

Review Article

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Overview of epidemiology and management of rickets among children in Saudi Arabia

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Abstract

Rickets is a common bone disease worldwide that is associated with disturbances in calcium and phosphate homeostasis and can lead to short stature and joint deformities. The study aimed to summarize the updated evidence as regards: Epidemiology, risk factors, etiology, pathophysiology, clinical manifestation, diagnosis and management. Rickets can be diagnosed based on history and physical examination, radiological features, and biochemical tests. The acquired rickets (nutritional) is the most common cause of rickets among children in Saudi Arabia which is due to vitamin D deficiency. Risk factors include, exclusively breast fed, immigrant adults in industrialized countries, decreased exposure to sunlight, use of sunscreen, old age of the housebound, morbid obesity and certain medications. Treatment strategies of rickets depend on the underlying etiology. There are several regimens utilized to treat rickets, all of them comprise some form of vitamin D administration and presence of adequate calcium and phosphate levels.

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Introduction

Rickets is a common bone disease worldwide that is associated with disturbances in calcium and phosphate homeostasis and can lead to short stature and joint deformities. Rickets can be diagnosed based on history and physical examination, radiological features, and biochemical tests. Rickets could be inherited or acquired. The acquired rickets (nutritional) is the most common cause of rickets worldwide [1]. The spectrum of presentation varies from being asymptomatic to irritability, growth retardation, and sudden death. In order to avoid long term complications, rickets must be promptly diagnosed and aggressively treated [2]. Public health research has identified traditional diets low in calcium, dark skin and cultural full body clothing, as the predominant causes of rickets in sunny parts of the world such as the Middle East and Africa. In high Northern

or Southern latitudes (more than approximately 34°), it is the seasonal lack of the ultraviolet-B (UV-B) spectrum of sunlight that causes seasonal vitamin D deficiency (also called 'vitamin D winter'). In high latitude countries, the dark-skinned immigrant and resident population is at greatest risk [3].

In most developing regions worldwide, nutritional rickets is a prominent health problem probably because the risk factors still operate. In the Kingdom of Saudi Arabia, despite having economic affluence and adequate sunshine all year round, Vitamin D deficiency is fairly common in infants, children, adolescents, as well as pregnant and lactating mothers [4]. Vitamin D is a prohormone that is essential for normal absorption of calcium from the gut, and deficiency of vitamin D is usually more common than either isolated calcium or phosphorus deficiency and is the commonest cause of rickets. Rickets can cause an

effect to the children growth and cause an impaction on their later life [5]. Identifying the prevalence of rickets in Saudi Arabia and comparing it with other countries can bring useful information about it in reaching the causes, risk factors and prevention methods that have been done in the community to avoid it. The prevalence of the disease has increased in both developed and developing countries. Yet, generally speaking, the prevalence of rickets is higher in developing countries than in developed countries [6].

Objectives

The study aims to summarize the updated evidence regards: epidemiology, risk factors, etiology, pathophysiology, clinical manifestation, diagnosis and management.

Epidemiology

The acquired rickets (nutritional) is the most common cause of rickets among children in Saudi Arabia which is due to vitamin D deficiency.

The prevalence of rickets has increased in both developed and developing countries. Yet, generally speaking, is higher in developing countries than in developed countries [7]. African, Middle Eastern, and Asian countries have a wide prevalence rate of 10% to 70%.

A cross-sectional study on knowing the prevalence of rickets among children living in Saudi Arabia was carried out on 864 participants within different social media platforms during the period from February to April 2018. Results: 15.3% of the children were diagnosed with rickets, 50.5. % of the diagnosed children was between the ages of 1 to 5 years [8]. Regarding risk factors, 41.9% of the children drink soft drinks and 15.4% of them were obese. Only 55% of the participants breast fed their children, 35.9% of the participants know what rickets is, 45.3% ask for medical help once their child has been diagnosed and 70.5% of the participants thought that vitamin D can prevent rickets [9]. At the end of this study, there were an increased number of children that have been diagnosed with rickets in Saudi Arabia.

Risk factors

Factors that can increase a child's risk of rickets include:

Dark skin, which has more of the pigment melanin, which in turn lowers the skin's ability to produce vitamin D from sunlight. The source of vitamin D during fetal life and in the postnatal period is through placental passage, mother's milk. Vitamin D levels in infants correlate with vitamin D levels in their mothers during the first 2 months of life [10]. Diet and sunlight determine the levels in the later months and years of life. Based on these facts, the insufficiency of vitamin D storage in mothers as well as exclusive breastfeeding without vitamin D supplementation constitute important risks for nutritional rickets in early life [11].

Premature birth, babies born before their due dates tend to have lower levels of vitamin D because they had less time to receive the vitamin from their mothers in the womb.

Medications: Certain types of anti-seizure medications, Phosphate – binding antacids (e.g. aluminum hydroxide) and

antiretroviral medications, used to treat HIV infections, appear to interfere with the body's ability to use vitamin D [12].

Etiology

Vitamin D deficiency is, by far, the most common cause of nutritional rickets. In patients with a history of extensive burn injuries, vitamin D synthesis in skin is below normal, even with sun exposure. Vitamin D plays an essential role in skeletal health by regulating normal blood levels of calcium and phosphorus [13]. There are two main forms of vitamin D: vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol). Vitamin D₂ is primarily derived from plant sources. In addition to being present in foods such as fish, eggs, milk, and cod liver oil, the synthesis of vitamin D₃ occurs naturally through the conversion of dehydrocholesterol to cholecalciferol in the skin by sunlight (ultraviolet B in the 290–315-nm range) [14]. Vitamin D binds to the vitamin D binding protein and is transported to the liver for hydroxylation, and converted by 25-hydroxylase into calcidiol which is then absorbed in the proximal tubule of the kidney through the endocytic receptors megalin and cubilin and hydroxylated by the enzyme 1 alpha-hydroxylase to form the active metabolite of vitamin D, calcitriol. 1,25-dihydroxy vitamin D acts on the vitamin D receptor in intestinal cells to increase the gut absorption of calcium by upregulating the calcium channel [15]. There is a complex interaction between the hormones produced by the kidneys (1,25 dihydroxy vitamin D), bone (FGF-23), and PTH. Understanding these interactions is essential for proper management of rickets and/or osteomalacia [16]. Other less frequent causes of rickets include genetic causes, and rickets secondary to liver diseases.

Based on the biochemical profile, rickets can be classified into calcipenic, phosphopenic, and rickets due to inhibited mineralization.

Deficiency of calcium results in calcipenic rickets, and vitamin D deficiency is the most common etiology for calcipenic rickets. Calcipenic rickets may result from inadequate dietary calcium intake, which is reported in a few developing countries [17]. Calcipenic rickets may also result from poor calcium absorption, such as in children with malabsorption syndromes, especially celiac disease and cystic fibrosis. Rickets can be the first presenting manifestation in patients with celiac disease. Additionally, calcipenic rickets may result from a genetic defect of vitamin D metabolism, either from a failure of vitamin D to switch to its active form (1,25-dihydroxy vitamin D) or due to end-organ resistance [18]. Low serum calcium is a common phenomenon in calcipenic rickets that stimulates the secretion of Parathyroid Hormone (PTH), which may result in the normalization of serum calcium. In the long term, this secondary hyperparathyroidism results in the internalization of sodium-dependent phosphate co-transporter proteins in the renal tubules. Subsequently, it causes renal phosphate loss and hypophosphatemia.

Phosphopenic rickets, on the other hand, is caused by conditions that cause chronic low serum phosphate levels, either from impaired intestinal absorption or, more commonly, from increased renal loss. Phosphate is abundant in our regular food, so phosphate deficiency does not usually occur from dietary insufficiency in healthy individuals. In premature children, dietary phosphate deficiency can result in osteopenia of prematurity. Low serum phosphate levels occur in conditions that increase

the production or decrease degradation of fibroblast growth factor 23 (FGF23), a hormone that reduces the reabsorption and increases the excretion of phosphate in the renal tubules [19]. Increased urinary phosphate loss due to mutations that cause inactivation of sodium-dependent phosphate transporters in the kidneys. Both conditions increase the urinary phosphate loss resulting in chronic hypophosphatemia. Both calcipenic rickets and phosphopenic rickets are characterized by hypophosphatemia, which eventually causes the clinical and radiological bone changes characteristic of rickets (rachitic changes) [20].

Pathogenesis

The osseous tissue in the growing long bones is created from the cartilage by a process called endochondral ossification. The chondrocytes in the cartilage grow to form the hypertrophic chondrocytes, which then start producing the cartilage matrix. This cartilage matrix is then calcified, which is reabsorbed and replaced with woven bone, which is later replaced by mature lamellar bone [21]. In these processes, there is a formation of unmineralized bone tissue (osteoid), and the osteoid is mineralized in the presence of adequate calcium and phosphate levels. Any defect in osteoid mineralization may cause rickets. In all types of rickets, the characteristic features occur at the growth plate. Calcium and phosphorus are required for the normal matrix mineralization. Reduction in these minerals causes abnormal mineralization. Normal serum calcium levels require sufficient dietary calcium intake, normal calcium absorption through the gastrointestinal tract, and adequate active form of vitamin D.

Diagnosis

Detailed history and a thorough physical examination are essential to diagnose patients with rickets. History should include the gestational age of the child, details of sunlight exposure, dietary history including intake of supplements, developmental/growth history, and pertinent family history [22]. Positive family history of skeletal abnormalities, stunted growth, alopecia, dental abnormalities, and parental consanguinity may suggest a genetic cause of rickets. Physical examinations should include detailed skeletal examination (with attention to any tenderness, deformities, softening, asymmetry, and neurological abnormalities) as well as a detailed dental evaluation. History and physical examination usually give clues to diagnose rickets. However, the absence of clinical signs of rickets doesn't exclude this diagnosis, especially in the early stages [23].

The clinical manifestations of rickets are variable based on the underlying etiology, severity, and duration of the disease. Rickets is frequently noted in children between 6 months to 2 years of life. Children frequently have some osseous clinical manifestations (often noted at the sites of rapid bone proliferation) such as:

1. Chest, ricketic rosary due to the widening of the costochondral junction, pigeon chest, and Harrison's groove (a depression at the lower side of the ribcage that occurs as the diaphragm pulls the soft ribcage at its insertion site) [24].
2. Skull, Craniotabes, which is softening of skull bone, seen in infants older than three months of age. Frontal bossing, and wide fontanels are noted.
3. Extremities, mainly during infancy, may present with deformities of the weight-bearing limbs that mostly involve the

rapidly growing bones. The crawling infants may present with upper limb deformities [25]. However, when the child starts walking, the deformities are noticed in the lower limbs. The potential lower limb deformities include bow legs (genu varus), knock knees (genu valgus), and joints (knees and ankles) swelling, whereas the deformities of the upper limbs include the wrist widening. The ulna grows relatively rapidly and hence it is significantly affected [26].

If the rickets is clinically suspected, biochemical tests and radiological images are the next steps to confirm the diagnosis.

Laboratory investigations

The most important laboratory marker to diagnose the rickets is serum alkaline phosphatase (ALP), which is typically high as this is a disease of abnormal mineralization and increased osteoblastic activity [27].

Serum 25-hydroxyvitamin D level is another laboratory marker that helps to diagnose rickets, especially the nutritional deficiency of vitamin D.

Measuring urine phosphate is helpful in evaluating the renal loss of phosphate in the genetic forms of hypophosphatemic rickets and other conditions such as Fanconi syndrome associated with phosphaturia [28].

Other biochemical investigations include blood urea nitrogen (BUN)/creatinine levels to screen for renal status, and liver enzymes to screen liver function.

Imaging

The radiological images should include the distal ends of rapidly growing bones in upper and lower extremities, and additionally, ribcage images are helpful as well. The appearance of radiolucent lines at the conjunction between epiphysis and metaphysis and widening of the epiphyseal plate, due to the accumulation of non-mineralized osteoid, is the earliest radiological change [29]. Rachitic changes also include the cupping, splaying, fraying, and trabecular formation of the metaphysis. The epiphyseal center formation may be delayed or appear small. The cortex of the bones may be thin and osteopenic. Chest images show rachitic rosary and widening of costochondral junctions. Angular deformities, along with pathological fractures of the upper and lower limb bones, may be noted in advanced stages [30].

Treatment and management

Treatment strategies of rickets depend on the underlying etiology. There are several regimens utilized to treat rickets, all of them comprise some form of vitamin D administration, vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol), with subsequent monitoring for healing. The intensive phase of vitamin D treatment is given for two to three months in conjunction with calcium supplementation (500 mg either through diet or by supplements) for children who have insufficient dietary calcium [31].

The dosing scheme recommended for treatment of vitamin D deficient rickets is 1000 IU daily for newborns <1 month, 1000–5000 IU daily for infants 1–12 months old, and 5000–10,000 IU daily for children 1 year and older. Treatment is continued until there is radiographic evidence of healing; subsequently, the dose of vitamin D is reduced to 400 IU daily [32]. Calcium intake should be maintained at approximately 1000

mg/day (30–75 mg/kg of elemental calcium per day in three divided doses) to avoid “hungry bone” syndrome (worsening hypocalcemia after the start of vitamin D therapy). This leads to resolution of the biochemical and radiological abnormalities within 3 months [33]. Skeletal deformities regress completely after medical therapy. However, orthopedic intervention can be done if deformities do not improve even after radiologic appearance of the growth plates has normalized. An alternative protocol is “stoss therapy,” which consists of a high dose of oral vitamin D (600,000 IU) given on a single day, then maintained at 400–1000 IU of vitamin D per day, or 50,000 IU of vitamin D2 weekly for 8 weeks orally (teenagers) followed by 400 IU/day [34]. This amount of vitamin D approximately corresponds to a 3-month course of 5000 IU/day and should be sufficient to induce healing within 3 months. High-dose vitamin D may need to be intermittently repeated (usually every 3 months) if poor compliance persists. Stoss therapy is useful when compliance is a problem. However, such high doses of vitamin D can lead to hypercalcemia. Doses of 150,000 or 300,000 IU are equally effective with lesser side effects [35].

Conclusion

Rickets is a common bone disease worldwide that is associated with disturbances in calcium and phosphate homeostasis and can lead to short stature and joint deformities. Rickets can be diagnosed based on history and physical examination, radiological features, and biochemical tests. The acquired rickets (nutritional) is the most common cause of rickets among children in Saudi Arabia which is due to vitamin D deficiency. Vitamin D is a prohormone that is essential for normal absorption of calcium from the gut, and deficiency of vitamin D is usually more common than either isolated calcium or phosphorus deficiency and is the commonest cause of rickets.

Risk factors include, exclusively breast fed, immigrant adults in industrialized countries, decreased exposure to sunlight, use of sunscreen, old age, housebound, morbid obesity and certain medications. Rickets develops on top of unmineralized bone tissue (osteoid) due to deficiency of calcium results in calcipenic rickets or chronic low serum phosphate result in phosphopenic rickets. Treatment strategies of rickets depend on the underlying etiology. There are several regimens utilized to treat rickets, all of them comprise some form of vitamin D administration and presence of adequate calcium and phosphate levels.

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