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Review

Nutritional rickets around the world☆

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ABSTRACT

Nutritional rickets is a major public health problem in many countries of the world. The disease is characterized by deformities of the long bones, enlargement of the wrists and costochondral junctions, hypotonia and, in infants, craniotabes and delayed fontanelle closure. Predominantly caused by severe vitamin D deficiency, rickets can also be associated with hypocalcemic seizures and cardiac failure. First presentation is typically at 6–24 months of age, although hypocalcemia may be evident in younger infants. In many affluent industrialized countries, the prevalence of rickets in the general population diminished after the introduction of clean-air legislation and dietary supplementation. However, in such countries, vitamin-D deficiency rickets has re-emerged in recent years, particularly among groups with limited exposure to UVB-containing sunshine. Infants at risk of rickets tend to be those whose mothers had poor vitamin D status during pregnancy and those exclusively breast-fed for a prolonged period with little skin exposure to UVB. In other countries of the world, the prevalence of rickets can be high, even in regions with abundant year-round UVB-containing sunshine. In general, this is also due to vitamin D deficiency related to limited sun exposure. However, reports from Africa and Asia suggest that there may be other etiological factors involved. Studies in South Africa, Nigeria, The Gambia and Bangladesh have identified rickets in children, typically 3–5 years old at first presentation, in whom plasma 25-hydroxyvitamin D concentrations are higher than those characteristic of primary vitamin D deficiency. Calcium deficiency has been implicated, and in some, but not all, disturbances of phosphate metabolism, renal compromise and iron deficiency may also be involved. Continuing studies of the etiology of nutritional rickets will provide evidence to underpin guidelines for the prevention and treatment of rickets world-wide.

This article is part of a Special Issue entitled 'Vitamin D Workshop'.

Contents

1. Rickets

Rickets is a disease of children characterized by a failure or delay in endochondral calcification of the growth plates of long bones [1]. This results in widening and splaying of the growth plates and leads to enlargement of the wrists and costochondral junctions, and the characteristic deformities of the lower limbs, notably genu varum (bow legs) and genu valgum (knock-knees). Rickets is generally

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Table 1
Classification of rickets by biochemical profile.

Type	Examples	Biochemical profile
Calciopenic	Vitamin D deficiency Dietary calcium deficiency	PCa ↓ PTH ↑ Urinary Ca ↓
Phosphopenic	Urinary phosphate loss with FGF23 abnormalities: Genetic disorders e.g. XLH, ADHR Tumor-associated rickets Urinary phosphate loss without FGF23 abnormalities: Fanconi syndrome Distal renal tubular acidosis Dietary phosphorus deficiency	PPO_4 ↓ PCa ↔ PTH ↔ FGF23 ↑ or ↔ Urinary TmP/GFR: Renal causes: ↓ Dietary phosphorus deficiency/intestinal causes: ↑
Inhibited mineralization	Hereditary hypophosphatasia Aluminum, fluoride toxicities Bisphosphonates (1st generation)	PCa, PPO_4

Table modified from [2], not all the causes of rickets have been included.
PCa: plasma calcium, PPO_4: plasma phosphate, PTH: parathyroid hormone, FGF23: fibroblast factor 23, TmP/GFR: tubular maximum reabsorption of phosphate, XLH: X-linked hypophosphatemic rickets, ADHR: autosomal dominant hypophosphatemic rickets.

accompanied by osteomalacia, i.e. defective mineralization of preformed osteoid in bone, fragility fractures and muscle weakness [2]. Young infants present with craniotabes and delayed fontanelle closure, hypotonia, hypocalcemia, seizures and cardiac failure [1].

Rickets can be classified into three main types depending on the biochemical profile: calciopenic, phosphopenic and inhibited mineralization [2,3], as described in Table 1. Typically, calciopenic rickets is associated with an elevated plasma parathyroid hormone concentration (PTH) in response to low plasma calcium, which results in internalization of phosphate transporters in the kidneys and decreased renal phosphate reabsorption. Phosphopenic rickets is associated with a chronically low plasma phosphate with normal PTH and results from increased production or gain-of-function of FGF23, a phosphaturic hormone, or from renal disorders that compromise phosphate reabsorption. In both cases the result is urinary phosphate loss and hypophosphatemia, leading to reduced apoptosis of hypertrophic chondrocytes in the growth plate and rickets. The third category, inhibition of mineralization, refers to rickets where the mineralization process in the growth plate is directly affected and typically the plasma concentrations of calcium and phosphate are normal. There are a variety of underlying causes responsible for the various forms of rickets, including genetic disorders, such as autosomal dominant hypophosphatemic rickets (ADHR) and X-linked hypophosphatemic rickets (XLH), tumors, organ malfunction, drugs and exposure to toxic agents such as aluminum and fluoride. This review will focus on rickets of public health concern caused by nutritional deficiencies, referred to as 'nutritional rickets'.

2. Rickets prevalence world-wide

Rickets was common in Europe until the mid- 20th century and was known as "The English Disease" because of its high prevalence in England. The seminal work of pioneers such as Harriette Chick and Elsie Dalyell demonstrated that this was due to vitamin D deficiency [4]. In their studies in a children's hospital in Vienna immediately after World War I, they demonstrated that rickets could be prevented and cured by being in the sunlight outdoors, in the summer not winter, or by exposure to mercury vapour quartz lamp and by cod liver oil, which is now know to contain cholecalciferol, vitamin D_3. Studies by Hume and Steenbock in rats further demonstrated the antirachitic activities of UVB radiation and some irradiated foods, now known to contain ergocalciferol, vitamin D_2 [4].

Since the 1950s, rickets has become far less common in the UK as a result of clean air legislation, food fortification and public awareness [5]. The National Diet and Nutrition Surveys and other data from the UK, however, have shown that sub-groups of the population in the UK continue to be at increased risk of vitamin D deficiency, particularly among its substantial South Asian ethnic minority [5–7]. These people, or their forebears, originally migrated from India, Pakistan and Bangladesh and often retain the close family networks and traditional diet and clothing customs of South Asia. In recent years, a resurgence of rickets cases has been reported from the major cities in the UK and other Northern European countries particularly among children from families of South Asian, African, Afro-Caribbean or Middle-Eastern origin [8–10]. Commonly, affected children are reported to be dark-skinned, to have had limited opportunities for skin UVB exposure, were born to mothers who were likely to have had poor vitamin D status during pregnancy, were exclusively breast-fed for an extended period and weaned onto poor diets [3].

There are currently no national statistics on the prevalence of nutritional rickets in the UK but there is considerable concern that this is a widespread problem despite public health recommendations for pregnant women, children and those with restricted sunshine exposure to consume a daily vitamin D supplement [5]. In Denmark, another northern European country with a sizeable immigrant population, a population-based retrospective estimate of the burden of nutritional rickets from medical records has confirmed a higher incidence of nutritional rickets among ethnic minorities, most commonly children of parents originating in Africa and the Middle East [11]. The recorded annual incidence in 1995–2005 among ethnic Danish children aged 0–2.9 years was 2.0 per 100,000 per year (less than the incidence of hereditary rickets of 4.3 per 100,000 per year) while that among those from immigrant families born in Denmark was fifty times greater at 100 per 100,000 per year.

Understandably, much of recent literature on the prevalence of nutritional rickets has come from those industrialized countries experiencing a resurgence of clinic presentations with rickets. However, the greatest burden of disease world-wide appears to be in Africa, the Middle East and Asia [2,6,12], where prevalence rates of 10–70% have been reported, as summarized in Table 2. It is difficult to compare such reported prevalence rates directly because of the different methodologies employed. Many of the estimates are based either on population surveys that recorded the presence of bone deformities and other signs consistent with rickets or on hospital records of rickets among patients admitted to hospital with acute diseases such as pneumonia (Table 2 [2,13–19]). This contrasts with clinic-based records of radiographically-confirmed rickets in countries where children in the general population have ready access to routine health-care. Some more recent estimates from Asia and Africa that have combined population surveys with confirmation by physician examination or X-rays have reported somewhat lower prevalence rates [20–22]. However, even the most conservative estimates provide evidence that prevalence rates in these countries are greater than in Western countries and are of a magnitude that represents a global public health concern.

3. Causes of nutritional rickets world-wide

Vitamin D deficiency appears to the major factor underlying nutritional rickets in many countries world-wide [23,24], even