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Review Article

The evolution of rickets through the ages

Aditi Chowdhury*, Ranjit Ranjan Roy, Tahmina Jesmin, Rumana Tazia Tonny

Department of Pediatric Nephrology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

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***Correspondence:**
Dr. Aditi Chowdhury,
E-mail: aditipurna2020@gmail.com

ABSTRACT

Rickets is an ancient disease and for centuries different conceptions were adopted regarding its type, causes, and treatment options. The discovery of vitamin D transformed the landscape of rickets and was followed by the discovery of several new therapies that improved treatment out-comes. In parallel, the development of rickets detection technology and new workup for vitamin D improved rickets management. Remarkably a century later, vitamin D remains the cornerstone of rickets treatment. In this review, we aim to highlight the lessons learned from the limitations of vitamin D knowledge over the past century. Finally, progress continues in the field of bu-rosumab, a human monoclonal antibody to FGF23, which is approved for the treatment of X-linked hypophosphatemia among children 1 year and older, perhaps the ultimate frontier in rickets management.

Keywords: Rickets, Vitamin D, FGF 23

INTRODUCTION

Rachitic skeletal abnormalities were observed as far back as Roman times. The earliest documented account of rickets was provided by Glisson in 1650 in his work "Treatise De Rachitidae".[1] The term "rickets" is believed to have originated from the German word "Wricken," meaning twisted, while "rachitis" is derived from the Greek word for spine, a notion Glisson proposed as the initial site of affliction.[2] They noticed that rickets primarily affect developing bones. The most severe cases of rickets spread throughout the industrialized regions of Europe and the United States during the nineteenth century, earning it the nickname "English disease".[3]

After knowing the fact that inadequate dietary sources of ergocalciferol (vitamin D2) play a significant role in rickets, its complete recovery can be possible by simply supplementing the micronutrient and mitigating the fear of irreversible disability in maximum cases.[4] After this era of vitamin D, scientists came to know that the illness may be brought on by dietary inadequacies as well as due to genetic flaws and other diseases. Moreover, high incidences of rickets have been documented in regions such as China, India, the Middle East, and Mongolia due to geographical location and environmental pollution.[5] This disease was particularly prevalent in densely populated urban areas characterized by reduced sunlight and atmospheric pollution from carbon dioxide. So, the clinical presentation varies depending on the pathophysiology and age of onset, however, it includes short stature, enlargement of the joints, and leg bowing abnormalities.[6] After this knowledge, in recent days, mutations in genes encoding proteins involved in bone mineralization, renal phosphate management, fibroblast growth factor 23 (FGF23) synthesis or degradation, or vitamin D metabolism or action have been found.[7] The incidence of nutritional rickets has significantly decreased in comparison to two centuries ago, but it has resurfaced in certain developed nations as well, newborns with dark skin types or those born prematurely.[8]

The whole world is suffering from environmental pollution, especially lead toxicity may contribute to devel-oping rickets. Ongoing studies will be essential to promote the well-being of families with VDDR and to improve the diagnostic and clinical management of these uncommon genetic disorders. This article describes the

continuous changes and additions in the concept of the type of rickets and its cure so that it will give a full picture of evolution and lessons learned from it which enable the low-resource countries to diagnose and treat rickets from cost-effective measures. We have not only focused on the past experiences but also the new therapeutic approaches according to recent clinical practice in this article.

RICKETS: IN THE PRE-VITAMIN D ERA

In 1926, De Jong established that calcium and phosphorus are vital constituents of bone composition.[9] The majority of calcium, about ninety-eight percent, is stored in bones and teeth, while approximately eighty-five percent of phosphate in the human body is also found in these struc-tures.[10]

Because of the four phases of vitamin D history, it can be divided into four sections each containing one particular time period. 1650–1890: history of rickets in pre vitamin D era, 1890–1930: discovery of vitamin D, 1930–1975: further discovery of vitamin D metabolites including 1,25 (OH) 2D3, 1975–present: history of the discovery of the vitamin D cellular machinery, functions, FGF 23 and genetic abnormalities in rickets. Historically, rickets have been considered a feature of poor socioeconomic conditions and a diet unable to provide sufficient amounts of vitamin D and/or calcium.[11] Early studies revealed that rickets were caused by both nutritional deficiency and a sunless environment and could be efficiently treated with cod liver oil.[12]

A chemical basis for the therapeutic effectiveness of cod liver oil was first proposed in 1919 by Mellanby et al, and subsequently, biochemist Elmer McCollum, pediatrician John Howland working in Johns Hopkins, and with Edwards A.[13] Park and Paul G. Shipley, showed the anti-rachitic substance to be a novel vitamin, named as the fourth letter vitamin "D".[14]

Parallel work during this time by many investigators led ultimately to the observation that ultraviolet light exerted a systemic effect to cure rickets.[15,16] Alfred Hess and Lester Unger defined sunlight as a preventer of rickets, later Harriette Chick conducted controlled studies of sunlight with cod liver oil that confirmed the effectiveness of each to prevent rickets.[17]

These studies necessitated commercial development of vitamin D, providing a sufficient cost-effective source of vitamin D that ensured worldwide prevention and cure of rickets to some extent.[18] The use of vitamin D (calciferol) to prevent and treat rickets led to a marked decrease in their prevalence.[19] Moreover, a lot of patients were not cured even after usual doses of calciferol, which led to the concept of genetic and clinical disorders that impaired activation with or without the responsiveness of target tissues to active metabolites of vitamin D. In 1937, Albright had studies of a child of rickets not responding to the usual doses of vitamin D, and described the newer concept of some types of rickets due to hereditary resistance to the actions of calciferol.[20] Lion cubs residing in the dimly lit confines of London Zoo and fed a diet lacking in adequate nutrients developed severe rickets, characterized by bone deformities. However, when their diet was supplemented with cod liver oil and ground bone, their condition improved.[21]

This finding was corroborated by another study three decades later, which observed rachitic symptoms in a dog pup deprived of similar essential nutrients. Subsequent investigations identified deficiencies in calcium, phosphate, and vitamin D as the underlying causes of nutritional rickets.[22] In 1937, Albright documented cases of a child who did not respond to standard doses of vitamin D, suggesting a possible hereditary resistance.[23]

REVOLUTION IN DIAGNOSTIC WORKUP:

Hereditary cases of rickets that were not responsive to calciferol were recognized after that. Still, most patients differed in biochemical aspect from patients with nutritional deficient calciferol, with normal serum calcium levels, reduced serum levels of phosphorus, and impaired net renal tubular reabsorption of phosphate anion.

This abnormality initially named as familial vitamin D-resistant rickets, was later termed X-linked hypophosphatemia (XLH) depicting of its X-linked dominant inheritance and the role of primary hypophosphatemia causing rickets and osteomalacia.[24] In recent years, we have come to know that there are varieties of inherited hypophosphatemic rickets in addition to XLH. Some of these additional forms share the same features with XLH such as the presence of excess circulating levels of FGF23, a phosphotonin responsible for decreased renal tubular reabsorption of phosphate and hypophosphatemia.[25]

True defects in vitamin D responsiveness were first identified as a cause of rickets in 1961 when Prader and colleagues described a distinctive form of hereditary rickets characterized by hypocalcemia with impaired bone mineralization not responding to traditional vitamin D therapy and this disorder was termed pseudodeficiency rickets.[26] Among the radiological literature is the 1977 study by Swischuk and Hayden that evaluated skull radiographs in infants with rickets. They considered less distinct cortical margins of the facial bones to depict demineralization. Fraser et al, found similar radiological findings. JS Dunbar interpreted the radiological findings according to their pathophysiological stages in 1967.[27]

NEW DISCOVERY: FGF 23 AND BEYOND

Rickets is often considered to be the tip of the iceberg of vitamin D deficiency referring to the many potential health benefits of vitamin D that extend beyond the

prevention of rickets and osteomalacia. As Perfitt has indicated despite its multiple effects on nontraditional tissues, the major role of vitamin D remains the prevention of rickets and osteomalacia.[28]

The discovery of new calcium and phosphate metabolism regulators, such as phosphaturic hormone fibroblast growth factor 23 together with the elucidation of the underlying genetic defects in many hereditary forms of rickets and the availability of comprehensive genetic testing has improved us understanding of the underlying pathophysiology and revolutionizing its diagnosis. Over time, bone disease emerged as a component of chronic kidney disease, with the discovery of fibroblast growth factor (FGF)-23 and the genetic factors involved in phosphaturic rickets becoming evident in the early twentieth century.[29]

JOURNEY OF RICKETS ROUND THE WORLD

Rickets was once pervasive among children in urban centers across North America and Europe for over two centuries. In 1870, reports indicated a prevalence of rickets affecting 25% of infants and young children in America. Adolf Windaus received the Nobel prize in Chemistry in 1928 for his research on the structure of sterols and their relationship to vitamins.[30] By the late 1900s, high rates of rickets persisted, with over 50% of the population in Tibet and Mongolia, and more than 10% in certain Middle Eastern and African nations, affected by the condition.[31]

Second wave of rickets

The dark-skinned immigrants from 1960 to 1970 from locations such as the West Indies, India, and South Asia to England and Europe led to the "second wave" of rickets. Meanwhile, a public health campaign of vitamin D supplementation including these recent immigrants led to decreased rickets presentations due to vitamin D deficiency.[32]

Third wave of rickets

Unfortunately, once again complacency has set in, and we are now in the middle of a "third wave" of rickets. This "third wave" has been documented in prospective surveillance studies of vitamin D deficiency rickets in Australia, Canada, and New Zealand, as well as in multiple retrospective studies from across the globe.

In part, this is due to less exposure to UVB for sun avoidance measures including sunscreen and clothing as per culture and tradition as well as other modern lifestyle factors.[33] Nutritional rickets were expected to be eradicated by the 1950s due to the introduction of cod liver oil treatment in the 1930s and the fortification of milk with vitamin D in the USA.[34]

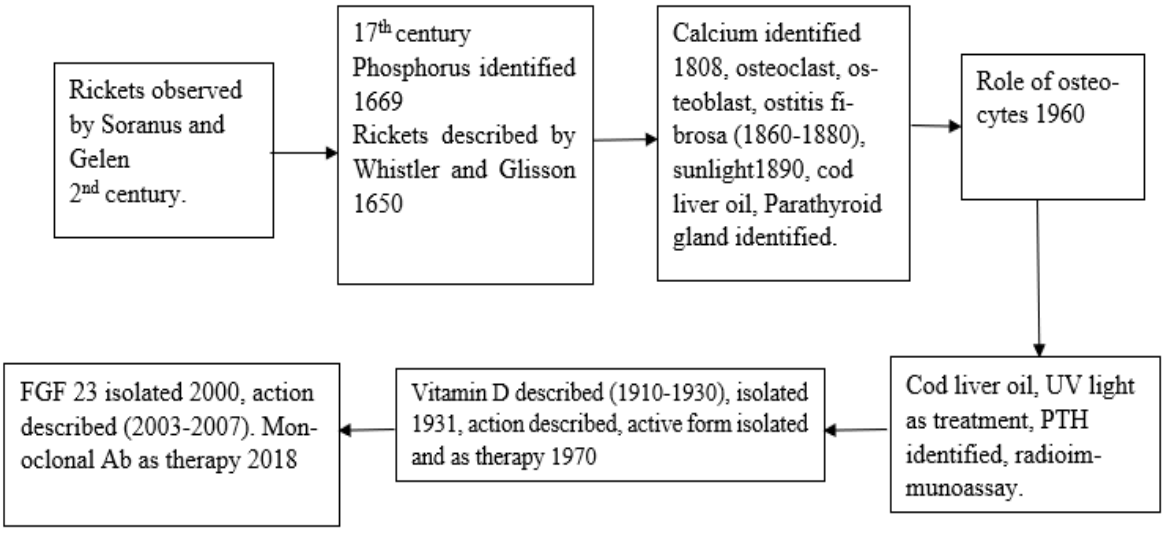

Figure 1: Phases of vitamin D history.

BURNING ISSUE: NOW A DAYS

The reduced prevalence of nutritional rickets has substantially but the condition has been reemerging even in some developed countries more in preterm and breastfed babies. So, rickets remains a prevalent condition globally, with studies describing an increasing incidence and prevalence, even in industrialized nations, prompting a focus on Vitamin D. In a survey conducted in the United States, it was found that only 20% of breastfed infants and 31% of non-breastfed infants achieved the recommended intake of 400IU of vitamin D.[35] Given the deficiency of vitamin D in breast milk, its insufficiency is often associated with breastfeeding in

Western countries.[36] A similar study in Britain revealed that 12% of adults of White ethnicity, 25% of African-Caribbean, and 25% of Asian descent were deficient in vitamin D. Moreover, 67% of American parents mistakenly believed that breast milk provided all necessary nutrients, leading only 3% to supplement their children's diets. Additionally, due to a lack of routine recommendations by two-thirds of physicians, only a small percentage of parents provided vitamin D supplements to their infants.[37]

BREAST FEEDING AND NUTRITIONAL RICKETS

In the early 1980s, the incidence of nutritional rickets in the United States was 2.2 per 100,000, which rose to 24.1 per 100,000 in the early 2020s. Similarly, in the United Kingdom, the reported incidence of rickets among children under five was 7.5 per 100,000 in early 2021.[38] In England, breastfed infants had a 67% deficiency rate in vitamin D, while formula-fed infants had a deficiency rate of only 2%. In 2021, Europe and America estimated that the rate of rickets cases ranged from 2.9 to 27 per 100,000 people.[11] Nutritional rickets remain a prevalent issue in low- and middle-income countries such as those in the Indian subcontinent, Africa, and the Middle East, in contrast to relatively lower rates observed in the USA, Europe, Australia, and New Zealand.[39]

The prevalence of hypovitaminosis D in Bangladesh ranges from 21% to 75% among infants, children, and adolescents, 38-100% among premenopausal women, 66 to 94% among women, 6 to 91.3% among adult men, and 82 to 95.8% among post-menopausal women.[40] From 1965 until 1975, the elements of the vitamin D endocrine system that regulate calcium and phosphorus became clear. The important recent development includes burosumab (KRN23), a human monoclonal antibody against FGF 23 that is effective in X-linked hypophosphatemia. It is expensive and its cost-effectiveness and long-term outcome data are awaited.[39]

CONCLUSION

Despite vitamin D originally having been discovered through its fundamental role in calcium ho-meostasis and bone formation, nowadays vitamin D metabolism and signalling are extensively being studied for also having a critical role in extra skeletal terms. However, a direct link between a potential target therapy via vitamin D supplementation is still unavailable. A great deal of work remains to be done to understand how this system works, what are the many additional regulators that can be found, gene polymorphism and epigenetic modification, and how they work in regulating the transcription and suppression of target genes.

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