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AN OVERVIEW OF RICKETS IN CHILDREN

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ABSTRACT

Rickets, a globally prevalent bone disease, arises from imbalances in calcium and phosphate regulation, resulting in potential short stature and joint abnormalities. Diagnosis typically involves historical review, physical examination, radiographic assessment, and biochemical analysis. The condition is broadly categorized into phosphopenic and calcipenic types based on phosphate or calcium levels, respectively. Prompt identification of the rickets subtype is crucial for effective treatment. Nutritional rickets, preventable through sufficient vitamin D intake from diet and sunlight exposure, represents one subtype. Others include vitamin D–dependent types 1 and 2 due to metabolic defects, renal rickets stemming from impaired kidney function, and hypophosphatemic rickets marked by vitamin D resistance and renal phosphate loss, often influenced by fibroblast growth factor-23 (FGF-23). Monitoring and supplementation with activated vitamin D and phosphate may be necessary for certain subtypes. Notably, burosumab, a human monoclonal antibody targeting FGF-23, has emerged as a significant advancement in treating X-linked hypophosphatemia in children aged one year and older.

I. INTRODUCTION

Rickets, a prevalent global affliction, significantly impacts the health and development of children and adolescents. It arises from irregularities in growth plate cartilage, primarily affecting longer bones, resulting in inadequate bone growth, impaired mineralization, and skeletal deformities like bow-legs and knock-knees. The condition typically stems from deficiencies in calcium or phosphorus, both crucial for normal bone development and mineralization. This review explores various forms of rickets and outlines suitable management strategies.

Pathogenesis and types of Rickets

Bones are composed of specialized cells with distinct functions in the bone formation process. Osteoblasts, responsible for bone formation, produce the extracellular matrix and facilitate osteoid mineralization, while osteoclasts degrade the bone matrix during remodeling, disease, or aging. In bone maturation, calcium salts must mineralize the organic component of the bone matrix, the osteoid. In rickets, this mineralization process is impaired, leading to accumulation of osteoid beneath the growth plate and gradual bone softening.[1] Rickets categorization typically divides the condition into two main groups: phosphopenic and calcipenic.(figure 1)

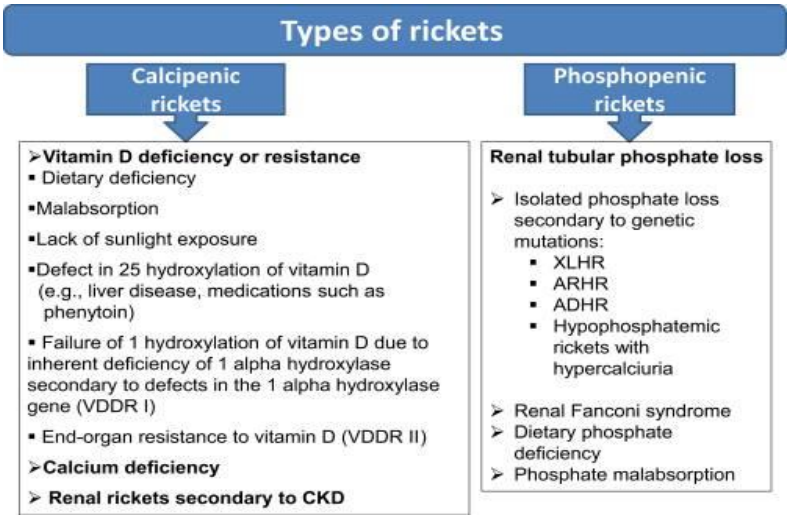

Figure 1: Different types of rickets. ADHR, autosomal dominant hypophosphatemic rickets; ARHR, autosomal recessive hypophosphatemic rickets; CKD, chronic kidney disease; VDDR, vitamin D–dependent type 1 rickets; XLHR, X-linked hypophosphatemic rickets.

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Phosphorus, abundantly present in all body tissues, plays a crucial role as a structural component for bone mineralization, alongside calcium, ensuring bone health and functionality. In phosphopenic or hypophosphatemic rickets, the underlying defect often stems from increased renal phosphate excretion. This urinary phosphate loss may result from generalized tubular dysfunction, as observed in conditions like Fanconi syndrome, or it may be secondary to factors such as elevated synthesis or reduced degradation of FGF-23, or mutations in genes encoding sodium-dependent phosphate transporters in the proximal renal tubule.[2]

Calcipenic rickets, on the other hand, primarily arises from insufficient calcium levels, typically due to inadequate availability or impaired function of vitamin D in the body. This deficiency can stem from various causes including severe vitamin D deficiency (nutritional), inability to form either 25-hydroxyvitamin D (as seen in liver failure or drug intoxication, e.g., phenytoin) or 1,25-dihydroxy vitamin D (as in chronic kidney disease), or resistance to 1,25-dihydroxy vitamin D3 at the end organ. Consequently, reduced calcium absorption in the gut prompts increased secretion of parathyroid hormone (PTH) by the parathyroid gland. PTH acts to maintain blood calcium levels by activating bone resorption via increased RANKL by osteoblasts, reducing renal calcium loss, and enhancing renal phosphate loss through internalization and degradation of sodium-dependent phosphate cotransporter protein (NaPi-2a and NaPi-2c), thereby decreasing tubular phosphate reabsorption.

Despite the differing etiologies, the common pathway leading to rickets development in both calcipenic and phosphopenic forms involves reduced phosphate concentration.

Calcipenic Rickets

Vitamin D plays a critical role in maintaining skeletal health by regulating calcium and phosphorus levels in the bloodstream. There exist two primary forms of vitamin D: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is mainly sourced from plants, while vitamin D3 is synthesized naturally in the skin through the conversion of dehydrocholesterol to cholecalciferol upon exposure to sunlight containing ultraviolet B rays within the 290–315-nm range.

Once formed, vitamin D binds to the vitamin D binding protein and is transported to the liver for hydroxylation. In the liver, it undergoes conversion by 25-hydroxylase (encoded by CYP2R1, Cytochrome P450 Family 2 Subfamily R Member 1) into calcidiol, also known as hydroxyl-cholecalciferol or 25-hydroxyvitamin D. Calcidiol is then absorbed in the proximal tubule of the kidney through endocytic receptors megalin and cubilin and further 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.

Calcitriol acts on the vitamin D receptor in intestinal cells, stimulating increased gut absorption of calcium by upregulating the calcium channel, TRPV6 (Transient receptor potential cation channel subfamily V member 6). Complex interactions occur among hormones produced by the kidneys (1,25 dihydroxy vitamin D), bone (FGF-23), and parathyroid hormone (PTH).[3] Understanding these interactions is crucial for effectively managing rickets.

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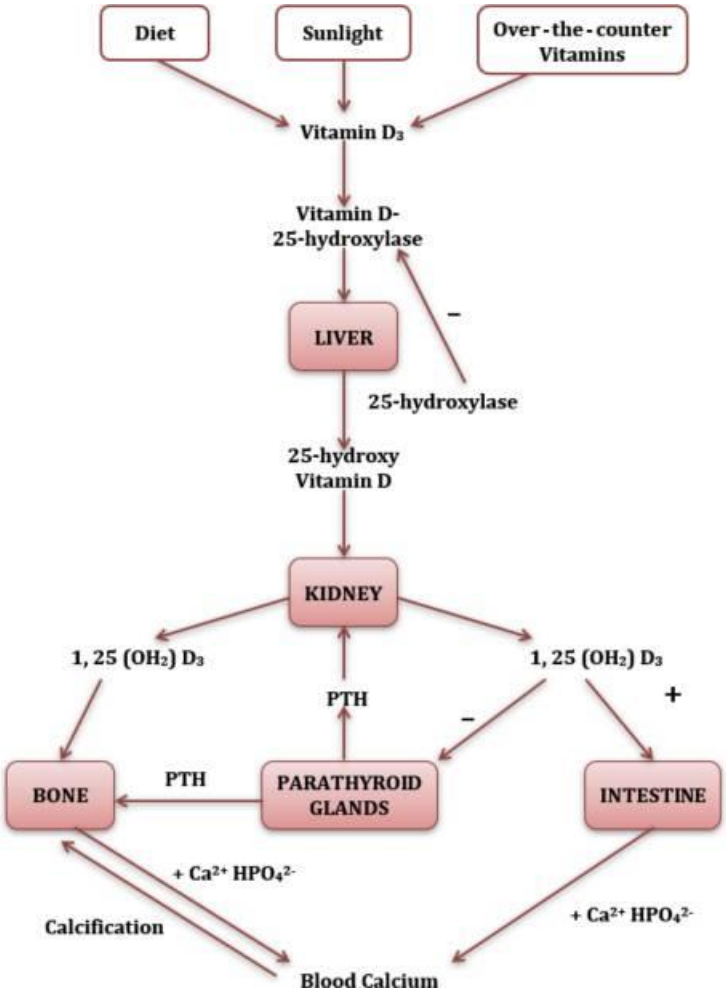

Figure 2: Sources and metabolism of vitamin D. PTH, parathyroid hormone.

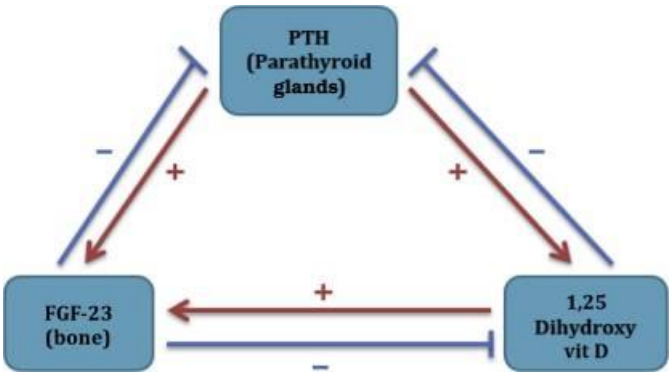

Figure 3: Parathyroid/bone/kidney axis. 1. Parathyroid hormone (PTH) increases 1,25 dihydroxy vitamin (vit) D synthesis in the kidney. 2. Fibroblast growth factor 23 (FGF-23) is produced by bone and it acts on the kidney. 3. FGF-23 decreases PTH and 1,25 dihydroxy vitamin D. 4. Both PTH and 1,25 dihydroxy vitamin D increase FGF-23 syntheses.

Nutritional rickets stands as the most prevalent bone disease, predominantly affecting infants and young children. While primarily stemming from a deficiency in vitamin D, calcium and phosphate insufficiencies also significantly contribute to its development.[4] Vitamin D governs the regulation of calcium and phosphorus in the bloodstream, and its deficiency leads to inadequate mineralization of osteoid produced by osteoblasts.

The primary causes of vitamin D deficiency typically involve a combination of nutritional inadequacy and insufficient exposure to sunlight, compounded by cultural, environmental, and genetic factors. Table 1 outlines the classification of the severity of vitamin D deficiency. Nonetheless, there remains a lack of consensus

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regarding the definition of normal vitamin D concentrations in healthy children, with guidelines varying in their target levels for optimal vitamin D status. The Global Consensus meeting on the prevention and management of nutritional rickets has defined deficiency as a vitamin D level below 30 ng/ml.

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

Severity of 25 (OH) vitamin D deficiency	
Vitamin D status	**ng/ml**
Deficiency	<30
Insufficiency	30–50
Adequate	>50
Toxicity	>250

Renal Ricket

The term "renal rickets" typically pertains to individuals with chronic kidney disease. Chronic kidney disease leads to a deficiency in the enzyme 1 alpha-hydroxylase, resulting in reduced production of 1,25 hydroxy vitamin D (calcitriol). A documented history of renal failure distinguishes this disorder from other bone diseases. Laboratory assessments commonly reveal low calcitriol levels, although levels of 25-hydroxyvitamin D may remain within normal range. A notable characteristic is the elevated phosphate level secondary to impaired renal function in chronic kidney disease.

Given the inability of patients with chronic kidney disease to convert calcidiol into the active form calcitriol, supplementation with vitamin D alone proves ineffective for renal rickets. Instead, management typically involves a low-phosphate diet, dietary phosphate binders, and oral administration of 1 alfacalcidol or calcitriol. Additionally, maintaining a normal level of 25-hydroxyvitamin D is recommended.

Hypophosphatemic Rickets

Hypophosphatemic rickets should not be conflated with hypophosphatasia, a rare inherited metabolic disorder stemming from dysfunction in the tissue nonspecific alkaline phosphatase enzyme. Childhood hypophosphatasia typically manifests between 6 months and 18 years, presenting symptoms such as rickets, decreased mobility, fractures, and poor growth. Notably, this condition is characterized by low alkaline phosphatase levels, which contrasts with other forms of rickets where alkaline phosphatase levels tend to be elevated.

X-Linked Dominant Hypophosphatemic Rickets stands as the most prevalent genetic type of hypophosphatemia, with an incidence rate of approximately 1 in 20,000 individuals. The disease arises from mutations in the phosphate-regulating gene located on the X chromosome (PHEX gene), which disrupts the inactivation of FGF-23 through mechanisms that are not fully elucidated. Elevated FGF-23 levels induce renal phosphorus wasting at the proximal tubule level, leading to hypophosphatemia.

II. CONCLUSION

Rickets, a condition affecting growing children, stems from impaired mineralization of the growth plate. Nutritional rickets, preventable with sufficient vitamin D intake from both diet and sunlight exposure, underscores the importance of maintaining adequate vitamin D levels. While vitamin D supplementation effectively addresses rickets caused by vitamin D deficiency, it may not suffice for most non-nutritional forms of the condition. Familiarity with these conditions is crucial for timely diagnosis and effective treatment.

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