Original Research Article

Dental Manifestations of Vitamin D Resistant Rickets in Orthopantomogram

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Abstract

Vitamin D is crucial for maintaining healthy bones by sustaining appropriate calcium and phosphorus levels in the blood. It is one factor responsible for maintenance of blood calcium and phosphate levels. Hence there exists Calcium, Vitamin D and Phosphorus axis. Rickets refers to any condition of Vitamin D, Calcium and phosphorus axis which causes hypominaralized bone matrix. It is a typical bone condition that causes problems with the calcium and phosphate balance and can cause low height and anomalies in the joints. Radiological findings, biochemical testing, and history and physical examinations can all be used to diagnose rickets, Depending on amounts of phosphate or calcium. It is classified into two broad groups Calcipenic and Phosphopenic .Knowledge of rickets classification is vital for quick diagnosis and adequate therapy. This article gives a brief overview of different types of rickets as well as describe dental manifestations of vitamin D resistant rickets in orthopantomogram in a 13 year old girl.

Keywords – Rickets, Vitamin D, Hypophosphatemia

Introduction & Background:

Vitamin D plays a pivotal role in maintaining healthy bones by sustaining appropriate calcium and phosphorus levels in the blood.[(1)] Ergocalciferol and cholecalciferol are the two forms of vitamin D. The main sources of vitamin D2 are plants and additional sources include cod liver oil, milk , eggs, fish. Vitamin D3 is naturally produced when dehydrocholesterol is converted to cholecalciferol by sunshine in the skin . In liver vitamin D is hydroxylated by 25- hydroxylase into calcidiol which is also called as 25 hydroxy cholecalciferol. Calcidiol is converted to calcitriol by enzyme 1 α hydroxylase in kidney.[(2)] as shown in the following figure 1 [(2)]

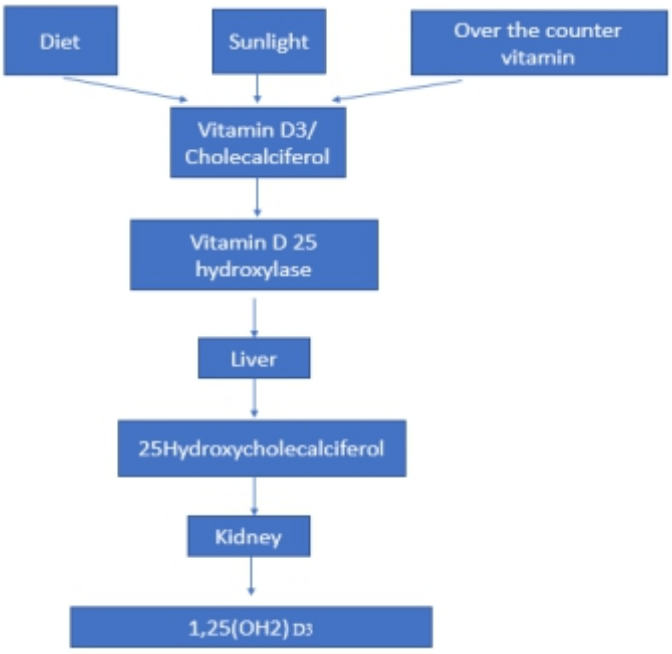

Figure 1 Diagrammatic representation showing fate of Vitamin D

Vitamin D increases the synthesis of calcium induced ATPase in the intestinal epithelium. It further facilitates the absorption of phosphate from intestine along with calcium. In this way vitamin D is one factor responsible for maintenance of blood calcium and phosphate levels hence there exists Vitamin D, Calcium and Phosphorus axis. Any condition of the vitamin D, calcium, and phosphorus axis that causes hypomineralized bone matrix is referred to as rickets.[4] The following table 1 gives brief overview of Rickets : Its discovery and relevance.

Table 1 Rickets : Its discovery and relevance

Year	Researcher	Notes
1645	Danial Whistler	Marks the beginning of medical knowledge of rickets when he wrote about it and osteomalacia in his MD thesis[5]
1650	Francis Glisson	Published text in Latin[6]
1668		Published text in English[7]
1772	Levacher de la Feutrie	Published a French literature on rickets that included details of tools to straighten malformed bones.[8]
1768-1838	Jedrzej Sniadecki	Polish doctor and chemist, first linked inadequate sunlight to the cause of rickets and suggested using it as a treatment.[9]
1924	Hess and Weinstock at Columbia University[10]	Demonstrated that UV radiation of either certain fats or plants endowed them with antirachitic properties and Connection between sunlight and dietary supplementation with a "vitamin" was made.[11]
	Steenbock & Black at the University of Wisconsin[11]	
1937	Fuller Albright	First reported vitamin D resistance giving rise to the term "vitamin D-resistant rickets" [12]
1961	Andrea Prader	Described a clinical phenocopy of vitamin D-resistant rickets that was responsive to high-dose vitamin D therapy, the condition known as "vitamin D_dependent rickets." [13]

These findings sparked a discussion over the molecular forms of Vitamin D that were physiologically active. Vitamin D, Parathyroid hormone and FGF 23 i.e., hormone produced by bone interact in a complex manner. Hence, understanding this relationship is important for good treatment of Rickets. The production of 1,25-dihydroxy vitamin D is stimulated by hypocalcemia, hypophosphatemia, and PTH . PTH, Hypophosphatemia and hypocalcemia stimulate the production of vitamin D Whereas FGF-23, an osteocyte-produced hormone is vital in bone metabolism- as it inhibits the synthesis of vitamin D[14].

Osteocytes produce two main proteins which are dentin matrix acidic phosphoprotein 1 (DMP1) and phosphate-regulating neutral endopeptidase homolog (PHEX) which control FGF 23. Dysregulation of these proteins results in osteomalacia.[15] Pathogenesis and types of rickets

Pathogenesis and types of rickets

Bones are made up of cells that play distinct functions in the bone production process..Production of extracellular matrix and minaralization of osteoid is done by osteoblasts which are bone forming cells whereas shredding of bone matrix is done by osteoclasts during remodelling, disease states or ageing. Rickets are categorised into two primary groups: phosphopenic and calcipenic [16].

Phosphopenic Rickets

Phosphorus, which is abundant in all body tissues is an essential component for bone mineralization. Calcium and phosphorus both help to keep the bone in good condition. The state of being healthy and functional.[15] The deficiency in phosphopenic/hypophosphatemic rickets is mainly caused by increased renal phosphate excretion.[16] Urinary phosphate loss can occur as part of generalised tubular dysfunction or as a result of reduced catabolism/ increased synthesis. [17]

Calcipenic Rickets

A lack of vitamin D availability or inappropriate vitamin D function in the body results in calcipenic rickets [16]. Calcium absorption in the intestines is therefore diminished which results in secretion of more parathyroid hormone by parathyroid glands which helps in maintaining blood calcium levels by

(i) Activating bone resorption via osteoblasts increasing RANKL(Receptor activator of nuclear factor kappa B ligand)

(ii) Decreasing loss of calcium from kidney

(iii) increasing loss of phosphate from kidney [6]

Table 2 : Types of rickets

Name	Etiology	Clinical Features	Treatment
Nutritional rickets / Vitamin D Deficient rickets	Vitamin D Deficiency Calcium and phosphate deficiency	Nutritional rickets patients have both skeletal and extraskeletal symptoms. Swollen wrists and ankles, delayed tooth eruption, leg deformity, rachitic rosary, frontal bossing, craniotabes, and bone discomfort are all skeletal signs.[18] Extraskeletal signs, on the other hand, include muscular weakness and hypocalcemic convulsions.[19]	The treatment of nutritional vitamin D insufficiency with cholecalciferol is divided into two phases: intense and maintenance. In the United Kingdom, the National Osteoporosis Society advises 3000 IU (in infants 6 months old), 6000 IU (6 months- 12 years old), and 10,000 IU (12-18 years old) of cholecalciferol per day in the intensive phase, followed by 400 to 600 IU/d in the maintenance phase.[20] The US Endocrine Society recommends 2000 IU/d cholecalciferol for 6 weeks in the intensive phase for all age groups, followed by 400 to 1000 IU/d in the maintenance phase.[21]
Vitamin D–Dependent Type 1 Rickets	Autosomal recessive disease due to homozygous inactivating mutations in the CYP27B1 gene which causes impaired production of the enzyme 1 alpha-hydroxylase[22]	Specific clinical signs include classic rickets characteristics such as growth failure, hypotonia, rachitic rosary, genu valgum, and increased fracture susceptibility, despite adequate vitamin D consumption.[22]	These youngsters, as predicted, will not react to large doses of cholecalciferol but will respond to physiologic amounts of calcitriol or 1α-hydroxyvitamin D (1-2 mg daily). A sufficient intake of dietary calcium (30-75 mg/kg of elemental calcium per day) should be maintained[23]
Vitamin D–Dependent Type 2 Rickets	It is a rare autosomal recessive disease due to defect in calcitriol receptor.[24]	Children with VDDR II may exhibit hypocalcemia, rickets, development failure, seizures, enamel hypoplasia, and dental cavities at a young age. Alopecia develops in two-thirds of cases due to a loss of vitamin D receptor activation inside keratinocytes and is a disease severity marker.[23]	Because VDDR II is a genetic condition that is resistant to 1,25-dihydroxyvitamin D, there is no entirely established therapy.[25] Despite the complexity, the most conceivable method is to overload the normal receptors with massive amounts of calcitriol and calcium. Without therapy, the disease progresses to severe bone deformities, respiratory infections, and mortality by the age of eight.[22]
Renal Rickets	Seen in those with chronic kidney disease which results in deficiency of enzyme 1-α hydroxylase 33[23]	There will be a history of renal failure, which rules out other bone disorders.	Vitamin D treatment alone is unsuccessful for renal rickets because individuals with chronic kidney disease cannot convert calcidiol to the active form calcitriol. A low-phosphate diet, dietary phosphate binders, and oral administration of calcitriol are recommended instead, as is maintaining a normal 25-hydroxyvitamin D level.[23]
X-Linked Dominant Hypophosphatemic Rickets	The disease results from mutations of the phosphate regulating gene on the X chromosome (PHEX gene[26]	Frontal bossing is one of the first clinical signs, which can present as early as 6 months of age. As the kid begins to walk, increasing limb abnormalities emerge, resulting in a disproportionately small height with shortened limbs.	Phosphate supplementation (elemental phosphorus in 3 to 5 dosages of 20 to 60 mg/kg per day) remains the cornerstone of therapy. Because FGF-23 inhibits the synthesis of 1,25 dihydroxy cholecalciferol, most of them benefit from calcitriol supplementation (20-30 ng/kg per day) or alfacalcidol (30-50 ng/kg per day).[15]

		Lower limbs are most damaged, resulting in coxa vara genu valgum or genu varum. Dental anomalies are widespread and are frequently the presenting issue.[27] Abscessed noncarious teeth, enamel defects , and enlarged pulp chambers are examples of these anomalies. Inadequate dentin mineralization causes gaps that allow systemic bacteria to enter, resulting in tooth abscess and serious infections, such as face cellulitis from dental focus in certain people.[28]	
Autosomal Dominant Hypophosphatemic Rickets	activating mutation in FGF-23 leading to phosphaturia.[29]	There are two divisions based on the age of presentation. One appears in childhood and is similar to X-linked dominant hypophosphatemic rickets. The other subgroup presents with bone discomfort, weakness, and pseudo fractures but no deformities during adolescence or maturity.	Evaluation and treatment of iron deficiency is critical in children with autosomal dominant hypophosphatemic rickets, in addition to the previous normal therapy, since iron deficiency induces increased expression of the FGF-23 gene.[30]
Autosomal Recessive Hypophosphatemic Rickets	ARHR type 1 is caused by mutations in DMP 1, a noncollagenous bone matrix protein produced in osteoblasts and osteocytes.[31] ARHR 2 is caused by loss of function mutations in the enzyme ectonucleotide pyrophosphatase/phosphodiesterase 1, which creates pyrophosphate from ATP, and pyrophosphate is a mineralization inhibitor.[32]	Clinical manifestations of patients ARHR are similar to those with X-linked dominant hypophosphatemic rickets	

The above table 2 gives brief overview of different varieties of rickets. Since rickets is a disorder related to Vitamin D, Calcium and phosphorus axis biochemical assay for the same becomes mandatory to know its types and address the condition appropriately. Table 3 reflects the parameters that undergo change in varied types of Rickets. [32] The following

Table 3 Biochemical findings in different types of rickets

Name	Biochemical Findings					
	Calcium	Phosphorus	Alkaline phosphatase	PTH (Parathyroid hormone)	25(OH)D (Calcidiol)	1,25(OH)$_2$D (Calcitriol)
Nutritional rickets / Vitamin D Deficient rickets	Decreased levels/ Normal	Decreased levels/ Normal	Increased levels	Increased levels	Decreased Levels	Variable

Vitamin D–Dependent Type 1 Rickets	Decreased Levels	Decreased levels/ Normal	Increased levels	Increased levels	Normal Levels	Decreased levels
Vitamin D–Dependent Type 2 Rickets	Decreased Levels	Decreased levels/ Normal	Increased levels	Increased levels	Normal Levels	Decreased levels/ Normal
X-Linked Dominant Hypophosphatemic Rickets	Normal Levels	Decreased Levels	Increased levels	Normal / slightly increased	Normal Levels	Decreased levels/ Normal
Autosomal Dominant Hypophosphatemic Rickets	Normal Levels	Decreased Levels	Increased levels	Normal Levels	Normal Levels	Decreased levels
Autosomal Recessive Hypophosphatemic Rickets	Normal Levels	Decreased Levels	Increased Levels	Normal Levels	Normal Levels	Decreased Levels

case report describes manifestations of vitamin D resistant rickets a type of phosphopenic rickets in orthopantomogram.

Case Report:

A 13 year old girl reported with a chief complaint of missing teeth. General and extraoral examination revealed a significant short stature and several skeletal abnormalities like Frontal bossing (Figure 2A) Widening and bending of ulnar bones (Figure 2B), both tibia(Figure 2C) ,bow legs , knock knees. The medical records revealed that she manifested Vitamin D Resistant Rickets (VDRR)- which was supported by reports. No relative had a similar medical history.

Figure 2A Figure 2B and C

Intraoral examination revealed multiple unerupted teeth in maxillary arch.(Figure 2D) Mandibular right and left first molar were carious with mobility ranging from grade II to III. Mandibular left first molar was carious (Figure 2E).

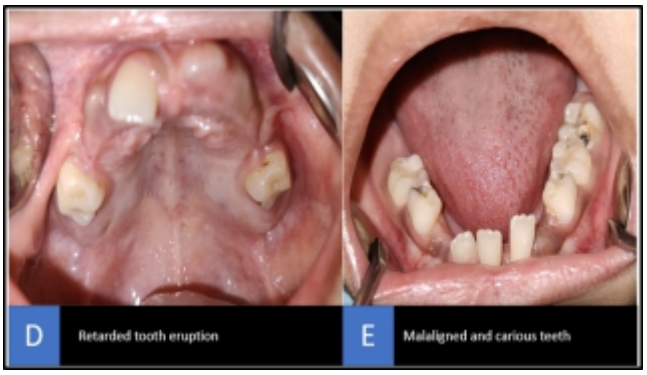

Figure 2 D Figure 2E

The Orthopantomogram revealed maxillary right and left second primary molar and mandibular right and left first and second primary molars with root resorption. All developing permanent teeth showed enlarged pulp chamber with decreased dentin thickness. Retarded tooth eruption was noted in upper and lower arch, Generalized decreased bone density noted. There was absence of lamina dura in all teeth. The alveolar bone height was inadequate and showed poor thickness of lower border of mandible.(Figure 2F)

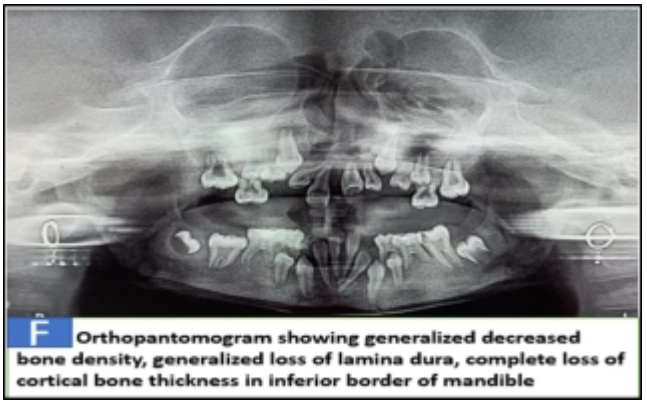

Figure 2F

Discussion:

Vitamin D resistance rickets, often referred to as hereditary or familial hypophosphatemia, is a metabolic disorder which results in improper calcification of mineralized structures. 33 It is a rare disease with a prevalence of 1:20,000. 34 Due to a genetic deficiency in renal transepithelial transport of phosphate, this disorder results in inadequate mineralization of bone, which reduces tubular phosphate reabsorption and results in persistent hypophosphatemia.[33] The present case was Vitamin D resistant hypophosphatemic rickets. Patient's biochemical profile revealed that Serum calcium, parathyroid hormone and calcidiol levels were normal with decreased levels of serum phosphorus and increased levels of alkaline phosphatase hence treatment of phosphate and calcitriol supplementation is recommended.

Numerous researches have been done to determine the connection between a lack of vitamin D and various diseases, including oncological processes like cancers of the breast, colon, and prostate.[35] . Reducing alcohol consumption, eating less fat and red meat, and increasing the quantity of fibre and vitamin D in the diet may all be preventative measures against breast cancer. 1,25-dihydroxyvitamin D can inhibit angiogenesis, invasion, and metastasis, induce apoptosis, promote cell differentiation, have anti-inflammatory and antiproliferative effects, and act in protective ways against cancer through a variety of distinct pathways. The finding that kidney and epithelial breast cells share an enzyme system makes the biological plausibility of vitamin D and its influence on breast cancer.Calcitriol induces suppression of cell proliferation and differentiation, particularly in healthy breast cells. CYP27B1 (1f hydroxylase), an enzyme that metabolises vitamin D, is expressed by cells in the mammary gland. It transforms 25-hydroxyvitamin D (25OHD) into 1,25OH2D, an active metabolite. Higher quantities of 25OHD shield breast epithelial cells against cell stressors like hypoxia, serum deprivation, oxidative stress, and the activation of apoptosis. In this way vitamin D plays protective role against breast cancer. [37].

A new infectious complication called Corona Virus Infectious Disease-19, caused by SARS-COV-2, was identified in Wuhan, China in December 2019 and since then it spread all over the world and became a pandemic. Cytokine storm may manifest in many SARS- COV-2 infected individuals as a result of an excessive cytokine production that results in ARS(Acute respiratory syndrome), organ failure and ultimately death. The disease prevention and treatment have consistently been the subject of research. It is well recognised that vitamin D can modify the immune response in autoimmune and infectious disorders. There is a possibility that vitamin D supplements could help with COVID-19 treatment.[39] A recent meta-analysis of more than 1500 studies on this subject found that taking vitamin D supplements can help prevent acute airways infections. The most prevalent respiratory viruses, such as the influenza virus, rhinovirus, and respiratory syncytial virus, are not directly affected by vitamin D, but it does substantially lower the production and secretion of pro-inflammatory chemokines and cytokines [38] Vitamin D and its metabolites can affect SARS-CoV-2 infection and the severity of COVID-19 in several ways as shown in the following figure 3[40]

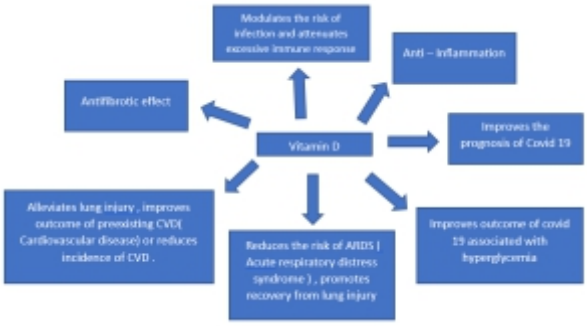

Figure 3 : Vitamin D and its effects on covid 19 infection

Conclusion:

With change in lifestyle, we do not venture out and often are indoor bound. Sunlight and fresh air are important ingredients that promote good health. A balanced diet along with support of essential nutrients goes a long way in maintaining healthy lifestyle. A clinician must always have sound knowledge about rickets and their subtypes, in order to facilitate diagnosis and proper patient care.

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