NUTREATION RECKITS: TREATMENT AND PREVENTION

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ABSTRACT

Vitamin D and calcium deficiencies are common worldwide, causing nutritional rickets and osteomalacia, which have a major impact on health, growth, and development of infants and children. Rickets is a bone disease that is associated with decreased serum calcium and/or phosphate levels in the blood, leading primarily to widening and delay of mineralization of growth plates in bones. Rickets is also associated with osteomalacia, which is characterized by a delay in the mineralization of bone matrix. Rickets can be caused by deficiencies of vitamin D, calcium or phosphate attributable to nutritional or environmental causes (that is, nutritional rickets). Nutritional rickets is the most common type of rickets globally, disabling childhood condition of impaired bone mineralization at the growth plate and bone-forming surfaces owing to inadequate availability of calcium or phosphorus. While it is found globally, the a etiology of nutritional rickets varies geographically.

Keywords: *vitamin D, calcium, nutritional rickets.*

AIM OF STUDY

A systematic literature search examining the definition, diagnosis, treatment, and prevention of nutritional rickets in children.

METHODS

PubMed , Medline and google scholar were searched for studies on nutritional rickets in English within the past 10 years (January 2010 to December 2020).

INTRODUCTION

Rickets is a bone disease that is associated with decreased serum calcium and/or phosphate levels in the blood, leading primarily to widening and delay of mineralization of growth plates in bones.[1] Rickets is also associated with osteomalacia, which is characterized by a delay in the mineralization of bone matrix. Rickets can be caused by deficiencies of vitamin D, calcium or phosphate attributable to nutritional or environmental causes (that is, nutritional rickets) or by mutations in genes encoding proteins involved in vitamin D activation and function, phosphate homeostasis and/or bone mineralization (that is, heritable rickets); rickets can also be the consequence of acquired defects in vitamin D metabolism (such as in severe liver disease) or renal tubular handling of minerals (which may occur with a number of drugs).Nutritional rickets is the most common type of rickets globally.[2]

--Nutritional rickets

Is a disabling childhood condition of impaired bone mineralization at the growth plate and bone-forming surfaces owing to inadequate availability of calcium or phosphorus. While it is found globally , the a etiology of nutritional rickets varies geographically [Table3]. Nutritional rickets in temperate countries is typically caused by vitamin D deficiency, having been born to a vitamin D-deficient mother, being exclusively breastfed without vitamin D supplementation, and/or having poor vitamin D intake, insufficient sun exposure, living in countries of high latitude, or practising customs which prevent adequate exposure to the sun.[3] Particular groups of children, such as those with darker skin, malabsorptive disorders such as coeliac disease and cystic fibrosis, or those with decreased synthesis or increased degradation of vitamin D secondary to liver disease or certain drugs, are at additional risk. Vitamin D deficiency as a cause of nutritional rickets in children typically presents between 3 and 18 months of age. Worldwide, dietary calcium deficiency plays a very important role in the development of nutritional rickets, especially in low- and middle-income countries (LMIC) in Asia and Africa. In children, this is typically related to a limited or absent intake of dairy produce. Low-calcium diets also tend to be higher in grains containing phytates, which may reduce calcium bio-availability. Nutritional rickets owing to calcium deficiency typically presents later than nutritio-nal rickets caused by vitamin D deficiency – at 1–16 years of age.[4]The primary cause of vitamin D deficiency usually involves interplay of nutritional inadequacy and lack of sunlight exposure with overlapping contributions by cultural, environmental, and genetic factors. [Table 1]. [5]

SOURCES AND METABOLISM OF VITAMIN D

Vitamin D plays an essential role in skeletal health by regulating normal blood levels of calcium and phosphorus [Figure 1].[5,6] There are 2 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). Vitamin D binds to the vitamin D binding protein and is transported to the liver for hydroxylation, and converted by 25-hydroxylase (encoded by CYP2R1, Cytochrome P450 Family 2 Subfamily R Member 1) into calcidiol (also known as hydroxyl-cholecalcifero l,25-hydroxyvitamin, calcifediol) which is then absorbed in the proximal tubule of the kidney through the endocytic receptors megalin and cubilin.[7] and hydroxylated by the enzyme 1 alpha-hydroxylase (encoded by CYP27B1, Cytochrome P450 Family 27 Subfamily B Member 1) to form the active metabolite of vitamin D, calcitriol (also known as 1,25-dihydroxy vitamin D).[8] 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, TRPV6 (Transient receptor potential cation channel subfamily V member 6).[5] As shown in , 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.

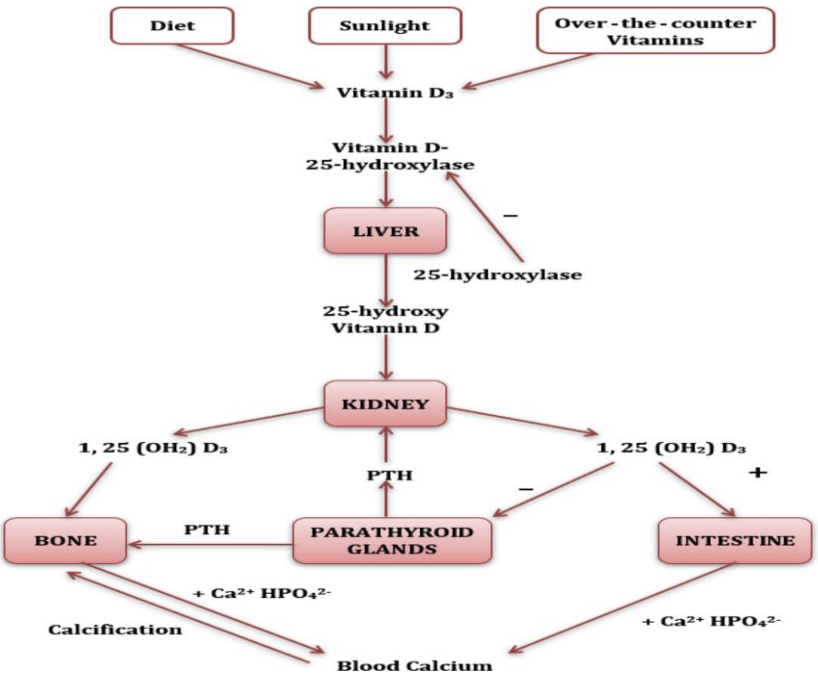

Figure 1. Sources and metabolism of vitamin D. PTH, parathyroid hormone

NUTRITIONAL AND ENVIRONMENTAL CAUSE

The central abnormality common to the two major causes of nutritional rickets (that is, dietary calcium deficiency and vitamin D deficiency) is an inability to absorb sufficient dietary calcium to meet the requirements of the growing skeleton.[9] The morbidity and mortality associated with NR can be devastating, with substantial but poorly recognized consequences for society and health economics. Features of NR and osteomalacia include: 1) hypocalcemia seizures and tetanic spasms; 2) life-threatening hypocalcemic cardiomyopathy; 3) bone pain and muscle weakness; 4) limb and pelvic deformities; 5) failure to thrive; 6) developmental delay; and 7) dental anomalies.[10,11]Alarmingly, NR can also lead to death from heart failure caused by hypocalcemia cardiomyopathy, even in developed countries.In addition, narrowing of the pelvic outlet after NR in childhood can result in obstructed labor and maternal and fetal death.[12] Trauma is one of the most important causes of mortality and morbidity in children.[13] The clinical features and consequences of NR are broad and potentially severe [Table5].[14].

The **diagnosis** of rickets is based on a history of poor vitamin D intake and little exposure to direct ultraviolet sunlight. The serum calcium usually is normal but may be low; the serum phosphorus level usually is reduced, and serum alkaline phosphatase activity is elevated. When serum calcium levels decline to less than 7.5 mg/dL, tetany may occur.Levels of 24,25-(OH)2-D are undetectable, and serum 1,25-(OH)2-D levels are commonly less than 7 ng/mL, although 1,25-(OH)2-D levels also may be normal. The best measure of vitamin D status is the level of 25-(OH)-D. Characteristic **radiographic** changes of the distalb ulna and radius include widening; concave cupping; and frayed, poorly demarcated ends. The increased space seen between the distal ends of the radius and ulna and the metacarpal bones is the enlarged, nonossified metaphysis.[15].

MANAGEMENT OF NUTRITIONAL RICKETS

The Global Consensus group recommended doses of vitamin D and calcium for treatment of NR. Evidence indicates that the oral route is preferred to parenteral (Stoss therapy)due to more rapid restoration of 25OHD levels. Both vitamin D2 and D3 are equally effective for daily treatment, whilst D3 with a longer half-life is preferred for single dose treatment.All children with NR should be treated with vitamin D for a minimum of 3 months with a daily dose of at least 2000 IU (50 μg) if aged <12 months, 3000–6000 IU (50–150 μg) if aged 12 months–12 years, and 6000 IU (150 μg) if aged >12 years[Table 2].[16] Single high dose (Stoss therapy) can be used in resource-limited settings in infants aged >3 months: 50,000 IU (1250 μg) for 3 months–12 months of age, 150,000 IU (3750 μg) for children aged 12 months– 12 years, and 300,000 IU (7500 μg) if aged >12 years.[16] All individuals should also receive concomitant calcium (minimum 500 mg/day) as supplements or via diet. All treatment should be followed by lifelong vitamin D supplements, since the underlying risk (ethnicity, culture and sunlight exposure) is unlikely to change.

PREVENTION OF NUTRITIONAL RICKETS

The prevention of nutritional rickets is potentially achievable by three mechanisms these being sunlight exposure, food fortification and vitamin D supplementation. Although many guidelines on prevention of Vitamin D deficiency recommend “safe sunlight exposure” it is often not clearly defined. However none of the South Asian subjects were able to achieve such a level and they would require a fourfold longer duration ie two hours three times per week. It is clear that reliance on sunlight exposure would not be adequate for many ethnic groups. Food fortification has been shown to be an effective strategy for improving Vitamin D Status.[17].

Table 1. Severity of 25 (OH) vitamin D deficiency

Vitamin D status	ng/ml
Deficiency	<30
Insufficiency	30–50
Adequate	>50
Toxicity	>250

Table 2. Treatment doses of vitamin D and calcium for nutrition rickets*.

Age	Vitamin D Daily dose for 90 days, IU	Vitamin D Single dose, IU	Vitamin D Daily maintenance dose, IU	Calcium mg/day
<3m	2000	N/A	400	500
3-12m	2000	50 000	400	500
>12m-12y	3000-6000	150 000	600	1000
>12y	6000	300 000	600	100

Table 3. Vitamin D *vs* calcium-predominant rickets.

Primary deficiency	Vitamin D	Calcium
Peak age	3–18 months	1–16 years
Risk factors	• Lack of supplementation for the breastfeeding Infant • Restricted diet • Insufficient sunshine exposure • Darker skin pigmentation • High latitude• Full-body clothing cover • Maternal deficiency	• Poverty, malnutrition • Competing dietary phytate and oxalates • Extended breastfeeding without complementary calcium-containing foods (extended breastfeeding may be modestly protective if no other calcium food sources are available)
Regions of highest prevalence	North America, South America, Europe, parts Of the Middle East	Africa, South-east Asia, parts of the Middle East
25(OH)D levels	Very low [<31 nmol/L (<12.5 ng/mL)]	Normal/low
1,25(OH)2D levels	Low/normal/high	Normal/high/very high
Prevention strategy	(1) Infant vitamin D supplementation birth to 12 months, longer for children at risk (2) Vitamin D food fortification programmers (3) Sunshine exposure when appropriate	(1) Adequate dietary calcium (200 mg/day0–6 m; 260 mg/day 6–12 m; 500 mg/ day > 12 m) (2) Staple food fortification, or supplementation if diet insufficient (3) Introduction of complementary foods

Table 4. Normal age-based serum calcium and phosphorus levels in Children.[5]

Age	Age-based serum calcium (mg/dl)	Age-based serum phosphorus (mg/dl)
0–3 mo	8.8–11.3	4.8–7.4
1–5 yr	9.4–10.8	4.5–6.5
6–12 yr	9.4–10.3	3.6–5.8
13–20 yr	8.8–10.2	2.3–4.5

To convert units: calcium 1 mg/dl ¼ 0.25 mmol/l; phosphorus 1 mg/dl ¼ 0.32 mmol/l.

Table 5. Clinical Features Associated With Nutritional rickets

Osseous signs and symptoms
Swelling wrists and ankles
Delayed fontanelle closure (normally closed by age 2 y)
Delayed tooth eruption (no incisors by age 10 mo, no molars by age 18 mo)
Leg deformity (genu varum, genu valgum, windswept deformity)
Rachitic rosary (enlarged costochondral joints—felt anteriorly, lateral to the nipple line)
Frontal bossing
Craniotabes (softening of skull bones, usually evident on palpation of cranial sutures in first 3 mo)
Bone pain, restlessness, and irritability
Radiographic features
Splaying, fraying, cupping, and coarse trabecular pattern of metaphysis
Widening of the growth plate
Osteopenia
Pelvic deformities including outlet narrowing (risk of obstructed labor and death)
Long-term deformities in keeping with clinical deformities
Minimal trauma fracture
Non-osseous features
Hypocalcemic seizure and tetany
Hypocalcemic dilated cardiomyopathy (heart failure arrhythmia, cardiac arrest, death)
Failure to thrive and poor linear growth
Delayed gross motor development with muscle weakness
Raised intracranial pressure

CONCLUSIONS

Rickets is a disorder of growing children that arises from defective mineralization of the growth plate. Nutritional rickets is a preventable disease by maintaining an adequate intake of vitamin D through both dietary and sunlight exposure. Vitamin D supplementation will work in nutritional rickets secondary to vitamin D deficiency but not in most of the non-nutritional variants of rickets.

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