, 1995). Even in older children there is no relationship between the radiological signs and the severity of the disorder as measured by serum 25-hydroxyvitamin D (Abdul-Motaal et al, 1985). One factor that can contribute to the discrepancy between radiological and biochemical evidence of vitamin D deficiency in children is the 'paradox of rickets' recognized by earlier authors. The classical radiological signs are not seen in a child who is not growing. As the deficiency worsens, the epiphyseal changes become less obvious.

As in adults with osteomalacia, children with rickets may have pseudofractures which are sometimes misinterpreted as true traumatic fractures (*Figure 3*).

It is probable that subclinical vitamin D deficiency in children leads to diminished bone mineralization as measured by dual X-ray absorptiometry (Winzenberg et

Figure 2. Pseudofracture of left scapula in a 51-year-old woman with osteomalacia found 9 years after a Polya partial gastrectomy. She also had a symmetrical pseudofracture of the other scapula and a fracture of the left pubic ramus.

Figure 3. Pseudofracture of lower right radius in an Asian child aged 18 months. He had other evidence of nutritional rickets.

al, 2011). This is likely to increase fracture risk at the time and in later life. It is important to recognize that assessment of bone density on ordinary radiographs is very unreliable (Mulugeta et al, 2011).

Bone biopsy

At one time bone biopsy, usually from the iliac crest, was regarded as an essential investigation for the diagnosis of osteomalacia. Bone histology, including the use of undecalcified sections for assessing the amount of uncalcified osteoid, was invaluable for confirming the diagnosis. However, with the availability of good biochemical investigations, bone biopsy is no longer needed for the diagnosis of osteomalacia.

Treatment

There is a fair degree of consensus that, in the management of symptomatic osteomalacia, it is important to restore the body stores of vitamin D rapidly. A large number of different regimens have been suggested, both oral and parenteral, and all seem to be effective. The typical amounts of ergocalciferol (vitamin D_2) or colecalciferol (vitamin D_3) suggested are in the range 300 000–600 000 iu (7.5–15 mg). Burns and Paterson (1985) used a single injection of ergocalciferol 600 000 iu (15 mg). Pearce and Cheetham (2010) suggested a daily oral dose of colecalci-ferol 10 000 iu (0.25 mg) over 8–12 weeks. Cipriani et al (2010) used a single oral dose of colecalciferol 600 000 iu (15 mg). Such an approach leads to a rapid improvement in the symptoms (often within 2 weeks), biochemistry and bone density. Serum 25-hydroxyvitamin D levels remain adequate for 6–12 months and toxicity is not seen.

Follow up is important not only to confirm that the patient has responded but also to identify the patient with both vitamin D deficiency and primary hyperparathyroidism. This combination, uncommon in the UK, is quite common in Asia. The serum calcium level may be normal, the serum parathyroid hormone level is often exceptionally high and the bones may be clearly abnormal. Treatment with vitamin D may unmask the hyperparathyroidism as the serum calcium level rises (Hannan et al, 2004).

In the UK at present, there are only limited supplies of ergocalciferol injections BP (300 000 iu). No licenced high-dose preparations of colecalciferol are available. Useful alternatives may be obtained from France, Germany, Switzerland and the United States. Widely available preparations of vitamin D and calcium are licenced in the UK but the amount of vitamin D, usually 400 iu (10 μg), is too low to be of value for treating symptomatic osteomalacia. Such preparations may have limited value in prevention or maintenance. Similarly, multivitamin capsules contain too little vitamin D to be useful. Preparations of vitamin D, including some giving 5000 iu or 10 000 iu, are marketed direct to the public. While such preparations may be valuable for devising a loading regimen, they should not be continued indefinitely because of the danger of vitamin D intoxication.

Various regimens have been suggested for the management of vitamin D deficiency rickets in childhood but, as in adults, it is important to build up body stores quickly. One simple approach is to give ergocalciferol or colecalciferol as a single oral dose of 200 000 iu (5 mg) or more (Holick, 2006). Another is to give a single injection of colecalciferol 10 000 iu/kg (0.25 mg/kg) (Soliman et al, 2010). Both in adults and in children it is reasonable to provide supplementary calcium while the bone disease is healing.

Conclusions

Rickets and osteomalacia are increasingly common today but are probably seriously under-diagnosed. In part this is because they are not considered at all, sometimes because patients may have been given a firm diagnosis of, for example, osteoporosis, arthritis or malignancy, and the symptoms of vitamin D deficiency are ascribed to these disorders. In children with fractures as a result of rickets non-accidental injury may be assumed. This article also outlines the pitfalls in the investigation of patients suspected to have vitamin D deficiency and the various approaches to its treatment. **BJHM**

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KEY POINTS

- Vitamin D deficiency, causing rickets in children and osteomalacia in adults, is common but often unrecognized.
- In adults, factors contributing to failure of diagnosis include a previous diagnosis of osteoporosis, rheumatoid arthritis, osteoarthritis, fibromyalgia or malignancy.
- In children with rickets fractures and pseudofractures may be attributed to non-accidental injury.
- Osteomalacia and rickets as a result of vitamin D deficiency are readily treated with early improvement in the symptoms and biochemistry