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# Nutritional rickets & osteomalacia: A practical approach to management

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Defective mineralization of the growth plate and preformed osteoid result in rickets and osteomalacia, respectively. The leading cause of rickets worldwide is solar vitamin D deficiency and/or dietary calcium deficiency collectively termed as nutritional rickets. Vitamin D deficiency predominates in high-latitude countries in at-risk groups (dark skin, reduced sun exposure, infants and pregnant and lactating women) but is emerging in some tropical countries due to sun avoidance behaviour. Calcium deficiency predominates in tropical countries, especially in the malnourished population. Nutritional rickets can have devastating health consequences beyond bony deformities (swollen wrist and ankle joints, rachitic rosary, soft skull, stunting and bowing) and include life-threatening hypocalcaemic complications of seizures and, in infancy, heart failure due to dilated cardiomyopathy. In children, diagnosis of rickets (always associated with osteomalacia) is confirmed on radiographs (cupping and flaring of metaphyses) and should be suspected in high risk individuals with the above clinical manifestations in the presence of abnormal blood biochemistry (high alkaline phosphatase and parathyroid hormone, low 25-hydroxyvitamin D and calcium and/or low phosphate). In adults or adolescents with closed growth plates, osteomalacia presents with non-specific symptoms (fatigue, malaise and muscle weakness) and abnormal blood biochemistry, but only in extreme cases, it is associated with radiographic findings of Looser's zone fractures. Bone biopsies could confirm osteomalacia at earlier disease stages, for definitive diagnosis. Treatment includes high-dose cholecalciferol or ergocalciferol daily for a minimum of 12 wk or stoss therapy in exceptional circumstances, each followed by lifelong maintenance supplementation. In addition, adequate calcium intake through diet or supplementation should be ensured. Preventative approaches should be tailored to the population needs and incorporate multiple strategies including targeted vitamin D supplementation of at-risk groups and food fortification with vitamin D and/or calcium. Economically, food fortification is certainly the most cost-effective way forward.

**Key words** Calcium - hormone - hypocalcaemic - micronutrient - multivitamin - nutrition - rickets - skin - sunlight - vitamin D

## Introduction

Rickets results from defective mineralization of the growth plate and is invariably seen in growing

children<sup>1</sup>. Osteomalacia, on the other hand, results from defective mineralization of the preformed osteoid and occurs both in adults and children alongside

rickets<sup>1</sup>. The leading causes of rickets and osteomalacia worldwide remain solar vitamin D deficiency and/or nutritional calcium deficiency<sup>2</sup>, collectively termed as nutritional rickets and osteomalacia. Previously, vitamin D deficiency was regarded as the main cause of nutritional rickets with exaggerated disease seen in the presence of concurrent calcium deficiency. However, subsequently, it was uncovered that dietary calcium deficiency in isolation can also result in rickets in the absence of vitamin D deficiency or insufficiency<sup>3</sup>. Rickets can manifest following isolated deficiency of calcium or vitamin D or following combined deficiency/insufficiency<sup>4</sup>. Calcium deficiency predominates in Asian<sup>5,6</sup> and African<sup>7</sup> continents and is mostly attributed to malnutrition and diets poor in calcium. Vitamin D deficiency rickets is on the rise in the developed countries<sup>8-11</sup> due to a multitude of factors such as lack of sunlight<sup>12</sup>, lack of food fortification<sup>13</sup>, ineffective supplementation programmes<sup>14</sup> and global migration trends<sup>15</sup>. While it is relatively straightforward to increase calcium intake in the diet, there is very little vitamin D in diet, and one relies on adequate skin synthesis following exposure to ultraviolet B (UVB) radiation in sunlight. Vitamin D synthesis in skin can be limited due to several factors such as dark skin, high-latitude residence, covered clothing, excessive use of sunscreen and sun avoidance<sup>16</sup>. The latter attributes have led to the resurgence of vitamin D deficiency even in sunshine-abundant countries<sup>17</sup>. However, the most vulnerable groups remain the dark-skinned immigrant and resident population of high-latitude countries<sup>18</sup>, infants<sup>15</sup> and pregnant women<sup>19</sup>, in particular.

### **Vitamin D synthesis, metabolism and terminology**

Vitamin D synthesis and its metabolism pathway towards calcitriol have been described elsewhere<sup>1</sup>. Here, we would clarify specific terminologies relating to various forms of vitamin D as the routine use of the term 'vitamin D' to refer to all its forms (active and inactive) is incorrect and creates confusion. Understanding the terminology has an implication on the choice of drug for the treatment of various forms of rickets.

Vitamin D is synthesised in the skin following sun exposure to UVB radiation at 290-315 nm, hence the terminology 'sunshine vitamin'. Cholecalciferol (vitamin D<sub>3</sub>) is synthesised from 7-dehydrocholesterol. Small amount of ergocalciferol (vitamin D<sub>2</sub>) and cholecalciferol can also be obtained through certain dietary sources (oily fish, eggs, mushrooms and cod liver oil). Both ergo- and cholecalciferol

undergo 25-hydroxylation in the liver to form 25-hydroxyvitamin D (25OHD) or calcidiol. The 25OHD then undergoes 1-hydroxylation in the kidney to form 1,25 dihydroxyvitamin D [1,25(OH)<sub>2</sub>D] or calcitriol<sup>1</sup>. Both calcidiol and calcitriol exist in the D<sub>2</sub> and D<sub>3</sub> forms. Only calcitriol is the active hormone which exerts all its systemic actions by binding to the calcitriol receptor (commonly referred to as the vitamin D receptor). As calcitriol has a very short half-life, calcidiol, which is more stable, is commonly measured to assess the vitamin D status of an individual<sup>1</sup>.

### **Defining vitamin D and calcium deficiency and sufficiency**

The evolving role of vitamin D in non-skeletal effects has led to additional debate about the optimum levels of serum 25OHD. The recommendations for sufficiency levels made by various societies differ. Most recommendations come from studies which have examined the threshold for 25OHD at which rickets<sup>20</sup> and/or secondary hyperparathyroidism<sup>21</sup> occurs. The National Academy of Medicine (previously known as the Institute of Medicine) recommends maintaining 25OHD levels >50 nmol/l (20 ng/ml)<sup>22</sup>. The Endocrine Society, however, defines deficiency as 25OHD levels <50 nmol/l and levels >75 nmol/l (30 ng/ml) are considered sufficient<sup>23</sup>. It is worth noting that there is a lack of consideration of calcium intake in these recommendations, and therefore, a lack of understanding of the pathophysiology of rickets. When setting thresholds for the prevention of nutritional rickets and osteomalacia, it is crucial to assess calcium intake along with vitamin D status as severe deficiency in each in isolation can cause rickets. While 25OHD is a good marker of vitamin D status, serum calcium is a very poor marker of calcium status in the body. The calcium stores in the body, mainly the bones, are exhausted before hypocalcaemia becomes evident. Therefore, evaluation of nutritional rickets is incomplete without an assessment of dietary calcium intake. The evidence-based global consensus recommendations on the prevention of nutritional rickets emphasize on the adequacy of vitamin D and dietary calcium intake and make threshold recommendations for each as detailed in Box I<sup>4</sup>.

### **Pathophysiology of rickets**

Nearly 50-70 per cent of the bone tissue consists of minerals, predominantly calcium and phosphorus<sup>24</sup>. Mineralization of the bone therefore, depends on the availability of adequate calcium and phosphorus and also calcitriol, which is essential for intestinal

**Box I.** Three-stage classification of vitamin D and dietary calcium sufficiency, insufficiency and deficiency

Stage	25OHD	Calcium intake for all individuals >12 months* (mg/day)
Sufficient	>50 nmol/l (20 ng/l)	>500
Insufficient	30-50 nmol/l (12-20 ng/l)	300-500
Deficient	<30 nmol/l (12 ng/l)	<300

\*Calcium requirement of infants aged 0-6 and 6-12 months is 200 and 260 mg/day, respectively. 25OHD, 25-hydroxy vitamin D. *Source:* Ref. 4

absorption of these minerals. Based on the primary aetiology, rickets can be classified as phosphopaenic rickets where there is a lack of phosphate and calcipaenic rickets where there is a lack of calcium supply and/or calcitriol action<sup>1</sup>. Bone mineralization in the growth plate is initiated by a cascade of events triggered by apoptosis of hypertrophic chondrocytes<sup>25</sup>. Availability of phosphate is essential for apoptosis and therefore, hypophosphataemia forms the basis of both phosphopaenic and calcipaenic rickets<sup>26</sup>.

The pathophysiology and clinical manifestations of calcium deprivation and hypophosphataemia as a result of vitamin D and/or dietary calcium deficiency are illustrated in the Figure. In the absence of vitamin D, intestinal calcium absorption is poor. Hence, whether rickets occurs as a result of vitamin D deficiency or dietary calcium deficiency, the ultimate consequence is low availability of calcium. Reduced calcium availability results in a drop in serum calcium, but does not result in immediate hypocalcaemia. When serum calcium drops below the genetically determined set point for the individual, the chief cells in the parathyroid glands will release more parathyroid hormone (PTH) in response<sup>28</sup>. The raised PTH increases renal 1-hydroxylase activity and also the conversion of calcidiol to calcitriol, which, in turn, maximizes intestinal calcium absorption. In addition, the secondary hyperparathyroidism restores serum calcium at the expense of bone damage by mobilizing the stored calcium, through PTH's action on osteoclasts. The raised PTH also conserves renal calcium by reduced calcium excretion but increases phosphate excretion. It is the prolonged phosphaturia and the resultant hypophosphataemia that cause rickets and

osteomalacia, manifesting as rachitic rosary, bowed legs or swollen wrist and ankle joints.

Ultimately, when the compensatory mechanism is exhausted, serum calcium will drop below the normal range, giving rise to hypocalcaemic complications such as seizures, tetany and heart failure due to dilated cardiomyopathy in infants. The body is deprived of calcium stores and bone health is compromised before hypocalcaemia occurs and symptoms appear<sup>29</sup>.

**At-risk groups**

At-risk individuals can be classed into two categories: those at risk of vitamin D deficiency and those at risk of dietary calcium deficiency (Box II).

Individuals with multiple predisposing factors are naturally at the highest risk of rickets and osteomalacia, such as the dark-skinned immigrants residing in high-latitude countries who retain cultural practices such as whole-body clothing, sun avoidance and a diet restricted in dairy products<sup>18</sup>. The South-Asian population in the UK are reported to be at the highest risk of vitamin D deficiency not only due to their skin pigmentation and latitude of residence, but also due to behavioural aspects such as sun avoidance and reduced oral intake of both vitamin D-containing food and supplements<sup>16</sup>. In the UK South Asians, dietary contribution towards vitamin D is reported

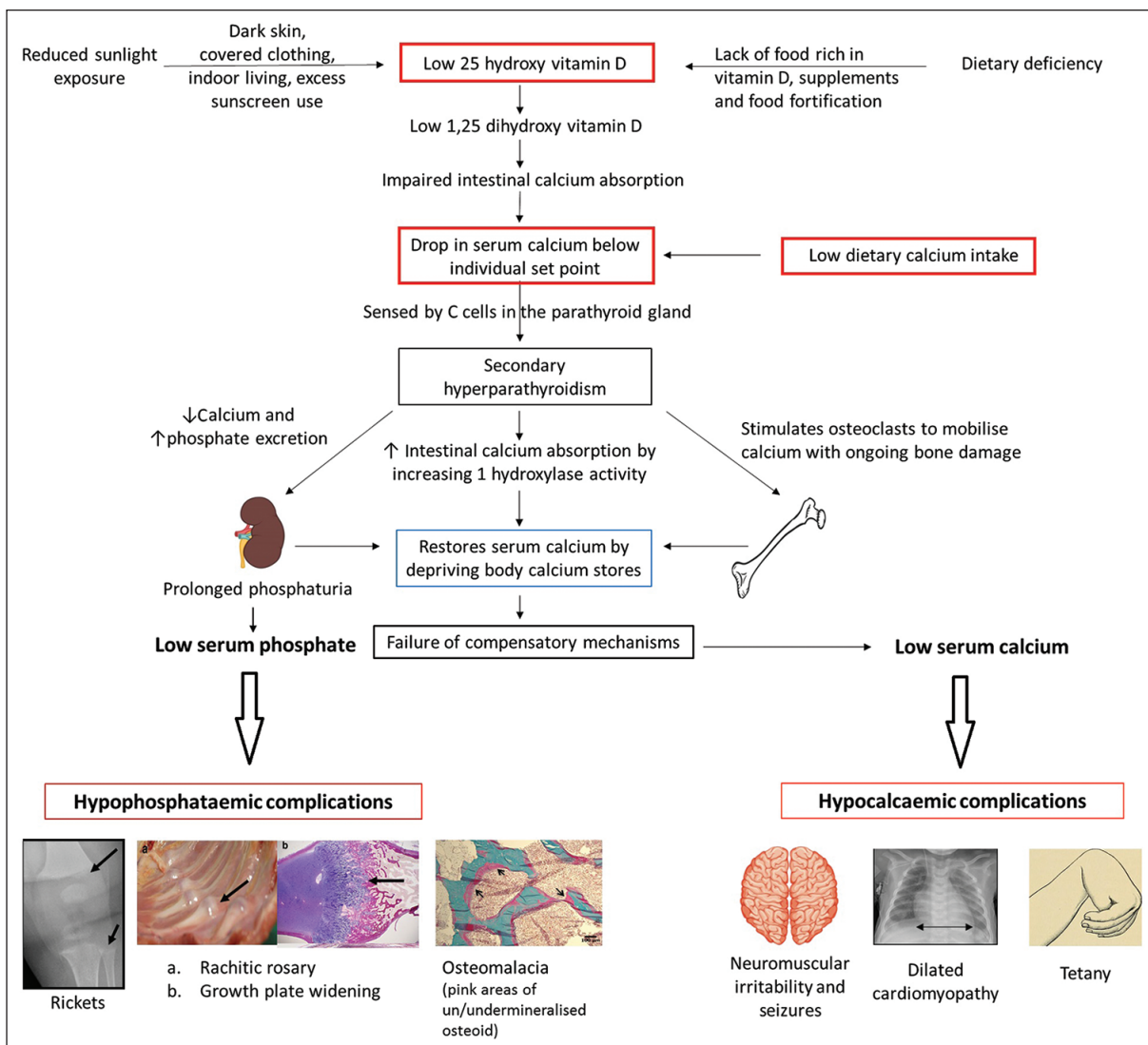
**Box II.** Risk factors for vitamin D and dietary calcium deficiency

Vitamin D deficiency risk	Calcium deficiency risk
<b>Skin pigmentation</b> <sup>30,31</sup> Dark skin produces less vitamin D due to excess melanin which reduces UVB penetration	Dairy restricted diet <sup>34-36</sup> Cultural reasons Food allergies Lactose intolerance Malnutrition
<b>Sun avoidance</b> <sup>16,18</sup> Whole body clothing Excessive sunscreen use Indoor living/ Institutionalization	Malabsorption
<b>Lack of sunlight</b> <sup>32,33</sup> High-latitude residence Environmental pollution	
<b>States of high physiological demand</b> <sup>4</sup> Infancy Pregnancy and lactation Old age	

Individuals with more than one risk factor are at highest risk. UVB, ultraviolet B

to be minimal in comparison to contribution from sun exposure<sup>32</sup>. However, reliability on sunlight is limited due to the long seasonal absence of UVB light (vitamin D winter) and the potential benefits in summer are limited due to darker skin pigmentation<sup>30</sup>. Melanin in skin prevents UVB penetration; therefore, individuals with darker skin require longer duration of exposure compared to those with lighter skin in order to produce the same amount of vitamin D. However, lack of recommendations specific to skin pigmentation and latitude of residence precludes reliability on sun exposure to optimize vitamin D status<sup>31</sup>. Unsurprisingly, vitamin D deficiency in

the UK South Asian population shows very little seasonal variation. A longitudinal study of South Asian residents of childbearing age group in the south of England has reported a high prevalence of severe vitamin D deficiency (25OHD <25 nmol/l) throughout the year; 81 per cent in winter and 79.2 per cent in autumn<sup>32</sup>. The UK South Asian pregnant women compared to their Caucasian counterparts have much lower median (interquartile range Q<sub>1</sub> and Q<sub>3</sub>) serum 25OHD concentrations [15 (10, 23) vs. 38 (27, 59) nmol/l, respectively] and higher median (interquartile range Q<sub>1</sub> and Q<sub>3</sub>) PTH concentrations [7.6 (5.0, 11.0) vs. 3.2 (2.3, 4.5) pmol/l, respectively]<sup>33</sup>.



**Figure.** Pathophysiology of vitamin D deficiency and dietary calcium deficiency. Both aetiologies lead to calcium deprivation, and secondary hyperparathyroidism ensues in an attempt to optimize serum calcium levels. Prolonged calcium deprivation and phosphate loss ultimately manifest in hypocalcaemic and hypophosphataemic complications seen in nutritional rickets. *Source:* Partially adopted from Ref. 27 in accordance with the Creative Commons License (<http://creativecommons.org/licenses/by/4.0/>).



When the vitamin D requirements in pregnancy are unmet, the deficiency state is passed onto the offspring which can manifest as congenital rickets<sup>37</sup> in its most severe form. If the vitamin D stores of an infant born to the deficient mother are not restored through supplementation, rickets and its hypocalcaemic manifestations will ensue<sup>27</sup>. Vitamin D deficiency rickets is more common in infancy and calcium deficiency rickets is more common in childhood<sup>34</sup>, especially in countries with adequate sunlight, such as India<sup>35</sup>. Calcium deficiency in developing countries is attributed to a diet low in dairy products and also partly to a diet rich in phytates and oxalates which reduce calcium bioavailability<sup>36</sup>.

### **Clinical presentation**

The clinical features of rickets and osteomalacia depend largely on the age of presentation<sup>38</sup> and also the severity and duration of deficiency<sup>29</sup>. Symptomatic hypocalcaemia has been reported to peak in infancy and also in adolescence due to high calcium demands during rapid growth<sup>38</sup>. The most recent prospective nutritional rickets survey in the UK reported the highest incidence (n=57/125) in children aged 12-23 months<sup>39</sup>, which correlates with the age group with the lowest reported intake of vitamin D in the UK National diet and Nutritional survey<sup>40</sup>. In the absence of fortified food sources and supplementation with vitamin D, children who are weaned off milk are at a high risk of developing nutritional rickets due to combined deficiency.

### **Neonates and infants**

Infants born to deficient mothers, who are breastfed and unsupplemented, are at highest risk of hypocalcaemic complications in the first few weeks and months of life. Presenting features in the neonatal period include poor feeding, irritability and hypocalcaemic seizures<sup>41</sup>. Rare presentations include apnoea and stridor<sup>38</sup>. Examination may reveal a soft skull (craniotabes) and large fontanelle<sup>42</sup>. Calcium deprivation in the first months of life, despite the same biochemical profile as later manifestations, usually does not manifest in rickets as prolonged hypophosphataemia from high PTH needs to prevail before radiological signs become apparent.

Older infants may present with delayed development, hypocalcaemic seizures or rarely heart failure due to cardiomyopathy<sup>27,43</sup>. Clinical features may include hypotonia, swollen joints (wrist, ankle and costochondral junctions of the rib, also termed rachitic

rosary) and features of heart failure such as tachycardia, tachypnoea, hepatomegaly and oedema. Presence of dilated cardiomyopathy and heart failure is associated with significant morbidity and also risk of death<sup>27,39,43</sup>.

Failure to thrive is not necessarily a feature of nutritional rickets, and adequate growth in some infants may masquerade the underlying bony abnormalities, making the diagnosis less obvious until they present with decompensation<sup>27</sup>.

### **Childhood**

Presentation in this age group may include proximal muscle weakness, delayed development<sup>44</sup>, abnormal dentition<sup>45</sup> and fractures. These are classical clinical signs of rickets and may include swelling of wrists and ankles, rachitic rosary, leg bowing deformities and stunting. It is usual for older children to be incidentally diagnosed<sup>38</sup>.

### **Adolescence**

Due to rapid growth, adolescents are at risk of hypocalcaemic features such as tingling, tetany and seizures<sup>38</sup>. Additional features may include bone pain, muscle weakness and fractures. Similar to adults, bony deformities and radiographic features of rickets and osteomalacia are not evident anymore in adolescents who have completed growth.

### **Adults and old age**

Features of osteomalacia are less obvious and non-specific than those of rickets. Deficiency can manifest as fatigue, bone pain, muscular pain and weakness<sup>46</sup>. Individuals may experience difficulty in rising from seated position, waddling gait, falls and fractures. Diagnosis can often be delayed or missed due to lack of specific clinical features<sup>2</sup>. It is usual for patients to present to neurologists as the clinical features of osteomalacia often mimic myopathies<sup>47</sup>. Because of widespread vitamin D deficiency and the often subtle signs, there is a huge dark figure of risk groups who suffer silently from the disease<sup>2</sup>. Only the most severe cases come to medical attention.

### **Pregnancy and labour**

Although presentation in pregnancy is no different to that in adulthood, the consequences on the offspring can be devastating. The most severe manifestation in the foetus is congenital rickets which is very rare but not unheard of<sup>37,48</sup>. Vitamin D deficiency has been implicated in many pregnancy-related outcomes such as pre-eclampsia, maternal gestational diabetes, pre-term labour

and intrauterine growth retardation<sup>49,50</sup>, some of which are debatable. There is little doubt that maternal vitamin D deficiency has a detrimental effect on the foetal bones and the effects can be long-lasting<sup>51</sup>. Prolonged severe rickets/osteomalacia in young girls during growth can cause obstructed labour in later life, which has been reported to worsen with subsequent pregnancies<sup>52</sup>.

### Practical approach to diagnosis and treatment

#### Diagnosis

A diagnosis of nutritional rickets/osteomalacia is suspected based on predisposing risk factors, dietary history and clinical presentation, and is established on biochemical markers of vitamin D and/or calcium deficiency [high serum PTH and alkaline phosphatase (ALP), low phosphate]. Definitive diagnosis in children requires radiographic confirmation, and diagnosis in adolescents and adults would, in fact, require bone histomorphometric confirmation. Limitations include lack of radiographic changes of rickets in the early stages of the disease and the invasiveness of bone biopsy, which preclude the routine use of histomorphometry in clinical practice.

A practical approach to investigating and treating individuals suspected to have nutritional rickets and/or osteomalacia is outlined in the Table. Assessment of predisposing risk factors (Box II) is crucial in differentiating nutritional and non-nutritional causes of rickets. In Western countries, the majority of infants presenting with hypocalcaemic seizures and rickets are from the high risk background and unsupplemented as detailed before<sup>9,10,27,39</sup>.

Abnormal biochemical markers such as raised PTH and ALP are seen before serum calcium and/or phosphate drop and long before radiographic changes of rickets become evident. In the presence of the above biochemical features, a low serum 25OHD and/or low dietary calcium intake (Box I) strongly suggest a diagnosis of nutritional rickets/osteomalacia. A calcitriol concentration [ $1,25(\text{OH})_2\text{D}$ ] can sometimes be useful in differentiating between vitamin D deficiency (low to normal, occasionally high) and calcium deficiency rickets (high)<sup>54</sup>, provided 25OHD concentrations are adequate.

Rickets is confirmed on radiographs of the knee and/or wrist in the presence of splaying, fraying, cupping, coarse trabecular pattern of metaphyses, widening of the growth plate and osteopenia<sup>4</sup>. Confirmation of osteomalacia requires a bone biopsy. Diagnosis based on a combination of history and non-invasive

investigations is possible but not yet established<sup>2,55</sup>. The classic radiological features of osteomalacia include Looser's zone fractures which occur only at a late stage in the disease course. On iliac bone biopsy, the presence of increased osteoid thickness and osteoid volume and a mineralization lag time of greater than 100 days following tetracycline labelling defines osteomalacia<sup>56</sup>.

Infants are a particularly vulnerable group due to their predisposition to dilated cardiomyopathy. Hence, infants who present with hypocalcaemic seizures which are suspected to be secondary to vitamin D and/or calcium deficiency need thorough investigations to assess cardiac function. Initial investigations should include an electrocardiography to identify arrhythmias and/or prolonged QT interval<sup>27</sup>. A chest radiograph may help screen for possible cardiomegaly and/or pulmonary oedema<sup>27</sup>. Subsequently, an echocardiogram should be performed to look for dilated cardiomyopathy and to assess left ventricular ejection fraction and fractional shortening<sup>27</sup>.

#### Differentials

Making a diagnosis of nutritional rickets is fairly straightforward with a careful history, assessment of risk factors and biochemical markers. Occasionally, presence of PTH resistance and high phosphate can mimic pseudohypoparathyroidism<sup>57</sup>, a feature which can be seen in calcium deficiency<sup>58</sup>. Response to treatment with vitamin D±calcium in the form of improved biochemistry (normalization of calcium, ALP and PTH) and reversal of rachitic changes confirms the diagnosis where there is a doubt. Absence of response to treatment should raise the suspicion of alternative diagnoses such as vitamin D-dependent rickets. Correction of any underlying vitamin D and/or calcium deficiency is important before considering further investigations for alternative diagnoses.

In adults with osteomalacia, elevated PTH introduces the differential of primary hyperparathyroidism for the less experienced. It is, however, important to note that primary hyperparathyroidism is easily distinguishable by high serum and urinary calcium levels in contrast to the normal/low serum calcium seen in osteomalacia. Osteoporosis, which results from an imbalance between bone formation and resorption, is a common differential in old age. In fact, osteomalacia and osteoporosis frequently co-exist. Long-standing undiagnosed and untreated osteomalacia may mimic malignancy and necessitate bone histomorphometry to establish a definitive diagnosis<sup>59</sup>.

**Table.** Practical approach to diagnosis and management in cases of suspected nutritional rickets/osteomalacia

Approach	Findings/Treatment
Suspect nutritional rickets/osteomalacia in	Individuals with risk factors (Box II) presenting with clinical features of: Hypocalcaemia such as seizure, tetany, tingling, cardiac failure due to cardiomyopathy <sup>27</sup> or Hypophosphataemia such as muscle weakness, delayed development, fatigue, hypotonia, bony deformities <sup>29</sup>
Detailed history	(i) Diet history should include feeding mode (breast or fortified or unfortified formula or mixed feed) and weaning in infants, rapid calcium intake assessment <sup>53</sup> (ii) vitamin D or calcium supplement use in the index case, mother and other family members
Investigations	(i) Blood gas: When available, a blood gas analysis can provide immediate information on ionized calcium (usually half of the serum calcium adjusted for albumin) which can help initiate emergency management (ii) Laboratory investigations: Blood: Bone profile (adjusted calcium, magnesium, phosphate, alkaline phosphatase in children and bone-specific alkaline phosphatase in adults), PTH, 25OHD, store sample for 1,25 dihydroxy vitamin D before commencing treatment <sup>1</sup> Urine: Urinary calcium and phosphate excretion can help in differentiating other forms of rickets <sup>1</sup> (iii) Radiographs: Knee and wrist for signs of rickets, chest for cardiomegaly <sup>27</sup> and hip for Looser's zone fractures <sup>2</sup> (iv) ECHO: To assess for hypertrophic cardiomyopathy +/- heart failure in hypocalcaemic infants <sup>27,43</sup> (v) Bone biopsy: Rarely required but may aid in the confirmation of diagnosis in osteomalacia especially when malignancy is a differential <sup>2</sup>
Treatment	Immediate: (i) iv calcium gluconate in symptomatic and oral calcium supplements in asymptomatic hypocalcaemia <sup>27</sup> (ii) Age-appropriate treatment doses of cholecalciferol (D <sub>3</sub> ) or ergocalciferol (D <sub>2</sub> ) pending 25OHD levels <sup>27</sup> (iii) Infants with heart failure should be managed by cardiologists <sup>27</sup> Ongoing: (i) Continue treatment dose D3 or D2 for a minimum of 12 wk if 25OHD deficiency is confirmed <sup>4</sup> (ii) Ensure adequate calcium intake through diet and continue supplements if unable to meet requirement through diet <sup>4</sup> (ii) Alfacalcidol can be used for a brief period of time in patients presenting with profound hypocalcaemia which is slow to respond to oral calcium and 25OHD alone <sup>27</sup> Long term: Ensure ongoing adequacy of both vitamin D and calcium in high risk individuals <sup>4</sup>
Holistic approach	(i) Assess risk factors in family members <sup>27</sup> (ii) Investigate and manage symptomatic family members <sup>27</sup> (iii) Recommend appropriate supplements (D2 or D3±calcium) to all at-risk household members <sup>2,27</sup> (iv) Educate family members on the need for adequate dietary calcium intake, adequate sunlight exposure or supplements or vitamin D-fortified food to meet vitamin D requirements <sup>2</sup>

PTH, parathyroid hormone; iv, intravenous; ECHO, echocardiogram

**Box III.** Vitamin D doses and calcium requirements in the treatment of nutritional rickets/osteomalacia as per the global consensus recommendations on the prevention and management of nutritional rickets

Treatment	Infants	12 months to 12 yr	>12 yr
Daily treatment dose for a minimum of 12 wk (with D <sub>2</sub> or D <sub>3</sub> ) (IU)	2000	3000-6000	6000
Stoss therapy (preferably with D <sub>3</sub> ) (IU)	50,000 only in infants >3 months	150,000	300,000
Calcium through diet or supplements where necessary (mg/day)	200-300	500	500
Minimum prevention dose of daily vitamin D (IU)	400	600	600

Source: Ref. 4

### **Treatment**

Treatment of rickets incorporates treatment doses of vitamin D±calcium (Box III). Both D2 and D3 can be used for daily oral supplementation, however D3 is preferred for stoss therapy *i.e.*, a single high-dose treatment, due to its longer half-life<sup>60</sup>. One study demonstrated that the efficacy and safety of weekly staggered oral doses (60,000 IU for 10 wk) was comparable to that of a single high-dose (600,000 IU) intramuscular injection<sup>61</sup>. Stoss therapy should, however, be restricted to individuals where compliance or follow up is an issue as there is a risk of hypercalcaemia<sup>62</sup>. A minimum of 12 wk treatment is recommended<sup>4</sup>; nonetheless, the duration should be tailored to the individual based on the response to treatment. Calcium (intravenous or oral) is used in the management of children presenting with acute hypocalcaemic complications such as seizures or heart failure. In acute situations, intravenous calcium gluconate bolus followed by an infusion is recommended until serum calcium normalizes<sup>4,27</sup>. Once the child is stable and normocalcaemia is achieved, a switch to oral calcium supplements can be made.

There is absolutely no role for phosphate supplements in the treatment of nutritional rickets; in fact, giving phosphate worsens secondary hyperparathyroidism<sup>63</sup>. Reversal of secondary hyperparathyroidism with vitamin D±calcium supplementation improves serum phosphate levels. Equally, calcitriol or alfacalcidol which is routinely used in the treatment of hypophosphataemic rickets, does not have a role in the treatment of nutritional rickets. Calcitriol is the active form of vitamin D, whereas alfacalcidol is the prohormone of calcitriol which has to undergo further 25-hydroxylation in the liver to form calcitriol. However, long-term use of alfacalcidol is not indicated.

In countries such as India where multiple preparations or combination preparations are available over the counter<sup>64</sup>, clinicians should recommend the most appropriate long-term supplements. A recent report of all the vitamin D supplements (n=258) available in the Indian market highlighted the lack of suitable preparations<sup>64</sup>. The majority of preparations contain calcitriol (n=120, 46.5%) or alfacalcidol (n=111, 43%), whereas cholecalciferol, the preferred treatment, only constitutes a small proportion (n=27, 10.5%)<sup>64</sup>. Of these 10.5 per cent of cholecalciferol preparations, nearly 63 per cent are available in the form of granules in sachets containing high doses of 60,000 IU,

suitable for stoss therapy. Only a few preparations of cholecalciferol are available in lower doses of 10 IU (0.25 µg) to 1000 IU (25 µg) suitable for daily use in the form of tablets or capsules. Very few preparations are available as single constituents. More than 75 per cent of the alfacalcidol preparations also contain added calcium, thereby predisposing to hypercalcaemia in the event of unrestricted and unmonitored use. Nearly 72 per cent of the calcitriol preparations contain zinc or zinc sulphate<sup>64</sup>.

Dilated cardiomyopathy is generally treated with a combination of diuretics and angiotensin-converting enzyme inhibitors but must be managed in conjunction with a paediatric cardiologist.

### **Screening family members**

Children who present with rickets only represent the tip of the hidden iceberg of widespread vitamin D deficiency in a given population. Screening of other family members is crucial to address the hidden crisis. It is almost certain that mothers of infants with nutritional rickets will be vitamin D deficient themselves and a comprehensive screening of other children in the household and any symptomatic adults is crucial to prevent morbidity<sup>27</sup>. Affected family members must be informed and treated as appropriate. Routine testing of asymptomatic individuals is not advisable; instead, appropriate information on diet including fortified food products available, sunlight exposure and supplementation should be provided.

### **Prevention**

Several factors need to be considered when addressing preventative strategies for vitamin D and/or dietary calcium deficiency. Some of the commonly adopted approaches are detailed below:

#### **Supplementation**

Vitamin D supplementation in high risk groups is a way to combat occurrence of nutritional rickets but attention to specific policy features and robust strategies for implementation is obligatory<sup>14</sup>.

#### **Food-based solutions**

Eradication of widespread vitamin D deficiency and achieving vitamin D sufficiency at a population level requires food-based solutions such as: (i) fortification with attention to specific key features, for example: voluntary versus mandatory fortification, dual- versus single-nutrient fortification (vitamin D and/or calcium), and the most appropriate vehicle/s



for fortification; and (ii) biofortification of frequently consumed food products.

### **Combined approach**

In the current climate, a combination of fortification and supplementation of high risk individuals<sup>65</sup> may be the most preferred approach to address both rickets and the vitamin D deficiency pandemic in developed and developing countries alike. Strategies to prevent nutritional rickets and osteomalacia should be tailored to the population and changing demographics of the individual nation. For instance, high-latitude countries with a high proportion of dark-skinned population<sup>18</sup> require robust public health initiatives to safeguard the most vulnerable groups such as immigrants<sup>15</sup>. Lack of mandatory food fortification results in low vitamin D status in the population including women of childbearing age group, which is then naturally passed on to the offspring<sup>66</sup>. A crucial step in the prevention of nutritional rickets worldwide is robust vitamin D supplementation in pregnancy and infancy<sup>67</sup>. Having a policy alone will not suffice<sup>68,69</sup> and its implementation is crucial. Some of the policy factors which are associated with increased adherence to supplementation in Europe include monitoring of supplements at healthcare visits, universal supplementation of both breast- and formula-fed infants, giving information to parents at discharge from neonatal units and providing financial healthcare benefits<sup>14</sup>. These strategies, however, are not suited for low- and middle-income countries where there is a lack of an established healthcare system.

In tropical countries such as Nigeria where calcium deficiency predominates in the presence of adequate sunshine and sun exposure, fortification of food with calcium or promotion of calcium-rich food should be considered<sup>70</sup>. In countries such as India where UVB exposure for skin synthesis cannot be ensured due to high proportion of the population practicing sun avoidance, food-based solutions may be the way forward<sup>71</sup>. A recent health economic analysis demonstrated the cost-effectiveness of food fortification, and the combined approach, with vitamin D supplementation<sup>65</sup>. Food fortification is economically more beneficial<sup>65</sup>.

Choosing the right vehicle/s for fortification is extremely crucial. Vitamin D fortification of milk<sup>72</sup> and other dairy products<sup>73</sup> is a proven strategy<sup>74</sup> to optimize serum 25OHD levels. However, concerns remain in the groups who do not consume adequate dairy<sup>75</sup> and therefore, alternatives such as fortification of wheat flour or multiple food sources<sup>76</sup> may have to

be considered to achieve sufficiency status in the wider population.

In countries where there is a general reluctance to adopt food fortification<sup>18</sup>, biofortification may be more acceptable. Biofortification, also known as bio-addition, involves enhancing the micronutrient content of a crop or food substance. For instance, addition of vitamin D to the livestock has enabled enhancement of the vitamin D content of animal products such as eggs<sup>77</sup> which are now commercially available in the UK supermarkets with no extra cost to the consumer. Consumption of vitamin D-biofortified eggs has been shown to improve vitamin D status in the winter in a small (n=55) randomized controlled trial<sup>78</sup>. Alternatives, such as UV enhancement of food products such as mushrooms and yeast, have been investigated to cater to the vegan or vegetarian consumers; however, the benefits of these approaches are debatable and need further investigation<sup>13</sup>.

Ultimately, most countries may have to adopt more than one approach to eradicate the widespread vitamin D deficiency<sup>12,79</sup>; such as food fortification in conjunction with supplementation of the high risk population<sup>65</sup>.

### **Conclusion**

Vitamin D and/or dietary calcium deficiency remains the leading cause of nutritional rickets worldwide. Life-threatening complications of nutritional rickets are entirely preventable through supplementation of high risk groups, especially pregnant women and infants in the short term and food fortification strategies in the long term. New evidence clearly demonstrates that food fortification works and is not just cost-effective, but cost saving. We call for developing countries to urgently adopt this approach.

**Conflicts of Interest:** None.

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