A Synopsis of Vitamin D and Rickets

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Dedicated
to
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Preface

We are delighted to welcome you to our updated vitamin D knowledge. Our goal has been to bridge the gap between multivolume research level publications and concise pocket booklets on this topic.

Following a critical review of global vitamin D, authors were timed to accumulate as much as possible of all the essential informations in a very concise manner. We expect that this tiny booklet will contribute to expanding our knowledge of vitamin D.

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বঙ্গবন্ধু শেখ মুজিব মেডিক্যাল বিশ্ববিদ্যালয়

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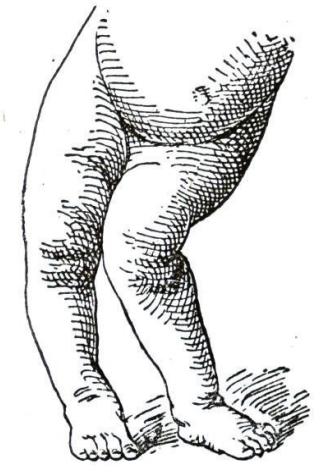

Rachitic bony deformities were identified in Roman times. The first description of rickets came into being by Glisson in 1650 in his Treatise De Rachitidae (1). The word rickets seems to be derived from the German word “Wricken” which means twisted. The word ‘rachitis’ is derived from the Greek word for the spine, which Glisson thought was the first organ affected (2). Rickets is a disease of growing bone. The worst form of rickets moved through the industrially revolutionized world in Europe and the United States (3). It was termed "ricket," or English disease, in the nineteenth century (4). The disease was more prevalent in overcrowded cities with less sunlight and darkened skies due to carbon dioxide pollution. Food sources of ergocalciferol (vitamin D2) also contributed to vitamin D deficiency (5). High prevalence of rickets has also been reported in China, India, Middle East & Mongolia (6).

Lion cubs living in the darkness of London Zoo with lean meat developed florid rickets. When cod liver oil and ground bones were added to their diet, they did recover. It was proved in another study 30 years later when a dog pup deprived of the above foods was found to develop rachitic symptoms. Subsequently, calcium, phosphate, and vitamin D deficiencies were discovered as the causes of nutritional rickets (7).

In 1937, Albright reported studies of a child who failed to respond to regular doses of vitamin D, suggesting hereditary resistance (8). In 1926, De Jong discovered that calcium and phosphorus are the main constituents that make bones (9). Ninety-eight percent of calcium remains in the bone and teeth, and eighty-five percent of phosphate in the human body is in the bone and teeth; sixty to seventy percent of bone comprises of hydroxyapatite (10). MacCallum kept the name vitamin D (11).

Bone disease as a part of chronic kidney disease was revealed in the course of time. Fibroblast growth factor (FGF)-23, phosphaturic rickets and genetic involvement came into human knowledge at the beginning of last century (12).

Rickets was universal among children in large cities and towns in North America and Europe 200 years (13). Rickets was widespread, with a prevalence of 25% among infants and young children in America, as reported in 1870 (14). In the late 1900s, a very high prevalence of rickets was reported, for example, in more than 50% of the population in Tibet and Mongolia and more than 10% in some Middle Eastern and African countries (13).

Nobel prize was awarded to Adoff Windous in 1928 on chemistry for his studies on the constitution of the sterols and their connections with vitamins(15).

Nutritional rickets was presumed to be eliminated by 1950s because of treatment with cod liver oil in 1930s & vitamin D fortification in milk in USA (16).

	DATE (century CE)				
	2nd	17th	19th	20th	21st
SUBJECT					
Phosphorus		*Identified(1669)			
Calcium			*Identified (1808)		
Bone			*Osteoclast/Osteoblast Osteitis Fibrosa Cystica (1860-1880s)	*Role of osteocytes (1960)	
Rickets	*Observation Soranus, Galen	*Description Whistler, Glisson (1650s)	*Role of sunlight(1890s) *Cod liver oil in lion cubs	*Cod liver oil as treatment *UV light as treatment (1920s-1930s)	
Parathyroid Hormone (PTH)			*Gland identified (1850-1880s) *Associated with tetany (1890s).	*Parathyroid gland & bone disease (1915) *PTH identified (1920s) *Function of PTH (1910s-1950) *Radioimmunoassay (1963)	
Vit D				*Described (1910-1920s) *Isolated(1931) *Action described (1930-60s) *Active forms isolated/synthesized (1960s-1970s) *Active forms as therapy (1970s-)	
					21st
FGF-23					*Isolated (2000) *Action described (2003-2007) *Monoclonal Ab used in therapy (2018)

CURRENT GLOBAL RACHITIC BURDEN

Rickets is still frequent condition globally. Reports of increased incidence and prevalence of the disease even in industrialized nations prompted us to write about vitamin D. In the United States survey, only 20% of breastfed and 31% of non-breastfed infants had a target (400 IU) vitamin D intake (17). Breast milk is deficient in vitamin D, so its deficiency is paralleled with breastfeeding in the West (22). A similar British study had shown that 12% of White adults, 25% of African-Caribbean, and 25% of Asian descent were found to be vitamin D deficient. In fact, that study revealed that 67% of American parents believed breast milk had all the necessary nutrients, and only 3% gave supplements to their children (23). Because two thirds of their physicians did not routinely recommended vitamin D intake. Only small percentage of parents gave vitamin D to their infants. In United States incidence of nutritional rickets was 2.2 per 100,000 in early 1980's, 24.1 per 100,000 in early 2020's. In United Kingdom, under five children has 7.5 per 100,000 reported incidence of rickets in the beginning of 2021 (18). Breastfed infants in England had a vitamin D deficiency rate of 67%, and formula-fed infants had a 2% deficiency rate. In 2021, Europe and America estimated that the ricket case rate was 2.9-27 per 100,000 people (18).

Nutritional rickets are common in low- and middle-income countries like Indian continent, Africa and the Middle East compared to USA, Europe, Australia & New Zealand (19) In another study in the USA, 15% of children were found to have vitamin D deficiency or insufficiency with 25(OH)D less than 20 ng/ml, and 1–2% had <10 ng/ml. A study in Boston (USA) showed that 42% were insufficient, 24% were deficient, and the highest deficiency prevalence (35.9%) was found in African-American people (20).

Rickets have been reported at a higher rate among Asian immigrants in the United Kingdom. In a vegetarian diet, the phytate form of phosphate fiber has been found to have a lower bioavailability, which can lead to an increased risk of developing rickets (21). Despite adequate sunshine, India has 70-100 % vitamin D deficiency rate in its adult population (22). Data of kingdom of Saudi Arabia (KSA) women shows 100 % vitamin deficiency rate (23)

Mineral bone disease associated with chronic renal disease (CKD-MBD) has similar sort of recent report of increasing prevalence, may be contributory to total rachitic load (24). Tanzanian exclusive breastfed infants with low birth weight have 33% prevalence of metabolic bone disease (25). Thirty percent of 0-5 years old children in rural central Tibet has at least one sign of nutritional rickets (18).

In Bangladesh, Nigeria and South Africa, nutritional rickets due to calcium and vitamin D deficiencies are found both in isolation and in combination (18). Afghanistan study had shown 5.5% of rickets in their highly prevalent (40% to 80%) stunted children(26).

Bangladesh data shows 70-95 % of its various sub group of population have vitamin D (calciferol) deficiency. Bangladesh report shows hypovitaminosis D ranged from 21 to 75% for infants, children, adolescent, 38-100% for premenopausal women, 66 to 94% for women, 6 to 91.3% for adult men and 82 to 95.8% for post-menopausal women (22,27).

Vitamin D Deficiency in Healthcare Provider

Bangabandhu Sheikh Mujib Medical University (BSMMU) staff data shows 95% of employees are vitamin D deficient. Even doctors are found to have high amount of vitamin D deficiency for example two third of Bangladeshi doctors has deficiency, only 10% of them has sufficient vitamin D (27). Young doctors of North India have 95% deficiency prevalence rate(28).

Health professional of Qatar has 87% deficiency rate (29), medical students of Saudi Arabia (96%) (23), medical student, residents, and doctors of urban university hospital in USA has 67% deficiency, physicians of Jerusalem (68%) and resident physicians of Brazil (57.4%) has similar disease load (30).

Genetics and Vitamin D

Except for nutritional rickets and rickets due to renal failure, almost all types of rickets have some genetics. Hereditary X-linked hypophosphatemia is the most common genetic cause of rickets. Improved genetic diagnostic facilities may result in increased detection of heritable rickets and higher total reported rachitic load (18). Genetic rickets has earlier presentation, low serum levels of vitamin D and refractory to standard treatment of nutritional rickets and need almost life long treatment (8)

Followings are the genetic rickets-

- Vitamin D dependent rickets (VDDR) type 1 A and 1B,
- Hereditary vitamin D resistant rickets (HVDRR, previously known as VDDR type 2 A and 2B)
- X-linked hypophosphatemic rickets (XLHR)
- Autosomal dominant hypophosphatemic rickets (ADHR)
- Autosomal recessive hypophosphatemic rickets (ARHR)
- Tumor induced osteomalacia (TIO)
- Fibrous dysplasia (FD)
- Cutaneous skeletal hypophosphatemia syndrome (McCune Albright Syndrome)
- Osteoglophonic dysplasia (OGD)
- Hypophosphatemic rickets and hyperparathyroidism (HRHP)
- Rickets and/or osteomalacia due to primary renal tubular phosphate wasting
- Hereditary hypophosphatemic rickets with hypercalciuria (HHRH)
- Cystinosis

Is it a non-communicable disease?

Non communicable disease is current global problem and relation of rickets with non-communicable disease (NCD) is widely talked issue now a days. Vitamin D exert gene pleotropic effect in wide range of extra skeletal disease such as cardiovascular disease, type 1 diabetes mellitus, breast, prostate & colon cancers, autoimmune disorders, pregnancy complication, cognitive impairment, depression, allergic condition, inflammatory bowel disease (IBD), mood disorders, dental carries and even frailty (31). It is not a simple nutritional disease. Vitamin D receptor (VDR) is universally expressed in all nucleated cells. Approximately 3 percent of the human genome is under the control of 1-25 dihydroxy vitamin D (32). Ten or more tissue sites other than kidney express 1- alpha hydroxylase (CYP27B1) enzyme and hence active form of 1-25 (OH)2 D can be generated in autocrine or paracrine way(33) This spectrum of activity is much wider than bone health, calcium phosphate homeostasis (33). Risks of cardiovascular disease, infection, autoimmune disease, and cancer are found high when 25(OH)D is less than 20 ng/ml but there are no

convincing randomized trial data that vitamin D supplements can decrease the risk, severity, and prognosis (33). Poor vitamin D <10 or <20 ng/ml [<25 nmol/L or <50 nmol] status is associated with muscle weakness, but a causal relationship is not clearly demonstrated (34).

Supplementation with vitamin D improves muscle weakness and recovery of mitochondrial energy storage as measured by vivo magnetic resonance spectroscopy after physical exercise (35). Various cancers have inconsistent on varied type of relationship with hypovitaminosis D(35). There exist two-fold increased risk of neuropsychiatric disorders like schizophrenia, depression, post-natal brain function or Alzheimer disease. In fact, vitamin D has effect on neuronal proliferation, differentiation, migration, and apoptosis (36). Both beneficial & unclear result of vitamin D status & chronic obstructive pulmonary disease (COPD) has been described in different literature (37)

Vitamin D reduces activation of acquired immune system, it activates the innate immune system specially monocyte and macrophages. Exposure of monocytes and macrophages to bacterial infections upregulates vitamin D receptor (VDR) & 1-alpha hydroxylase expression leading to increased production of natural defenses (38,39). Seasonal prevalence of virological disease may be linked to seasonal variation of vitamin D status. Vitamin D enhances clearance of sputum in patients with tuberculosis. Small reduction in the occurrence of acute respiratory infection is seen in few studies while other studies show no clear benefit(40). Few studies in COVID period have shown inverse relationship with vitamin D levels & COVID-19 cases. Larger observational studies report has mixed findings, subsequent studies with vitamin D supplementation has not shown clear benefit (41,42). Association between hypovitaminosis and cardiovascular event & hypertension was found but no difference was seen by vitamin D supplementation (43). Reduced thrombogenesis and increased fibrinolysis are observed in vivo (43). Coronary heart disease is more common in adults with 25(OH)D levels <20 ng/ml compared to ≥30 ng/ml, however there was no effect of supplementation in prevention of myocardial infarction & stroke (43,44). Vitamin D deficiency has been linked to type 1 diabetes, and early childhood supplementation has been shown to reduce the risk of type 1 diabetes by 30% in the future. Type 2 diabetes, metabolic syndrome

and obesity are also associated with low vitamin D status but no causal relation is found between them (45–47). Poor pregnancy outcome & impact on neonatal health in vitamin D deficiency is well documented though precise levels with deleterious effect are unknown (48,49). Roth et al. did not find difference in the incidence of preterm birth, small for gestational age or low birth weight in the supplemented pregnant Bangladeshi women. Maternal supplementation has also not found to influence late childhood mineral bone content (50,51). Mother with higher dose supplementation is found to have some bone parameters improved state even after 6 years of age. There is a moderate reduction of all-cause mortality with vitamin D supplementation in older, non-critically ill vitamin D deficient patients (52). Low vitamin D levels of less than 20 ng/ml [50 nmol/L] in the White populations of North America and Europe have been associated with higher all-cause mortality, and severe vitamin D deficiency of less than 12 ng/ml [30 nmol/L] has been linked to an even greater risk. Some studies suggest a U or reverse J-shaped association, indicating higher all-cause mortality rates in those with lower levels (<20 ng/dl) and higher levels (>30-50 ng/dl) (53,54). Genetic polymorphisms associated with vitamin D were found to have all-cause mortality(55) . National Health and Nutrition Examination Survey (NHANES) data shows no association between overall cause mortality & hypovitaminosis D, but higher mortality is found in some cancer patients. (56). Hence vitamin D should be supplemented with vitamin D in deficiency (<12 ng/ml [30 mmol/L]) or insufficiency (12 to 50 ng/ml [30-50 nmol/L]) (56).

Rickets has been a global health issue for centuries, merits discussion, and needs attention even in the internet time of 2024. This review is a state of the art presentation of vitamin D and rickets.

PATHOPHYSIOLOGY OF RICKETS

Vitamin D is a precursor hormone (prohormone) calcitriol. Vitamin D exists in four forms namely –vitamin D3 (cholecalciferol), vitamin D2 (ergocalciferol), 25 hydroxyvitamin D (calcidiol, calcifidiol), 1,25 dihydroxy vitamin D (calcitriol) (57).

Older people have less endogenous vitamin D generation, also decreased storage, and has age dependent resistance. Moreover, they remain

more home bound and has less sun exposure. Hence geriatric group can have hypocalcemia and consequent secondary hyperparathyroidism (58).

It is not a vitamin by definition because it is produced in the skin. It is involved primarily in calcium and to a lesser extent in phosphorus metabolism (59). Vitamin D increases calcium and phosphorus absorption from the gut. Calcium and phosphorus are needed for mineralization of bone(60).

In high concentration vitamin D causes bone reabsorption to meet the demand of calcium and phosphorus to the other tissues. Ultraviolet rays of wavelength 290–315 nm, which are like those required for sunburn, convert hydroxycholesterol into cholecalciferol (D3) in the epidermal keratinocyte and dermal fibroblast. The skin comprises 90% of the vitamin sources in the human body (61).

Adequate sunlight may not be able to prevent deficiency. It is non enzymatic temperature dependent rearrangement & conversion of previtamin D to vitamin D3 (cholecalciferol) (61).

In liver, 25- hydroxylation takes place by 25 hydroxylase and 25 hydroxyvitamin D (25 OHD) or calcidiol is produced, which is the storage form of vitamin D, it has 2–3-week long half-life (62). Calcidiol (25OHD) is then hydroxylated by 1 alpha hydroxylase at renal proximal convoluted tubules and converted to 1, 25 hydroxyvitamin D (calcitriol). Calcitriol [1-25 (OH)2 D3] is the active form of vitamin D has only 4-6 hours of half-life (62). The CYP2R1 gene encodes the hepatic 25-hydroxylase enzyme, and the renal 1-hydroxylase enzyme is encoded by the CYPB1 gene of cytochrome p450 family 27 subfamily member 1 (63). A comparison of two terminal vitamin D products shows 25(OH)D is metabolically tenfold potent, while 1-25 (OH)2D is 1000-fold more potent compared to their parent calciferol (cholecalciferol/ergocalciferol) (64).

Cholecalciferol is more potent than ergocalciferol and is widely used globally. Ergocalciferol (D2) is only 1% as potent as cholecalciferol (D3). Both the molecules bind with vitamin D receptors expressed in all nucleated cells in most of the organs and tissues. The half-life of cholecalciferol and ergocalciferol is 24 hours (57).

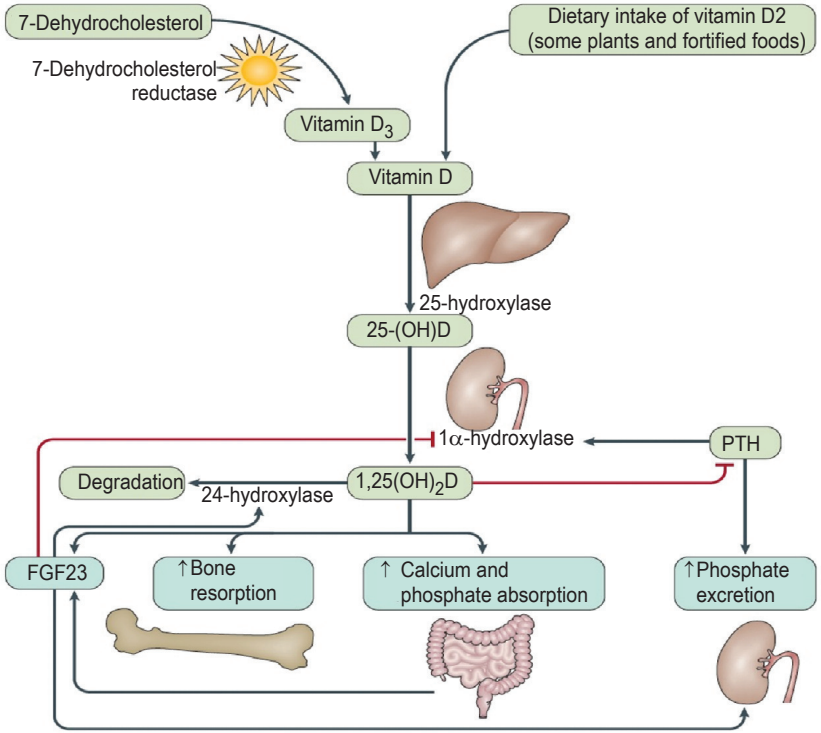

Figure 2: *Synthesis Of vitamin D (65)*

1,25 (OH)2D binds with intracellular receptors in target tissue which is also regulated by gene expression. There exists compensatory reduced vitamin D production that is why sunrise does not produce toxic amount of vitamin D3 rather it is converted to inactive vitamin D3 such as lumisterol, tachysterol, 5,6 trans vitamin D and suprasterol 1 and 2 in the skin (66).

On the other hand, both 1-25 (OH)2 D and 25(OH)D are degraded to less active, almost nonfunctional 24 $(OH)_2$ D mediated by 24- hydroxylase. It is controlled by CYP24 gene in proximal convoluted tubular cell and hepatocyte (63). Sunlight also induces melanin production which reduces vitamin D3 production in the skin. Countries distant to >30 degree has sunrays falling in oblique manner, thereby generate low amount of vitamin D (66).

Vitamin D receptor (VDR) is a member of class 2 steroid hormone receptor, it is intranuclear in location and is closely related to retinoid

acid and thyroid hormone. It promotes enterocyte differentiation, absorption of calcium and some amount of phosphate, suppression of parathyroid hormone (PTH) secretion and regulates osteoblast function. It also permits parathyroid induced osteoblast function and bone resorption (67–69). Eighty to ninety percent of vitamin D remains in bound form with vitamin D binding protein (VDBP), 10-20% remain albumin bounded and <1% remain in free form. Only 3-5% of total circulatory vitamin D binding sites are occupied usually and hence hypoproteinemia is not always a rate limiting factor for vitamin D dynamics except in massive proteinuria of nephrotic syndrome (70).

In proximal convoluted tubule cubalin and megalin are two receptor proteins for vitamin D uptake. Deficiency of megalin and cubalin leads to 1, 25 (OH)2 D3 deficiency and bone disease. This process is driven by parathyroid hormone, hypophosphatemia, and growth hormone (65,71–73). Other minor extra renal sites of one alpha hydroxylase activity mediated by CYP2 B1 gene are lymph node, breast, osteoblast, osteoclast, skin, alveolar macrophage, activated macrophage, blood vessel and keratinocytes indicates autocrine paracrine rule for calcitriol (74).

Vitamin D produced in extrarenal sites are consumed by that site (organ) only. But vitamin D produced in non-renal site can cause systemic hypervitaminosis D, hypercalcemia and hypercalciuria for example in sarcoidosis (75). In the target tissue including intestine, bone, and others calcitriol (D3) binds with cytoplasmic vitamin D receptor with the help of retinoid X co-receptor (RXR). Hence vitamin A antagonizes vitamin D by competing with same nuclear receptors and thereby reduces toxicity of each other at higher concentration (76).

Genomic actions of 1-25(OH)2D are mediated by intranuclear high affinity VDR and non-genomic actions are mediated by binding of 1,25 (OH)2 D to unidentified plasma membrane receptors called vitamin D binding receptor element (VDRE) which is a ribonucleoprotein (77). Both VDR and plasma membrane receptors are identical to steroid receptor. Membrane bound vitamin D receptor is said to be contributory to fracture healing and chondrocyte maturation. Coreceptor, retinoid X receptor (RXR) is associated with VDR. (66)

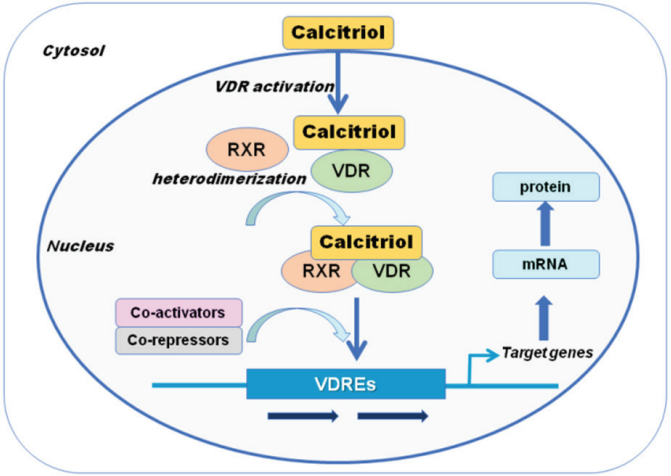

Figure 3: *Vitamin D receptor (VDR) action at target cells. Intracellular calcitriol [1,25(OH)2D] binds to the VDR; thus, causing its dimerization with the retinoid X receptor (RXR). The ligand-bound VDR-RXR complex binds to structurally distinct vitamin D response elements (VDREs) in multiple, widely spaced vitamin D-responsive regions, and this causes a modification in the recruitment of co-activators or co-repressors, which leads to positive or negative transcriptional regulation of gene expression. (78)*

Calcitriol acts on VDR of enterocyte, facilitate calcium phosphate absorption (79).

Steroid inhibits vitamin D at receptor binding RXR and hence inhibition of receptors at intestine prevents absorption of vitamin D. Anticonvulsant and antiretroviral drugs enhance catabolism of 25 (OH) D into inactive 24 (OH) D which is an almost nonfunctional molecule. Ketoconazole and some antifungal agents block one alpha hydroxylase at proximal renal tubules (80,81). Intestinal fat emulsion and chylomicron facilitation are related to vitamin D receptor (VDR) and retinoid X receptor (coreceptor), both are well absorbed in presence of fat (82).

$1,25(OH)_2D$ acts on intestinal cells to increase gut absorption of calcium by upregulating calcium channel TRP V6 (transient receptor potential cation channel, sub family V member 6, TRPV6) and phosphate absorption by phosphate co-transporter, sodium phosphate

2B (NaPi-2B) (83). Calcium absorbed from the gut enters circulation, is deposited into bone, is secreted again in the intestine, or is filtered and later reabsorbed via the TRPV5 channel in the kidney; children usually have a net positive calcium balance (83,84). Calcium sensing receptors (CaSR) of the C-cell of the parathyroid gland respond to hypocalcemia and increase PTH secretion. PTH activates Receptor Activation of Nuclear Factor Kappa-B-Ligand (RANK-L) which mediates osteoblastic resorption, decreases renal calcium loss, and promotes renal phosphate excretion by removing sodium dependent phosphate cotransporter proteins (NaPi-2A and NaPi-2C) (85). Thereby PTH elevates calcium, decreases phosphate levels. PTH also stimulates the synthesis of 1-25 (OH)2 D causing increased intestinal calcium and phosphate absorption. Vitamin D (calciferol) regulates osteoblastic function and permissively allowing PTH induced osteoclast activation & bone reabsorption (86). PTH decreases phosphate and bicarbonate reabsorption in proximal convoluted tubule resulting in hypophos- phatemia & hyperchloremic acidosis (87). Calcipenic nutritional rickets is due to lack of vitamin D mediated Ca absorption at duodenum and decreased mobilization of calcium from bone (88).

Insufficient Ca-Pi hydroxyapatite formation because of calcium and phosphate deficiency is the important event, and failure of caspase-mediated chondrocyte apoptosis is the central event (89). Bone formation is regulated by plenty of cytokines including bone matrix derived transforming growth factor beta (TGF-β), bone morphogenic protein 2 (BMP-2), BMP-4, BMP-7, and inhibitors insulin like growth factor-1 (IGF-1), osteopontin (OPN) and fibroblast growth factors (FGFs) (90).

Insulin-like growth hormone factor 1 (IGF-1) facilitates growth hormone action and phosphate absorption at proximal tubules by upregulating NaPi2A and NaPi2C (91). Similarly, calcium absorption is upregulated at proximal tubule by 1-25 (OH)2 D and PTH by acting upon TRPV5 calcium channel (92).

Even in idiopathic hypercalciuria there can be mild hypercalcemia. Chronic hypercalciuria may lead to renal stone disease. It takes months and years to affect bone mineralization and hence development of rickets and osteomalacia (93).

Fibroblast growth factor (FGF-23) is a hormone produced by osteocytes, osteoblast in bone, odontoblast in teeth & lungs cell (94). It binds with

its receptor FGFR1 with the help of membrane bound protein or cofactor klotho, reduces, and replaces NaPi-2A and NaPi-2C receptors in the apical surface of proximal convoluted tubular cell. Hence, it prevents phosphate absorption, thereby causing phosphaturia, and it also inhibits 1,25 (OH)2 D synthesis and intestinal calcium and phosphate reabsorption (95).

Table 01 **Fibroblast growth factor regulator (96)**

Upregulator	Down regulator
Phosphate	Dentin matrix protein phosphoprotein (DMP1)
Calcitriol	Ectonucleotide pyrophosphatase phosphodiesterase 1 (ENPP)
Parathyroid hormone	Phosphate-regulating endopeptidase homolog on the X chromosome (PHEX)
Leptin	Iron

Parathyroid hormone (PTH), 1-25$(OH)_2$D and FGF-23 inhibit and stimulate each other in a feedback loop manner to maintain normalcy or homeostasis (97). These hormones act in concert as per physiological need of the body.

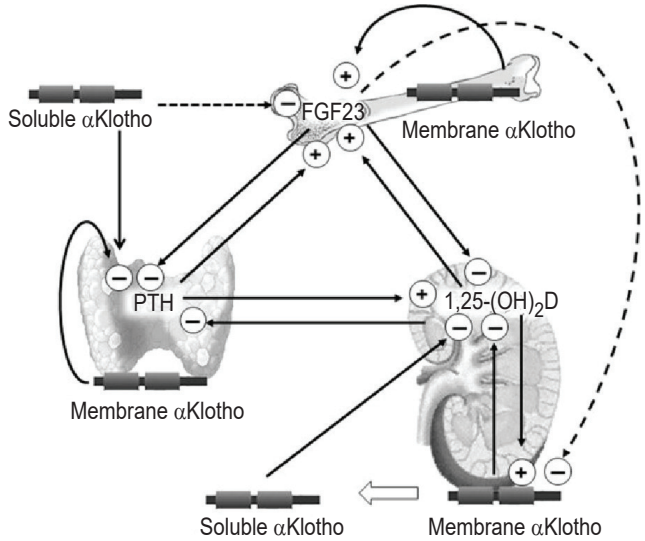

Figure 4: *Feedback loop of PTH, FGF-23,1-25 (OH)2 D (98)*

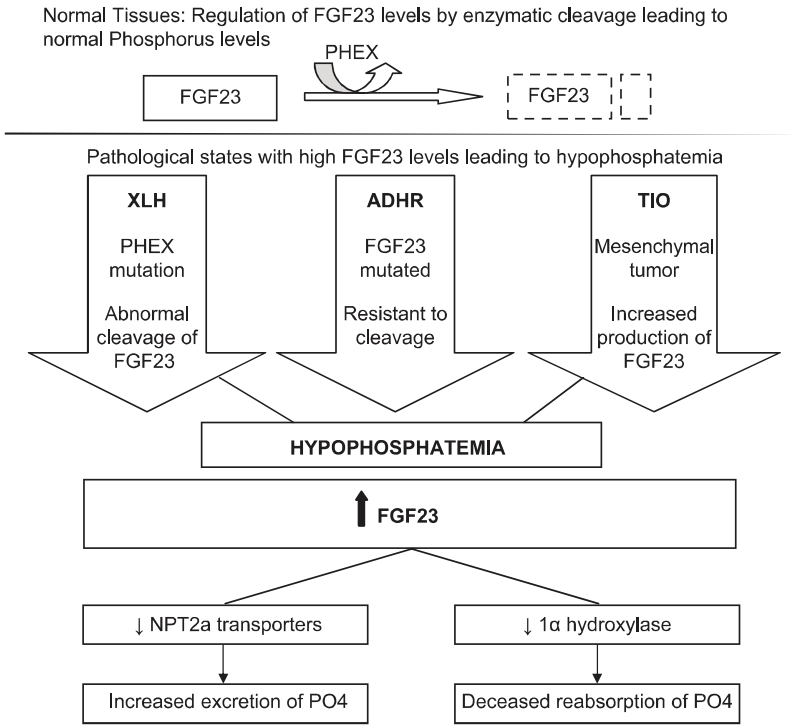

Figure 5: *Hypophosphatemic rickets (99)*

1-25 (OH)2 D is downregulated by phosphate regulating endopeptidase homolog on the X chromosome (PHEX), dentin matrix acidic phospho-peptidase1 (DMP1) and endonucleotide pyrophosphatidase (ENPP) and iron. PHEX, DMP1 and ENPP mutations cause upregulation of FGF 23 and hence hypophosphatemic rickets occurs (100). FGF 23 upregulates CYP24A1 and down regulates expression of CYP27B1 and hence regulates vitamin D synthesis with degradation (101).

Parathyroid hormone (PTH) predominantly responds to hypocalcemia. PTH also increases in renal vitamin D3 synthesis, FGF 23 decreases vitamin D3 and PTH. Calcitonin from the thyroid gland reduces bone calcium and phosphate (102). FGF 23 expression is promoted by encoding GALNT 3 gene. FGF 23 and PTH have opposing effects on vitamin D metabolism. FGF 23 inhibits vitamin synthesis via 1-α-hydroxylase and enhances its degradation (103). Conversion of 25

(OH)D to 1,25(OH)2D by 1 alpha hydroxylase in proximal convo- luted tubular cell of kidney is accelerated by parathyroid hormone (PTH), calcitonin, hypocalcemia, hypophosphatemia and inhibited by hyper-phosphatemia, hypercalcemia, 1-25(OH)2D and fibroblast growth factor, i.e., feedback for normalization and homeostasis (104).

In renal failure, 1-25(OH)2D production is reduced due to VDR endocytosis, low glomerular filtration, reduced megalin and cubalin mediated reabsorption of glomerular filtered 1-25(OH)2D at proximal tubular cells, reduced 1α hydroxylase enzyme activity due to its suppression by hyperphosphatemia, circulating FGF 23, anatomical loss of renal tissue. Moreover, children with CKD are less active and have less sunlight exposure and uremia reduces vitamin D rich food intake, uremia also reduces the endogenous synthesis of vitamin D in the skin, losses of VDBP in urine and peritoneal dialysis leads to reduced hepatic synthesis of 25 (OH)D (71).

Net effect is hypocalcemia, hyperphosphatemia, secondary hyper-parathyroidism, and metabolic bone disease called chronic kidney disease mineral bone disorder (CKD-MBD). Vitamin D has a possible role in the anemia care of CKD and enhances the immune response, reduces proteinuria, and attenuates CKD progression (105,106).

One alpha-hydroxylase deficiency gives rise to vitamin D deficiency rickets (VDDR type 1A), also called pseudo-vitamin D deficient rickets, because of their normal 25(OH)D levels. It also has low 1-25(OH)2D and biochemical and clinical evidence of rickets unresponsive to 25(OH)D but responsive to 1-25(OH)2D (107).

In proximal tubule Pi absorption occurs by NaPi-2A (SLC 34 A1) and NaPi-2C (SLC 34 A3) (65). Ninety percent of the renal phosphate is reabsorbed by NaPi 2A and 10% is by NaPi 2C (108).

Genetic defect of NaPi 2A and NaPi 2C result in renal phosphate wasting hypercalciuria termed idiopathic infantile hypercalciuria (IIH) and hypophosphatemic rickets with hypercalciuria (HHRH) (109–111). Intestinal brush border helps dietary absorption of intestinal phosphate by an NaPi 2B localized at enterocytes(109) . In fact, 50% of intestinal phosphate absorption is mediated by NaPi 2B.

Chronic significant hypophosphatemia with phosphate concentration below 1 mg/dl (or 0.32 mmol/l) may be symptomatic. Symptoms are due to intracellular phosphate depletion. Secondary effect of hypophos-phatemia may be hypercalciuria and renal stone disease (112).

Hypophosphatemia for months and years leads to rickets and osteomalacia. Distal tubular reabsorption of magnesium may be impaired in hypo-phosphatemia. Hypophosphatemia causes low intracellular ATP leading to metabolic encephalopathy, impaired myocardial contractility, respiratory failure due to diaphragmatic muscle non contractility. It can also cause rhabdomyolysis, release of myocyte phosphate to cover hypo- phosphatemic symptoms. Intracellular low ATP may cause red blood cell hemolysis, reduce 2-3 diphosphoglycerate (DPG) causing increase oxygen binding, decreased release at tissue, defective white cell phagocytosis, chemotaxis and finally, there can be thrombocytopenia and defective clot retraction (112,113).

Renal phosphaturia by genetic disorders like X linked hypophos-phatemic rickets (XLH), autosomal recessive hypophosphatemic rickets (ARHR), autosomal dominant hypophosphatemic rickets (ADHR), hereditary hypophosphatemia with hypercalciuria (HRHR) common in literature review (114).

Hypophosphatemia is more common in hospitalized patient (2.2-3.1%), intensive care unit (29 to 35%), patient with sepsis (65 to 80%), major trauma (75%), chronic pulmonary disease (21.5%), and chronic alcoholism (2.5-30.4%) (112). Dietary phosphate deficiency is usually found in combination with vitamin D, calcium, and other nutritional deficiency. Hypophosphatemia may be acute or chronic, maybe mild (serum phosphate of 0.6-0.8 mmol/l or 1.8-2.5 mg/dL), moderate (0.4-0.5 mmol/l or 1.0-1.7 mg/dl) or severe (phosphate level <0.3 mmoL/l or 0.9 mg/dl) (113,115).

Phosphaturia causing substances are called phosphatanins, for example FGF 23 in X linked hypophosphatemia (116). FGF-23 is also produced in epidermal nevus syndrome, McCune-Albright syndrome, mesenchymal tumor. Hypophosphatemia consequent to phosphaturia due to familial hereditary tubular disease and tumor etiology is distinct from hypophosphatemia caused by secondary hyperparathyroidism in nutritional calcipenic rickets (117). Secondary hyperparathyroidism in

hypocalcemic rickets results in trivial phosphaturia; in phosphopenic rickets, on the other hand, phosphaturia is massive and causes a normal or mild elevation of parathyroid hormone (115).

Normal bone formation, reduction with metabolism

Osteocytes, osteoblasts, and osteoclasts are the three types of cells involved in bone growth, reabsorption, and remodeling (118). Calcium and phosphate are the main components of crystalline mineral bone matrix known as hydroxyapatite. Three key regulators of calcium and phosphate are 1,25(OH)2D, parathyroid hormone and fibroblast growth factor-23 (119). Osteoblasts and osteocytes are the bone forming cells and osteoclasts are involved in bone resorption. Pro and anti-osteoclastogenic factors like receptor activator of nuclear factor Kappa B ligand (RANK-L), macrophage colony stimulating factor (M-CSF) and osteopontin (OPN) secreted predominantly by osteoblasts. Osteopontin (OPN) secreted by osteocytes helps in the mineralization and homeostasis. OPN is inhibited by sclerostin secreted by osteocyte (120). Sclerostin also directly inhibits bone formation. Osteoprotegerin inhibits osteoblast differentiation, and bone absorption is also inhibited by calcitonin. Hypophosphatemia enhances accumulation of undermineralized osteoid where hypocalcemic hyperparathyroidism enhances bone resorption. In the face of hypocalcemia, 1-25 (OH)2 D interacts with VDR in osteoblasts to produce RANK-L which binds into osteoclast which ultimately cause bone resorption and release of calcium and phosphorus in the circulation (121)

Rickets is a disease of growing child due to alteration of calcium and phosphate homeostasis causing impaired apoptosis of hypertrophied chondrocytes in the growth plate (111). Enough calcium and phosphate are necessary for bone growth with bone health maintenance. Vitamin D, parathyroid hormone and FGF 23 are the three hormones who interacts with each other to maintain homeostasis. Ninety percent of calcium is stored in the bone and less than 0.5% remain in circulation in the blood and bound to albumin or globulin. The prime source of calcium is milk; 35% of dietary calcium is absorbed in the small intestine through the membrane channel TRPV6, reabsorbed in the

renal tubule via TRPV5, and deposited in bone. Adequate availability of calcium is essential for hydroxyapatite [CaS(PO4)3OH] formation in the bone (111).

Inorganic phosphate (Pi) comprises about 0.6% of neonate and 1% of adult body weight respectively. Bone and teeth contain 85% of total body Pi and rest tissue contain approximately 14% and it is distributed in the intracellular compartment. Apart from bone mineralization phosphate is involved in cellular energy (ATP), membrane function, cell signaling, DNA-RNA biosynthesis and acid base buffer (122). Hypophosphatemia impairs many cellular functions and may cause neuromuscular dysfunction. A steady state of phosphate concentration can be maintained by a balanced diet with dietary phosphate absorption of 16 mg/kg/day and the same amount (10 mg/kg/day) of bone turnover and urine excretion (3 mg/kg/day) (89). Growing children need positive balance, and a protein-rich diet such as milk, meat, and eggs are good sources of inorganic phosphate and essential for bone mineralization (111)

Phosphaturia is calculated by tubular reabsorption of phosphate (TRP) and tubular maximum phosphate reabsorption per glomerular filtration rate (TMP/GFR)

TRP= 1- ((Up/Pp) x (Pcr/Ucr)) (123)

Abbreviation: Up: urinary phosphate; Pp- Plasma phosphate; Pcr- Plasma creatinine; cr Urinary creatinine

An online calculator is available at https://gpn.de/service/tmp- gfr= calculator

Low TRP and TmP/GFR suggest phosphate wasting and high TRP and TmP/GFR are consistent with nutritional phosphate deficiency.

Stages of vitamin D deficiency

Stage I: In this stage 25 (OH)D decreases resulting in hypocalcemia and euphosphatemia, 1-25(0H)2 D may increase or may remain unchanged, this stage is mostly asymptomatic, it may rarely have features of hypocalcemia and even seizure with tetany

Stage II: Continued 25 OHD deficiency causes hypocalcemia which increases parathyroid hormone by binding with CaSR as compensatory phenomenon to maintain eucalcemia through demineralization of bone (124).

Patient develops hypophosphatemia and has slightly increased alkaline phosphatase. Calcitriol may be elevated at this stage and hence may not have symptoms of deficiency, and its measurement does not give rise to an actual deficiency state. Clinical features of rickets may start appearing, as well as radiological changes (125).

Stage III: Continued worsening leads to a stage of universal hypophosphatemia & hypocalcemia, evidence of overt signs of demineralization, & both clinical and radiological evidence of raised alkaline phosphatase. Hypophosphatemia is a universal final entity in all types of rickets (124). Failure of the compensatory mechanism leads to low Ca and Pi (111)

In hypocalcemia, secondary hyperparathyroidism causes some amount of phosphaturia where as in phosphopenic rickets phosphaturia is large and prime cause, it has normal or slightly elevated parathormone (126). At this stage some amount of aminoaciduria is characteristics. Dietary calcium absorption in the gut decreases to 10 -15% from 35% when vitamin D deficiency occurs. Calcium deficiency is recognized by calcium sensory receptor (CaSR) of parathyroid gland causing parathormone release (127).

Table II **Biochemical markers and radiography of vitamin deficiency in children (128)**

	Stages		
	Early	Moderate	Severe
Serum calcium	N/ ↓	N/↓	↓↓
Serum phosphorus	↓ /N	↓	↓ /N
ALP	↑	↑↑	↑↑↑
PTH	↑	↑↑	↑↑↑
25(OH)D	↓	↓↓	↓↓↓
$1,25(OH)_2D$	N	↑	↑ / N / ↓
Radiography	Osteopenia	Rachitic Changes 1+	Rachitic Changes 2+

Parathormone increase calcium reabsorption from the gut and kidneys' excretion of phosphate. It also regulates the conversion of 1-25 (OH)2D by influencing mobilizing calcium from the bone to maintain normalized calcium status. In doing so, PTH causes hypophosphatemia (129).

During growth up to puberty, rickets and osteomalacia co-exist in hypophosphatemia. After epiphyseal closure, only osteomalacia is common. The growth plate lies between the epiphysis and metaphysis and has three zones: resting, proliferating & hypertrophic (129).

Apoptosis of epiphyseal chondrocytes ensures the removal of terminal differentiated cells from cartilage and promotes the invasion of vascular elements of bone marrow, including osteoblasts and osteoclasts, for new bone formation (118).

Phosphate induces chondrocyte death in programmed manner via apoptotic protease activity sector 1 (APAF1), capcase 9 and apoptosis inducing factor (AIF). Apoptosis is the result of capcase 3 activity which is activated by capcase 9 which is in turn activated by APAF1. Phosphate induces cell death in dose time dependent fashion. Osteoblast differentiation and matrix mineralization need enzymatic activity of alkaline phosphatase. Increased alkaline phosphatase activity recruits' phosphate from pyrophosphate. Free phosphate enters the cells through sodium dependent phosphate transport(122).

Failure of apoptosis leads to excessive compensatory proliferation of cartilage of growth plate, enlarging its size without sufficient mineralization. It results in cup shaped widened soft metaphysis. Normally vascular invasion of growth take place, conversion into primary bone require mineralization of calcium and phosphate. In the absence of mineralization growth plate cartilage of metaphysis becomes organized, maintains loose columnar orientation, mineralization defects lead to osteoid accumulation (112).

Osteomalacia increases bone mass, disrupts growth plate, and impairs longitudinal growth (24).

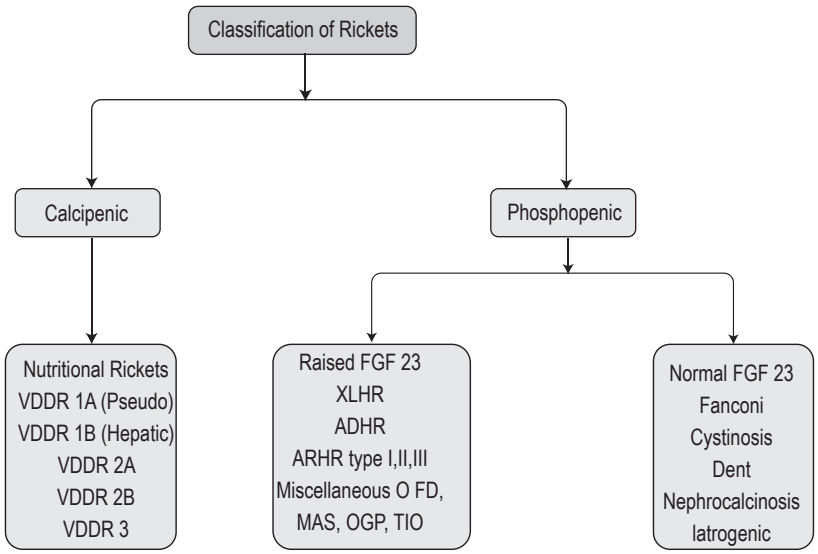

Figure 6: *Classification of Rickets*

*VDDR- vitamin D dependent rickets, FGF 23- Fibroblast growth factors, XLHR- X linked hypophosphatemic rickets, ADHR – autosomal dominant hypophosphatemic rickets, ARHR- autosomal recessive hypophosphatemic rickets, FD- fibrous dysplasia, MAS- McCune Albright syndrome, OGD- osteoglophonic dysplasia, TIO- tumor induced osteomalacia, HHRH- hereditary hypophosphatemic rickets with hypercalciuria

Calcipenic rickets has low calcium as initiating event, but it has normal or low calcium because of compensatory high PTH activity.

Calcipenic rickets is predominantly caused by less calcium intake (nutritional) being most common type of rickets. Less often it is due to defects in the metabolic pathways of vitamin D or from its target tissue resistant. Hypocalcemia stimulates PTH release with consequent renal calcium conservation & its phosphate excretion (111,124)

Phosphopenic rickets on the other hand, is mostly due to phosphaturia and less often by means of insufficient phosphate intake or gut disease. Phosphopenia, phosphaturia are the final pathway of all rickets but massive phosphaturia & significant phosphopenia is characteristic of phosphopenic rickets (99,115,125).

Table 3 **Summarized vitamin D with rickets [Courtesy: Haffner D et al. (123)**

Disorder	Gene (location)	Pathogenesis	Ca	P_i	ALP	$U_{P/crea}$	PTH	25 (OH)D	FGF23
Rickets and/or osteomalacia with high PTH levels (calcipenic rickets)									
Nutritional rickets (vitamin D and/or calcium deficiency)	NA	Vitamin D deficiency	N,↓	N,↓	↑↑↑	Varies	↑↑↑	↓↓,N	N
Vitamin-D-dependent rickets type 1A	*CYP27B1* (12q14.1)	Impaired synthesis of 1,25$(OH)_2$D	↓	N,↓	↑↑↑	Varies	↑↑↑	N	N,↓
Vitamin-D-dependent rickets type 1B	*CYP2R1* (11p15.2)	Impaired synthesis of 25(OH)D	↓	N,↓	↑↑↑	Varies	↑↑↑	↓↓	N
Vitamin-D-dependent rickets type 2A	*VDR* (12q13.11)	Impaired signalling of the VDR	↓	N,↓	↑↑↑	Varies	↑↑↑	N	N,↓
Vitamin-D-dependent rickets type 2B	*HNRNPC* (14q11.2)	Impaired signalling of the VDR	↓	N,↓	↑↑↑	Varies	↑↑↑	N	N
Vitamin-D-dependent rickets type 3	*CYP3A4* (7q21.1)	↑ Inactivation of 1,25$(OH)_2$D	↓	↓	↑↑↑	Varies	↑↑↑	↓	?

Table 3 Summarized vitamin D with rickets [Courtesy: Haffner D et al. (123) (Cont'd)

Disorder	Gene (location)	Pathogenesis	Ca	P_i	ALP	$U_{P/crea}$	PTH	25 (OH)D	FGF23
Phosphopenic rickets and/or osteomalacia due to dietary phosphate deficiency or impaired bioavailability									
• Breastfed very-low-birthweight infants • Use of elemental or hypoallergenic formula diet or parental nutrition • Excessive use of phosphate binders • Gastrointestinal surgery or disorders	NA	Phosphate deficiency	N, ↑	↓	↑, ↑↑	?	N	N	N, ↓
Phosphopenic rickets and/or osteomalacia with renal tubular phosphate wasting due to elevated FGF23 levels and/or signalling									
X-linked hypophosphataemia	*PHEX* (Xp22.1)	↑ FGF23 expression in bone and impaired FGF23 cleavage	N	↓	↑, ↑↑	↓	N, ↑	N	↑, N
Autosomal dominant hypophosphataemic rickets	*FGF23* (12p13.3)	FGF23 protein resistant to degradation	N	↓	↑, ↑↑	↓	N, ↑	N	↑, N
Autosomal recessive hypophosphataemic rickets 1	*DMP1* (4q22.1)	↑ FGF23 expression in bone	N	↓	↑, ↑↑	↓	N, ↑	N	↑, N

Table 3 Summarized vitamin D with rickets [Courtesy: Haffner D et al. (123) (Cont'd)

Disorder	Gene (location)	Pathogenesis	Ca	P_i	ALP	$U_{P/crea}$	PTH	25 (OH)D	FGF23
Autosomal recessive hypophosphataemic rickets 2	ENPP1 (6q23.2)	↑ FGF23 expression in bone	N	↓	↑, ↑↑	↑	N, ↑[c]	N	↑, N
Raine syndrome associated (ARHR3;	*FAM20C* (7q22.3)	↑ FGF23 expression in bone	N	↓	↑, ↑↑	↑	N, ↑[c]	N	↑, N
Fibrous dysplasia	*GNAS* (20q13.3)	↑ FGF23 expression in bone	N,	↓	↑, ↑↑	↑	N, ↑[c]	N	N, ↑
Tumour-induced osteomalacia (TIO)	NA	↑ FGF23 expression in tumoural cells	N,	↓	↑, ↑↑	↑	N, ↑[c]	N	N, ↑
Cutaneous skeletal hypophosphataemia syndrome	NRAS (1p13.2) HRAS (11p15.5) KRAS (12p12.1_	↑ FGF23 in dysplastic bone lesion	N,	↓	↑, ↑↑	↑	N, ↑[c]	N	N, ↑
Osteoglophonic dysplasia (OGD)	*FGFR1* (8p11.23)	↑ FGF23 expression in bone	N, ↓	↓	↑, N	↑	N, ↑[c]	N	N

Table 3 **Summarized vitamin D with rickets [Courtesy: Haffner D et al. (123) (Cont'd)**

Disorder	Gene (location)	Pathogenesis	Ca	P_i	ALP	$U_{P/crea}$	PTH	25 (OH)D	FGF23
Hypophosphataemic rickets and hyperparathyroidism	*KLOTHO* (13q13.1)	Unknown; translocation of the KLOTHO promoter	N,↓	↓	↑,↑↑	↓	↑↑	N	↑
Phosphopenic rickets and/or osteomalacia due to primary renal tubular phosphate wasting (Independent of FGF)									
Hereditary hypophosphataemic rickets with hypercalciuria	*SLC34A3* (9q34.3)	Loss of function of NaPi2c in the proximal tubule	N	↓	↑(↑↑)	↑	Low N,↓	N	N, ↑[e]
X-linked recessive hypophosphataemic (Dent disease 1)	*CLCN5* (Xp11.23)	Loss of function of CLCN5 in the proximal tubule	N	↓	↑(↑↑)	↑	Varies	N	N
Hypophosphataemia and nephrocalcinosis	*SLC34A1*	Loss of function of NaPi2a in the proximal tubule	N	↓	↑(↑↑)	↑	Varies	N	
Fanconi renotubular syndrome	(5q35.3)			↓	↑(↑↑)	↑	Varies	N	↑
Cystinosis (OMIM#219800) and other hereditary forms of Fanconi syndrome	*CTNS* (17p13.2)	Cysteine accumulation in the proximal tubule	N	↓	↑(↑↑)	↑	N, ↑[e]	N	
Iatrogenic proximal tubulopathy	NA	Drug toxicity	N	↓	↑(↑↑)	↑	Varies	N	

Currently more than 20 types of rickets are known and broadly they are grouped under calcipenic and phosphopenic rickets (130).

A. Calcipenic rickets: Nutritional and hypocalcemic rickets are common. The hypocalcemia can be caused by calcium and vitamin D deficiency and abnormal vitamin D metabolism and action. Rickets is caused by deficiency of UV radiation, dietary deficiency with reduced intestinal absorption (88).

1. Vitamin D deficiency due to inadequate sun exposure (90% of source of vitamin D) and food fortification-supplementation (10% of source)
2. Dietary vitamin D and calcium deficiency
3. Intestinal disease and malabsorption
4. Vitamin D dependent rickets (VDDR) type 1A: Vitamin D dependent rickets type 1 A (VDDR 1A) is due to CYP27B gene mutation leading to 1 α hydroxylase enzyme defect & hence impaired conversion of 25 (OH)D (calcidiol) to 1-25 (OH)2 D (calcitriol). Hence, they have normal 25 (OH)D & low 1-25(OH)2 D, these are calcipenic rickets with very high parathyroid hormone, alkaline phosphate (ALP) with minimal urinary phosphate (73). They are called pseudo deficiency rickets because of normal 25 (OH)D status (131). VDDR 1A has early infancy presentation.
5. Vitamin D dependent rickets type 1B (VDDR 1B) is due to mutations of CYP2R1 gene resulting impaired hepatic 25- hydroxylase enzyme activity & hence impaired production of 25 (OH) D. It is also a calcipenic rickets with raised parathyroid hormone (PTH) & very high ALP & trivial amount of phosphaturia (32). They have low 25(OH)D & variable amount of 1-25 (OH)2D. They respond clinically with 25 (OH) D (calcidiol) (132). Hepatic disease with 90% function loss can have type 1B VDDR (88). VDDR 1B may have milder presentation and may improve with age (111,129)
6. Vitamin D dependent rickets type 2A (VDDR 2A): Now a days called hereditary 1,25 (OH)2D resistant rickets (HVDRR) due to mutation in vitamin D receptors (VDR) gene. Due to VDR mutations with proximity of vitamin D and vitamin A receptors, 50% of

HVDRR has partial or total absence of eyelash and eyebrow. Multiple milia, epidermal cysts and oligodontia are additional ectodermal anomalies that can be found here. Clinical features start appearing by 2-8 months of age. Spared eyelashes, hypotonia, irritability, seizure, tetany, and failure to thrive may present in the first few months of life. Late cases have frontal bossing, long bone deformity, rib case abnormalities and fractures, progressive skeletal disease. Late diagnosis has high mortality (133)

7. Vitamin D dependent rickets type 2B (VDDR 2B) resembles VDDR2A but is not caused by a defect in the VDR gene. Rather, the molecular defect appears to be overexpression of a nuclear protein that specifically interacts with a DNA response element that binds retinoid X receptor-VDR heterodimers. This dominant-negative protein appears to be a member of the family of heterogeneous nuclear ribonucleoproteins (hnRNPs), which attenuate gene transcription via their role as hormone response element- binding proteins (8,133).

8. Vitamin D dependent type 3 (VDDR3) is due to mutated CYP3A4 gene leading to inactivation of 1-25 (OH)2 D is a rare type of refractory rickets, needs higher dose (5000 IU daily) to control the disease (134). Its presentation is like VDDR type 1 A with bone deformities. They have low 25 (OH) D & 1-25(OH)2 D, require high dose of 1-25 (OH)2 D (135)

9. Primary hyperparathyroidism

B. Phosphopenic rickets: Due to renal phosphate wasting and less intake of phosphate containing food or gastrointestinal loss.

1. Rickets due to dietary phosphate deficiency or bioavailability, breastfed, prematurity, low birth weight infants, have high phosphate need (112).

2. Gastrointestinal diseases or surgery including bariatric surgery, refeeding in malnourished has phosphate deficiency.

3. Excessive use of phosphate binder, elemental hypoallergic formula deficit of phosphate or parental nutrition.

4. Soy formula, rice, cereals have high phytate which decreases phosphate absorption (112).

5. Renal loss of phosphate:

X-linked hypophosphatemic rickets (XLH)

X- linked hypophosphatemia is due to mutation of PHEX gene causing dominantly inherited disease responsible for 80% of hypophosphatemic rickets. PHEX is underlying gene in 90% of familial cases and 10 % of sporadic cases (35). The PHEX gene regulates the expression of FGF-23 by affecting its cleavage and impairing bone mineralization (111,136,137). The hormone FGF-23 inhibits the transcription of genes encoding NaPi2A and NaPi2C. FGF-23 can downregulate the CYP271B gene, which encodes 1α hydroxylase, and upregulate the cytochrome P450 family, which encodes 24-hydroxylase and hence causes reduced synthesis of 1-25 (OH)2D. FGF-23 acts via its receptors (FGFRIs) on proximal tubular cells. FGF-23 level is five times higher in X-linked hypophosphatemia (XLH) compared to general population (138,139)

XLH usually manifests in first 2 years of life. These children remain short of stature and have a waddling gait, which is evident by coxa vera. When they start walking, they may have osteoarthritis, enthesopathies, and pseudo facture (cortical infarction surrounded by thickened periosteum). Rarely they have sensorineural hearing loss. Boys show full range of disease, girls have asymptomatic isolated hypophosphatemia to full blown disease. Many women present after pregnancy (95).

Infants with a family history of XLH have disease beginning at 4-6 months; others have bowing when they start walking at around two years. Bowing of the leg up to 2 years is considered physiological. In XLH, waddling gait becomes apparent; height velocity decelerates, and genu valgus or varus develops if not treated. These children may have poorly grown pulp chambers and root canals because of the non-mineralization of dentin. Hence, tooth malposition, abscess, and early tooth decay occur in young adults (140).

X linked dominant hypophosphatemic (XLH) rickets have additional features like craniosynostosis & sensorineural hearing loss. These children have high FGF-23, significant phosphaturia and hypophosphatemia(141,142).

These children are conventionally treated with oral phosphate. Phosphate supplementation should not be targeted to normalize serum phosphate because it may cause secondary hyperpara- thyroidism (139). FGF-23 levels remain two-fold higher in treated XLH rickets. FGF-23 has

age related reference value for its intact molecule and C-terminal FGF-23. For the diagnosis of XLH hypophosphatemia, FGF-23 above 30 pg/ml can be taken as standard. PHEX gene assay may be confirmatory (143)

Autosomal dominant hypophosphatemic rickets (ADHR)

Autosomal dominant hypophosphatemic rickets (ADHR, FGF-23 mutation) is a rare disease with XLH-like presentation, usually after early childhood, adolescence, and adulthood (130). They present with disproportionate short stature, bony deformities, dental abscess (130). After puberty, they may present with osteomalacia symptoms, including weakness, bone pain, and pseudo-fractures(130,144). Treatment of iron deficiency anemia has a role in the treatment of ADHR (130,145). These children have low levels of 1-25(OH)2 D. ADHR has milder presentation than XLH and may undergrow spontaneous resolution (146)

It has 2 subgroups, first one presenting at childhood simulating XLH rickets and other group presenting with adolescent bone weakness and pseudo fracture.

Autosomal recessive hypophosphatemic rickets (AHRH)

Autosomal recessive hypophosphatemic rickets (ARHR) are of 3 types ARHR 1, ARHR 2 and ARHR 3 (Raine syndrome) due to mutations of DMP 1(dentin matrix acidic phosphoprotein 1) ENPP1 (Endoneucleotide pyrophosphate 1) & FAM 20 C (Family with sequence similarity 20) genes respectively (147).

Mutations of DMP1, ENPP1 & FAM20 C cause increased fibroblast growth factors (FGF-23) expression in osteocytes & osteoblasts (bone) and hence phosphaturia, phosphopenia, trivial ALP excess and PTH excess. These children have normal calcium, 25(OH)D & 1-25(OH)2 D level (130)

The mechanism of raised FGF-23 in DMP1 mutation is unclear.

ARHR type 2 (ENPP1 mutations)- ENPP1 is a cell surface protein catalyzing ATP to pyrophosphate, reported first in the Bedouin families with infantile arterial calcification (124,148,149). The mechanism of raised FGF-23 by ENPP1 is not clearly known. ENPP1 is an enzyme responsible for mineralization that inhibits pyrophosphate formation from ATP. Therefore, ENPP1-deficiency results in pathological calcification and over-mineralization in vessels and soft tissues. Generalized arterial calcification of infancy (GACI) of large, medium-sized arteries, myocardial

infarction, and early death are presentations of ARHR type 2 (ENPP-1 gene mutations). Arterial and cardiac calcification must be assessed by carotid intimal medial thickness (CIMT) and cardiac ultrasound (147).

ARHR type 3 (Raine syndrome, FM20 C mutation)- FM20 C is an important key regulator of osteoblasts & osteocytes, it also promotes FGF-23 breakdown. Raine syndrome is a very rare disease with a wide range of presentations, starting from mild phosphaturia and hypophosphatemia to severe disease with generalized osteosclerosis, midfacial hypoplasia, hypoplastic nose, exophthalmos, intracranial calcification, sensorineural hearing loss, development delay, large fontanelle, epilepsy, and amelogenesis imperfect (130,150). These children rarely survive infancy. Non-lethal cases present with osteosclerosis of long bones rather than rickets. A high phosphate diet can improve bone disease, as demonstrated in FAM20 disease (150,151).

Other causes of hypophosphatemic rickets include fibrous dysplasia (FD) is due to GNAS mutation, tumor induced osteomalacia (TIO) due to increased FGF23 expressions, cutaneous skeletal hypophosphatemic syndrome due to (renin aldosterone system) RAS gene mutation, KLOTHO gene deficiency causing hypophosphatemic rickets and hyperparathyroidism, osteoglophonic dysplasia due to FGFR1 gene defect, cutaneous skeletal hypophosphatemic syndrome (epidermal nevi, congenital melanocytic nevi) due to NRAS or HRAS with KRAS gene mutation with increased FGF 23 expressions in dysplastic bone (152).

Fibrous dysplasia (FD) when associated with skin pigmentation, and premature sexual development it is called Mc Cune Albright syndrome (MAS). FD/MAS is a rare disease with gain of function mutation in GNAS gene that encodes stimulatory protein which leads to raised FGF-23 expression and can have phosphoturic rickets. Approximately 50 % Mc Cune Albright syndrome (MAS) or fibrous dysplasia (FD) may develop hypophosphetemic rickets or osteomalacia (153). Fibrous dysplasia, osteoglophonic dysplasia (FGFR1 receptor defect) and mesenchymal tumor may cause increased FGF-23 expression and hence same sort of presentation.

Defect in the gene encoding Klotho can also cause hypophosphatemic rickets with hyperparathyroidism. Mutations in the gene encoding the sodium-hydrogen regulatory factor 1 (NHERF 1) leads to impaired interaction of NHERF 1 & NPT2A and hence phosphaturia and osteomalacia (154).

Phosphaturic rickets with tubulopathy

In these group important diseases are Dent disease & Fanconi syndrome and hereditary hypophosphatemic rickets with hypercalciuria (HHRH) due to SLC34A3 gene defect.

Dent disease due to mutations on CLCN5 gene encoding CLC5 protein can present in early infancy with fractures and renal tubular acidosis features come in adolescence or early adulthood. Genetic abnormalities lead to failure of 1, 25 (OH)2 D3 binding, reduction of binding sites, abnormal binding affinity, insufficient translocation of 1, 25(OH)D3 receptor complex to nucleus (155).

Fanconi renotubular syndrome is due to mutations of SLC34A1 gene causing loss of function of NaPi2A in the proximal tubule leading to hypophosphatemia and nephrocalcinosis(130). It has phosphaturia, high alkaline phosphatase (ALP), normal 25 (OH)D & raised 1-25(OH)2 D (130).

Drug induced hypophosphatemic rickets by cisplatin, ifosfamide, tenofovir or protease inhibitors occurs in only 1 % of children with these medication (130,137,156)

These children can also have nephrolithiasis & they have normal PTH (157)

Table 4 **Classification of vitamin D status**

	Shroff R et al. (158)	Hoffner D (111)
Sufficiency	>75 nmol/L (30ng/ml)	> 50 nmol/L
Insufficiency	50-75 nmol/ (20-30 ng/ml)	30-50 nmol/L
Deficiency	12-50 nmol/L (5-20 ng/ml)	<30 nmol/L
Severe deficiency	<12 nmol/L (<5 ng/ml)	

Optimum level of 25(OH)D level above 30 ng/ml (75 nmol/L) is suggested in children with CKD stages 2-5 D (159)

US Institute of Medicine defines serum 25 (OH)D levels of <30 nmol per litre as value for the risk of developing rickets and metabolic bone disease (160)

Table 5 **Physiological disturbances reported at different serum 25(OH)D levels (158)**

25 (OH) D level (nmol/L)	Physiological disturbances
<10	Rickets or osteomalacia, severe hyperparathyroidism, calcium malabsorption
10-30	PTH stimulation, reduced calcium absorption
30-40	Sometimes raised PTH
>40	No further increase in 1-25(OH)2D production or increased calcium absorption; abolition of seasonal variation in PTH
>75	No Pathologic mineralization defects or growth plate abnormalities
>120	Associated with increased mortality
>250	Risk of hypercalcemia and hypercalciuria

*To convert nmol/L to ng/ml divide by 2.5

International Osteoporosis Foundation (IOF), American Geriatrics society (AGS) suggest that a minimum level 30 ng/ml (75 nmol/L) is necessary in older adults to minimize the risk of falls and fracture. Tolerable upper level of 25(OH)D is 100 ng/ml. Serum 25(OH) D levels of 30 nmol/L can be protective against bone disease (161). US Institute of Medicine also defines cut off value as <30 nmol/L for risk of rickets.

Occasionally, but very rarely, rickets may be present at birth. Most patients who develop rickets during infancy do not have evidence of this condition at birth. Bone mineralization is poor and ribs are very soft in these patients, giving rise to a chest deformity, which present radiologically as a bell-shaped chest. Respiratory function is impaired, and respiratory support may be required. Hypocalcemia and hypophosphatemia are present, 25 OHD is low, PTH is elevated and the maternal vitamine D is low or undetectable. Treatment consists of providing adequate vitamine D and calcium supplementation together with appropriate respiratory support (162).

Sources of vitamin D

Photoisomerization of skin contributes 90% of human vitamin D requirement, and the remaining 10 % comprises foods, fortified foods & supplement foods. Vitamin D3-rich foods are fatty fish like pangas, salmon, sardine, tilapia, mackerel, egg yolk, milk and milk products, liver, cod liver oil, and egg yolk. Rich sources of calcium phosphate are milk and milk products, meat, fish, and eggs. Number of food items containing vitamin D are limited. Vitamin D is stored mainly in the liver and a small amount in adipose tissue(24)

RISK FACTORS FOR RICKETS (138,163)

1. Low dietary calcium, phosphate, and vitamin D for example in malnutrition, poor diet choice, restriction by culture, vegan diet which is low in calcium.
2. Low sunlight exposure for example in indoor living, whole body clothing, high altitude living, environmental pollution and winter season.
3. Pigmented skin of African & Asian descent. Melatonin acts as sunscreen with rickets which is more common in African, Asian people than white
4. Prematurity
5. High physiological demand in infancy, pregnancy, lactation, old age, post-menopausal women
6. Prolonged exclusive breast feeding
7. Maternal vitamin D deficiency- Breast milk contains only 15 - 50 IU/L (0.4 to 1.2 microgram/L) even without maternal deficiency, average breast milk of 750 ML per day contains 10 - 40 IU/day (0.25-1 mcg/day) which is equivalent to 25 IU (0.6 microgram) per litre (164) . Breast milk has low phosphate as well. More than 95% of the exclusive breast-fed infant has vitamin D deficiency (81)
8. Non supplementation, non-food fortification
9. Chronic renal disease has lack of conversion of 25 (OH)D3 because of anatomical loss of renal tissue, increased FGF-23 production, suppressed 1-α-hydroxylase activity by hyperphosphatemia, and suppressed megalin-mediated absorption of 25(OH)D (25).

10. Gastrointestinal disease with malabsorption of fat with steatorrhea causes reduced fat emulsification and chylomicron facilitated absorption. Gastrectomy for bariatric surgery has reduced acid secretion and proximal intestinal malfunction which causes vitamin D deficiency.
11. Protein pump inhibitors decrease calcium and phosphate solubility and hence reduce intestinal absorption.
12. Hepatic disease both parenchymal and obstructive type with 90% loss of liver function, cause decreased calcidiol 25(OH)D production. Hence rickets is rare late presentation of substantial hepatic dysfunction Replacement of vitamin D has quick response in these patients
13. Extensive burn and severe skin disease can cause less vitamin D production
14. Too sick children in ICU setting, hospitalized for long period may have different grades of vitamin D deficiency
15. Obesity can have vitamin D deficiency due to its sequestration in fat
16. Nephrotic children have a loss of vitamin D binding protein (VDBP) and calcidiol (25(OH)D). Eighty-90% of vitamin D remain bound with VDBP, 10-20% remain in bound form with albumin, and less than 1% in free form, but only 3-5 % of vitamin D binding sites of VDBP are occupied. Hence, vitamin D binding protein is not a rate-limiting except in nephrotic syndrome where a large number of proteins are lost (165). Free 25 (OH) remains plenty despite reducing the VDBP bound formed of 25 (OH)D. Free form is bioavailable, a physiologically important biomarker & may be a normal genetic morphism of VDBP that varies markedly between race & ethnicity, e.g., hepatocyte GC1 and GC2 in black predisposes low VDBP & 25 (OH)D (81)
17. Drugs that increase vitamin D catabolism by increasing P-450 enzyme activity are phenytoin, phenobarbitone, carbamazepine, oxcarbazepine, gentamycin, isoniazid, theophylline, rifampicin, antiretroviral drugs. Both 25OHD, and 1-25 $(OH)_2D$ are converted into inactive metabolite 24(OH)D (165).

Insufficiency of formula fortification and even with maternal deficiency can give rise to low vitamin D in mixed fed infants. Low phosphate containing formula and formula designed for multiple food allergies may have phosphate with low bioavailability and hence may cause rickets. Low intake of dietary sources of vitamin D such as salmon, mackerel, sardines, and other food sources like liver, egg yolk, cod liver oil, fortified food like milk and milk-based foods(166,167).

Sunlight falls in oblique manner and ultraviolet rays scatter in winter days. Melanin act as sunscreen, as a result rickets is more common in African black people, followed by brown Asian people than White children. Hence beyond a latitude of 40°, little or no ultraviolet ray reaches on the surface of the globe. Today many low-income countries have higher low birth weight prevalence rate and hence more rachitic loads (5,59,65).

The following factors increase the possibility of rickets in infants-

1. Prematurity and VLBW (<1500gm)- Premature infants have low calcium and phosphorus
2. Intrauterine growth retardation (IUGR) with birth weight <3rd percentile for gestational age.
3. Food with low mineral content, poor tolerance of fortified foods.
4. Parenteral nutrition >4 weeks
5. Renal disease
6. Concomitant severe cholestasis.
7. Long-term steroid use. Steroids inhibit vitamin D absorption by receptor binding competiton.
8. Intestinal failure in necrotizing colitis & resection.
9. Broncho pulmonary dysplasia treated by loop diuretics and or fluid restriction

Rickets develops in 2% of infants born of <32 weeks gestation, of <1500 gm birth weight and 0.1 percent of 32 to 36 weaker. Another study found 15 percent rickets in <1000 gm neonate despite fortified food (168). Infants, disabled persons, and older adults can have less sun exposure, at the same time skin of the people older than 70 years does not convert vitamin-D effectively, they may have tissue resistance, may have hypocalcemia leading to secondary hyperparathyroidism (169)

Phosphopenia due to phosphaturia is less commonly due to reduced intake and malabsorption of food. Phosphopenia is found in a) 2.2-3.1% of hospitalized patients, b) 29-34% in ICU, c) 65-80% in patient with sepsis, d) 75% with major trauma, e) 21.5% with chronic pulmonary disease, f) 2.5-30.4% in chronic alcoholism, g) Rarely it can also be due to inadequate dietary intake, malabsorption, prolonged antacid intake, use of phosphate binder, refeeding syndrome, elderly people, receiver of continuous renal replacement therapy (CRRT), hungry bone syndrome, acute respiratory alkalosis and during treatment of diabetic ketosis, h) Dietary phosphate deficiency usually found in combination with vitamin D, calcium and other nutrients deficiency.

CLINICAL FEATURE :

Bone deformities are the hallmark of rickets. Rickets is more often reported between 4-18 months of age. Weight bearing patterns of the limbs includes forearm deformities in crawling infant, whereas genu varum (bow legs) & genu valgum (knock knee) are found in walking toddler (162).

Bone deformities are the hallmark of rickets. Rickets is more often reported between 4-18 months of age. Weight-bearing patterns of the limbs include forearm deformities in crawling infants, whereas genu varum (bow legs) & genu valgum (knock knee) are found in walking toddlers (161).

Rickets is characterized by a variety of symptoms affecting different parts of the body. Common features include aches and growing pains, failure to thrive, listlessness, and a protruding abdomen due to hypotonia and visceroptosis. Muscle weakness, particularly in proximal areas, is often observed, along with difficulty climbing and getting up from squatting positions (Gower sign). Delayed motor milestones and dentition are typical, with no eruption of incisors by 10 months and no molars by 18 months, accompanied by dental issues like caries and enamel defects. Neonatal jitteriness and alopecia are also indicators, as well as raised intracranial pressure. Head-related symptoms include craniotabes, frontal bossing, delayed fontanel closure, craniosynostosis, Chiari malformation, and dolichocephaly. Chest symptoms encompass

the Harrison groove, funnel chest, forward projection of the breastbone, and rib cage abnormalities like the rachitic rosary. Back-related issues involve scoliosis, kyphosis, lordosis, osteoarthritis of the hip, and pseudo-fractures. Extremities may show enlargement of wrists and ankles, varus or valgus deformities, windswept deformity, anterior bowing of the tibia and femur, and coxavara causing a waddling gait. Ear abnormalities such as hearing loss and tinnitus may also be present. (18,24,162)

Additionally, dysmorphism, heterotopic calcification of ligaments and joint capsules, hypocalcemic symptoms like tetany and seizures, poor feeding, irritability, and calcification in autosomal recessive hypophosphatemic rickets are observed. Iron and trace element deficiencies may coexist, exacerbating the condition.

Autosomal recessive hypophosphatemic rickets type 1 (ARHR1) may have localized arterial calcification whereas AHHR type 2 may have generalized arterial calcification which are detected by carotid intimal media thickness (CMIT) and cardiac ultrasound (130). There can be early death (147).

In Raine syndrome children may have midfacial hypoplasia, seizures, sensory neural hearing loss, large fontanel, developmental delay may be overt form or trivial (130,170,171)

Table 6 **Difference between calcipenic and phosphopenic rickets (99)**

Features	Calcipenic rickets	Phosphopenic rickets
Muscle weakness	Present	Absent
Bony pain	Common	Uncommon
Extremities involved	All limbs	Predominantly lower limb
Tetany	May be present	Absent
Enamael hypoplasia	May be present	May be present
Dental abscess	Absent	May be present
Serum calcium	Low/normal	Normal
Serum phosphorus	Low	Low
Alkaline phosphatase	Elevated	Elevated
Parathyroid hormone	Elevated	Normal/ minimally elevated
Osteopenia and osteitis fibrosa	Present	Absent

Chronic Kidney Disease-Mineral bone disease (CKD-MBD)

Deteriorating renal function with reduced calcitriol (1-25$(OH)_2$D) formation leads to hypocalcemia, secondary hyperparathyroidism, hyperphosphatemia & raised FGF-23 (172).

FGF-23 is raised in CKD stage 2 to keep phosphate at normal level. The absence of FGF-23 cofactor klotho may cause the compensatory further increase of FGF-23 to maintain phosphate homeostasis by phosphaturia. Parathormone (PTH) is found raised in 50 % of pediatric CKD with estimated glomerular filtration rate (eGFR) <50 ml/min/1.73m2. In CKD-MBD growth is usually arrested when severe secondary hyperparathyroidism causes destruction of growth plate. Mean PTH may have a positive association with annual height (95). Modest PTH elevation (3-5 times upper normal limit) is associated with better outcome compared to high (>500 pg/ml, 9 times upper limit normal). CKD-MBD has bone pain, rickets, fracture, leg deformity, growth failure, and ectopic vascular calcification including coronary artery and left ventricular hypertrophy. Mesenchymal cells are converted to osteoblast in uremia and cause vascular calcification. Advanced CKD leads to 1-25 (OH)2 D3 declination, obvious hypocalcemia, hyperphosphatemia, and hence higher PTH (173).

Parathormone (PTH) starts rising in CKD- stage 2 to maintain normal calcium phosphate and vitamin-D. Hyperparathyroidism causes vascular smooth muscle cell apoptosis, calcification, increased thickness, and stiffness and thereby increased cardiovascular mortality (174). Parathyroid hormone (PTH) has both anabolic (bone formation) and catabolic (bone resorption) effects on bone. It acts via PTH type1 receptor (PTHIR) expressed in osteoblasts and osteocytes, it increases osteoanabolic signaling by decreasing osteolytic sclerostin. PTH generally overestimates biological activity in advanced CKD as it can be oxidized to inactive PTH (175). Long C terminal fragment has long half-life, resistance, or hypo responsiveness to tissue receptor (PTH1R), FGF-23 stimulated Klotho inhibits binding of PTH to its (PTH1R) receptor. So PTH level may not always correlate with CKD severity. Hence PTH hypo responsiveness in advanced CKD may cause low turnover disease despite high PTH level (176). However severe secondary hyperparathyroidism may cause high bone turnover and overt renal osteodystrophy. Growth hormone (GH), insulin like growth factor I (IGF-1) has a positive rule in the proliferation & differentiation of chondrocytes in the

epithelial epiphyseal growth plate. Growth hormone (GH) also stimulates tubular phosphate reabsorption through insulin-like growth factor 1 (IGF-1) and PTH-independent mechanisms. GH is also increased directly and indirectly by increased PTH secretion (177).

Differential diagnosis of genu varum and valgum

Physiological bowing appears at 2-4 years of age, improves by 4-7 years, they have normal height, normal radiology and normal biochemical data and these children are asymptomatic (81).

Clinical and radiographic features help to distinguish physiologic from pathologic bowing. Clues to pathologic valgus include age <2 year or >7-year, unilateral valgus, short stature, medial thrust, asymmetry, and progression rather than improvement(178)

Metaphyseal dysplasia has normal radiology and biochemical data. In Schmid variety of metaphyseal chondrodysplasia patient has short stature and waddling gait with normal serum biochemistry. Janson variety of metaphyseal chondrodysplasia has mutation of PTHR1 (encoding for PTH 1 receptor) and can have similar type of radiological change as in rickets(179).

Hereditary hypophosphatasia is due to inactivating mutations in encoding tissue nonspecific alkaline phosphatase (TNSALP) and may present in first 6 months of life with poor feeding, failure to thrive due to poorly mineralized ribcage, respiratory insufficiency. Hypophosphatasia may have rachitic presentation with low phosphate and low alkaline phosphatase (ALP), other lab data are distinguishing. They have high mortality and treated with recombinant alkaline phosphates (180).

Blount disease has negative lab data for rickets.

Achondroplasia has different radiological findings and normal biochemical parameter.

Mucopolysaccharidosis has grotesque faces, hepatosplenomegaly, negative lab data for rickets.(178)

Infants with osteopetrosis may simulate or may have concomitant rachitic presentation called osteopetrorickets. Osteopetrosis has dense brittle long bone. In severe disease they have hypocalcemia and hyperparathyroidism. (178)

Multiple hereditary exostosis, post traumatic Cozen fracture of proximal tibial metaphysis where medial physeal over growth deformity develops after injuries, may also simulate rickets.(178)

To differentiate, it is important to know which part of the bone is involved, such as, physis in rickets, skeletal dysplasia, physeal fracture; metaphysis in skeletal dysplasia, Cozen fracture; diaphysis in trauma; epiphysis in skeletal dysplasia.(178)

INVESTIGATION:

Elevated alkaline phosphatase (ALP) and low phosphate (Pi) confirm the diagnosis of rickets in a child with bone deformities of rickets in a child with bone deformities & metaphyseal widening. ALP is 10 times or more higher in nutritional & hypocalcemic rickets compared to hypophosphatemic rickets where it is 1-3 times upper limit of normal. ALP is a marker of disease activity & hence used to diagnose & monitor the disease (130). Tubular reabsorption of phosphate (TRP) and maximal tubular reabsorption of phosphate per glomerular filtration rate (TmP/GFR) are low in all rickets but in hypophosphatemic ricket both are markedly low along with significantly low phosphate (Pi). So, diagnosis of rickets virtually relies upon low phosphate, high alkaline phosphatase, radiological evidence, phosphaturia (low TRP & low Tmp/GFR) along with clinical signs. Genetic study if feasible, helpful in refractory rickets (130)

Infant bony deformities & enlargement of physis along with raised ALP confirms rickets & excludes differentials (130). ALP is normal in physiological bowing, metaphyseal dysplasia and low in hypophos- phatasia (181).

Table 7 Normal aged based serum calcium and phosphorus (182)

Age	Calcium(mg/dl)	Phosphorus(mg/dl)
0-3 mo	8.8-11.3	4.8-7.4
1-5 yrs	9.4-10.8	4.5-6.5
6-12 yrs	9.4-10.3	3.6-5.8
13-20 yrs	8.8-10.2	2.3-4.5

Why we do not measure 1-25(OH)$_2$D?

The serum 1-25(OH)$_2$D is not a good measure of vitamin D (60) because it has a half-life of around 4 hours. Its conversion from 25(OH)D is controlled by calcium, phosphate, parathormone, and FGF-23, and the conversion of 1-25(OH)$_2$D also depends on the availability of 25(OH)D. 1-25(OH)$_2$D levels may be high in vitamin D dependent 2A and 2B due to receptor non responsiveness. Serum levels of 1-25(OH)2D vary widely upon methodology. Canadian Laboratory Initiative in Pediatric Reference Interval (CALIPER) has pediatric references measured by automated chemiluminescence immunoassay. Serum levels of 1-25 (OH)$_2$D are higher in infancy and stable after three years. Serum levels of 1-25(OH)$_2$D are high in inherited tubulopathy with NaPi2A and NaPi2C transporter defects. In FGF-23 mediated phosphoturic phosphopenic rickets, 1-25(OH)$_2$D levels are low or inappropriately normal. Patient with cystinosis nephropathy has normal or low 1-25(OH)$_2$D depending on CKD stages (59,65,73,165)

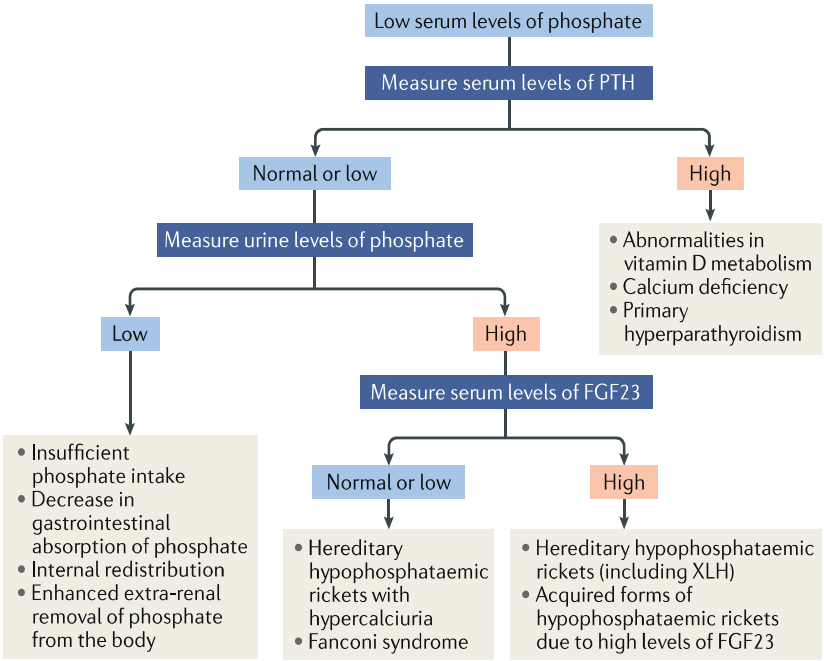

Figure 6: *Evaluation of hypophosphatemic rickets (125)*

Alkaline phosphatase is a marker of osteoblastic activity and hence severity of rickets. It is a screening & diagnostic test & it is normalized in healing rickets.

Imaging:

X-ray of wrist and knee has following radiological finding in rickets

Earliest sign of rickets is loss of clear demarcation between growth plate and metaphysis or crisp line produced by provisional calcification (LOC) at epiphysis & metaphysis. Widening of growth plate and (metaphysis) occur due to increased distance between epiphysis and the visible end of shaft due to uncalcified metaphysis. There can be cupping, fraying, flaring. Changes in epiphysis includes rarefaction and delayed bone age. Changes in diaphysis include thinning of cortex resulting in green stick fractures and looser zones. Deformities of the long bone, cortical spur, stippling may be present (146).

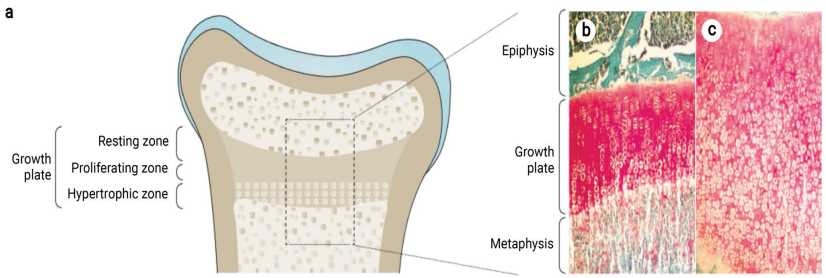

Figure 7: *Growth plate in rickets (111)*

Looser zones or Milkman's fracture or pseudo fracture are narrow radiolucent lines of 2-5 mm in width with sclerotic borders in severe cases of rickets. Angular deformities of the arm and leg bones and the formation of cortical spurs and stippling are seen in rickets. These findings are best seen in the femoral neck and shaft mostly in XLH rickets, lesser trochanter, pubic and ischial rami, ulnar, clavicle, and metatarsal bone. Pseudo fractures are also seen as hot spots on bone scans. Healing rickets has a dense line of calcification with the restoration of normal density of bone starting from the subperiosteal layer (24).

Clinical and radiological findings are almost similar in different types of rickets. Calcepenic rickets has secondary hyperparathyroidism and

hence has osteopenia, sub periosteal bone reabsorption and periosteal reaction along the diaphysis (18,107). Hypophosphatemic rickets has less prominent radiological findings, thickening of cortex is common (107)

Radiological findings of rickets are best seen at distal end of radius and ulna in non-ambulatory infant and tibial and femoral growth plate around in weight bearing > 1 year. Hence X-ray of wrist and knee is usually done in infancy & thereafter respectively (189).

Cupping, fraying and widening are less marked in XLH than nutritional deficiency ricket (65). XLH has severe x-ray evidences in the lower limb.

Rickets severity score (RSS)

RSS is a quantitative scale developed for nutritional rickets by Tom Thacher based on the degree of metaphyseal fraying and concavity and proportion of growth pate affected at the wrist and knees. Rickets severity score (RSS) or Thacher score is designed based upon radiological metaphyseal fraying, concavity and growth plate changes in wrist and knee and scored in a scale of 10. It needs X-rays of both wrist and knee, hence higher x-ray exposure. Because XLH does not have bone reabsorption features and no radiolucency hence only scoring of XLH rickets score 3 out 10 (146).

Changes during healing of rickets:

Appearance of a dense line of provisional calcification, normal density of bone is restored, starting from subperiosteal layer.

Dual energy X-ray absorptiometry (DXA) for bone density assessment does not differentiate osteomalacia and osteoporosis. Bone biopsy with tetracycline leveling diagnose rickets-osteomalacia accurately but it is not a frequent practice (187).

MRI of knee depicts rachitic changes in cartilage, precise findings of metaphyseal changes & other features of rickets with minimum radiation. Along with X ray MRI is good diagnostic tool (130)

Biochemical parameter

Pediatric age group has elevated alkaline phosphatase (ALP) >500 IU/L in neonates or > 1000 IU/L in children up to 9 years and then it decreases after puberty. Alkaline phosphatase may be raised by 1000

units/L (2–5 times the upper normal limit) found in 2.8% of infancy and early childhood, called transient hyperphosphatemia. Alkaline phosphatase is high up to 2000 IU/L (up to 10-fold) in calcepenic and moderately high 400 to 800 unit/L (up to 1-3-fold) in phosphopenic rickets. Hypophosphatemia is the ultimate common path in all types of ricket (183). Elevated ALP with bony deformities & epiphyseal enlargement almost confirming diagnosis of rickets.

Not a single test is diagnostic of rickets. Raised alkaline phosphatase (ALP) is found in all patients, but in general population 10–20% of raised alkaline phosphatase (ALP) can be due to liver disease, and 80–90% of ALP has a bone source. Hypozincemia can prevent elevation of ALP. ALP is produced by breakdown of pyrophosphate (PPi), adenosine triphosphate (ATP) and protein bound phosphate. ALP is a marker of osteoblastic and osteoclastic activity. It is highest in infancy and puberty and has 2 troughs in mid childhood and post puberty, and 2 plateaus, so it is tetra phasic. Its mean value in phosphopenic rickets is 4.2± 1.6 IU/L, in calcipenic rickets it is 7.1± 3.8 IU/L and 11.2± 2.6 IU/L in VDDR.

PTH increases many folds (up to 10-fold) in calcipenic rickets and normal and slightly increased in phosphopenic rickets (183) .

25(OH)D is normal in most hypophosphatemic rickets. Fasting urine and blood sample of phosphate and creatinine can be used to calculate tubular reabsorption of phosphate (TRP) expressed per glomerular filtration rate (TMP/GFR)(184)

FGF-23 dependent phosphopenic rickets has normal or low serum 1-25$(OH)_2$D and urinary calcium. Low TRP suggest phosphate wasting and high TRP suggest nutritional phosphopenic ricket with renal conservation. Serum creatinine and liver enzymes can be measured to check renal and hepatic disease respectively (185).

In tumor-induced osteomalacia (TIO), mesenchymal tumors like hemangiopericytoma produce PTH-related peptides (PTHrP), which increase FGF-23 and hence phosphaturia. Tumor localization by positron emission tomography (PET) or computerized tomography (CT), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), and bone scans may be of the whole body (186).

X-Ray KUB: Renal stones are found in hypercalciuria, dRTA, Dent's disease, hypophosphatemic rickets with hypercalciuria

DTPA based GFR measurement may be useful.

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Laboratory findings in various disorders causing rickets (24)								
Disorder	Ca	Pi	PTH	25-(OH)D	1,25-(OH)2 D	ALP	URINE Ca	URINE Pi
Vitamin D deficiency	N,↓	↓	↑	↓	↓, N,↑	↑	↓	↑
VDDR, type 1A	N,↓	↓	↑	N	↓	↑	↓	↑
VDDR, type 1B	N,↓	↓	↑	↓	N	↑	↓	↑
VDDR, type 2A	N,↓	↓	↑	N	↑↑	↑	↓	↑
VDDR, type 2B	N,↓	↓	↑	N	↑↑	↑	↓	↑
Chronic kidney disease	N,↓	↑	↑	N	↓	↑	N, ↓	↓
Dietary Pi deficiency	N	↓	N,↓	N	↑	↑	↑	↓
XLH*	N	↓	N,↓	N	RD	↑	↓	↑
ADHR*	N	↓	N	N	RD	↑	↓	↑
HHRD*	N	↓	N,↓	N	↑	↑	↑	↑
ARHR, type 1 or type 2*	N	↓	N	N	RD	↑	↓	↑
Tumor-induced rickets **	N	↓	N	N	RD	↑	↓	↑
Fanconi syndrome	N	↓	N	N	RD or ↑	↑	↓ or ↑	↑
Dent's disease	N	↓	N	N	N	↑	↑	↑
Dietary Ca deficiency	N,↓	↓	↑	N	↑	↑	↓	↑

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TREATMENT

Table 9	Recommendation of vitamin D treatment in children (165)		
	RCPCH (UK, 2013) (RCPCH-Royal college of pediatrics and child health)	**National osteoporosis society (UK,2015)**	**The Endocrine society (USA,2011)**
Deficiency	<25 nmol/L	< 25 nmol/L	< 50 nmol/L
Insufficiency	25-50 nmol/L	25-50 nmol/L	52.5-72.5 nmol/L
Intensive Regimen			
Age 6 months	1000-3000 IU/day orally for 4- 8 weeks	3000 IU/day PO for 8-6 weeks	2000 IU/day Po for 6 weeks
6 mo-2 yrs	6000 IU/day Po for 4-8 weeks	6000 IU/day Po for 8-12 weeks	2000 IU/day PO for 6 weeks
12-18 yrs	1000 IU/Day Po 4-8 weeks	1000 IU/day Po for 4-8 weeks	2000 IU/Day Po for 6 weeks
Maintenance			
Alternative recommended dosages	Weekly or monthly doses	Weekly doses	Weekly doses
Up to 1 month	300-400 IU/day PO	400-600 IU/day PO	400-1000 IU/day PO
1 month -18 yrs	400-1000 IU PO	400-600 IU	600-1000 IU/day

2016 Global consensus categorization was as follows- Vitamin D sufficiency- 20 to 100 ng/ml (50- 250 nmol/L), vitamin D insufficiency 12-20 ng/ml (30-50 nmol/L), vitamin D deficiency < 12 ng/ml (<30 nmol/L) (161).

There is a lack of consensus on the need for vitamin D for healthy bone growth and maintaining an optimum 25-OHD concentration. The Endocrine Society (USA) suggest vitamin D level more than 75 nmol/L (>30 ng/ml) for the prevention of nutritional rickets, PTH suppression and optimum gut calcium absorption. Post mortem histological findings of bone disease reveals 25(OH)D concentration 50 nmol/ml (20 ng/ml) is optimum(187) .

Healthy children may have nutritional rickets at 25(OH)D levels less than 30 nmol/L specially if there is concomitant calcium deficiency. In another study 25(OH) D level < 35 nmol/L has been seen to be associated with lumbar spine demineralization. There is seasonal variation of 25(OH)D and influence of vitamin D receptor (VDR) genotype. Optimum vitamin 25(OH)D level in chronic kidney disease seems to be higher, not yet determined, but certainly levels >75 nmol/L is associated with no secondary hyperparathyroidism. KDOQI recommends to maintain 25(OH)D above 75 nmol/L because this level prevents hyperparathyroidism, low bone marrow density (BMD), and fracture. Tibial and lumbar spine bone mineral density (BMD) on DEXA scan or peripheral quantitative computed tomoscan is usually employed to diagnose CKD MBD. Though bone biopsy is the gold standard, it is not in practice globally because of its invasive nature. Global researchers are not sure about optimum vitamin D levels for health (146,163).

Nutritional rickets

Treatment of nutritional rickets comprises of intensive phase followed by maintenance phase. There exist wide range of recommendations.

The US Endocrine society recommends 2000 IU/day cholecalciferol for all age groups in intensive phase followed by 400-600 IU/day in maintenance phase. The National Osteoprosis Society of United Kingdom recommends 3000 IU in infants <6 months old, 6000 IU in 6 months to 12 years old and 10000 IU in 12-18 years old of cholecalciferol per day in intensive phase followed by 400-600 IU/day in maintenance phase(188).

Other recommendations are 1000 IU/day for <1 month old, 1000-5000 IU/day for infants 1-12 months old, 5000-10000 IU/day for children more than 12 months old. There is also a recommendation for stoss therapy, or mega dose, for non-complaint and acute fracture pain patients (165). Stoss therapy (mega dose) is vitamin D 300000- 600000 IU orally over 1-5 days or 2-4 doses in a day or as single intramuscular to dose each buttock. Stoss therapy is not recommended below 3 months. Cholecalciferol (vitamin D3) is preferable to ergocalciferol (vitamin D2) because of its longer half-life and higher efficacy. Minimum duration of 3 months is recommended for intensive phase (88)Another schedule of stoss therapy in infants 3 to 12 months of age is a single dose of 50000 IU; for children 1 to 12 years, a single dose of 150000 IU; and for more than 12 years, a single dose of 300000 IU. Alternative regimen may be 50000 international units once a week for 6 weeks followed by maintenance dose specially in adults (81). Non response of nutritional rickets after 2-3 weeks of intensive phase therapy and non-healing of x-ray evidence at 2-3 weeks should be investigated for refractory rickets (126). Notable vitamin D refractory rickets are vitamin D dependent ricket type 1A,1B,2A, type 3, FGF-23 dependent hypophosphatemic rickets including X linked, autosomal dominant, autosomal recessive (type 1,2, and 3) and FGF independent hypophosphatemic rickets including tubulopathy like Fanconi syndrome, Dent disease, drug induced proximal tubulopathy. Very high dose of vitamin D of 10000 to 50000 unit daily may be needed to replete vitamin D in celiac disease, gastrectomy, inflammatory bowel disease and other serious sicknesses (124,138). Drug induced vitamin D deficiency may need 400-4000 IU (164).

Toxicities are seen in adult supplementation of > 60000 IU daily. Case reports with high vitamin D levels have inadvertently described excessively fortified formulas, manufacturing errors, and prescription errors.

Calcium supplementation at 500 mg daily, irrespective of age or weight, should be provided to prevent “hungry bone syndrome.”

Physiological calcium requirements are- 0-6 months: 200 mg/day, 6-12 months: 260 mg/day, 1 year- 18 year: 500 mg/day. (18)

Rarely vitamin D supplementation may trigger idiopathic infantile hypercalciuria which is characterized by hypercalciuria, nephro-calcinosis, vomiting,

dehydration, and failure to thrive (81). It is due to mutations in CYP24A1 gene which encodes the enzyme responsible for conversion of degradation of 25(OH)D & 1-25 (OH)2 D. It is dose dependent & hence more common in stoss therapy than standard therapy, mostly in bolus doses of 60000 IU in infants given at 3 months apart. (81)

Within a given population, individuals with special risk factors may require doses of vitamin D that are higher than those recommended above. As examples, children with obesity and those on anti-convulsants, glucocorticoids, and medications for HIV infection may require much higher doses of vitamin D to maintain their serum 25(OH)D concentrations in the sufficient range (as much as 6000 IU daily) (81). Obesity may require a 2-3 times higher replacement dose, followed by a maintenance dose (81).

Calcipenic nutritional rickets may be supplemented with calcium ≥ 1000 mg/day. Calcium supplement is usually not required during maintenance phase if dietary sources are ensured. Intravenous calcium gluconate is needed for hypocalcemic seizure. Mainstay of treatment of calcipenic rickets is correction of underlying deficit, adequate calcium, and vitamin D supplementation. Dietary calcium deficiency rickets may be cured with calcium supplement only (65). Normalization of urinary calcium suggest adequate calcium intake (189). Calcium prevents hungry bone syndrome as well.

Normalization of calcium, phosphate levels and significant reduction of PTH take place within 3 weeks whereas normalization of ALP levels may need several months.

Response pattern of nutritional rickets include improvements in clinical symptoms likes aches and pains occurs by 2 weeks, the disappearance of metaphyseal swelling by 6 months. Total correction of bowed legs & knock knees may need 2 years, adolescents are usually left with some residual deformities which require surgical correction (146). In nutritional rickets skeletal deformities regress completely after medical therapy. Correction of bowing defects may take months to year. Orthopedic intervention is needed if deformities do not eventually improve.

Treatment of VDDR 1A:

Megadose of vitamin D and calcium are needed to treat VDDR1A (pseudo vitamin deficiency rickets)

High concentrations (2-5-fold higher dose) of calcidiol 25(OH)D can bind and activate vitamin D receptor (VDR). There may be a risk of hypercalcemia with minimal response during successful treatment of vitamin D (chole or ergocalciferol) and 25(OH)D (calciferol). Serum 25(OH)D levels may be very high (150–250 ng/ml), but plasma concentrations of 1–25(OH)2D may remain low or even undetectable. During the first 3-6 months of treatment, calciferol in dosage 2-5 times those expected for long-term maintenance may be needed lifelong. Elemental calcium supplements at 50 mg/kg/day should be given in initial treatment to manage worsening of hypocalcemia due to remineralization of bone called “hungry bones” phenomenon. Usually, normal biochemistry is resumed and treatment is continued for almost lifelong (181).

Treatment of vitamin D- dependent rickets type 1B (VDDR 1B) is pharmacological doses of ergocalciferol or cholecalciferol or physiological doses of calcitriol plus calcium supplementation. Calcifediol [25(OH)D] is superior because it bypasses defect in 25-hydroxylation. Alphacalcidol [1 α (OH)D] has shown promising. Dose of calcitriol is 0.05-0.2μg/kg/day. VDDR1B resembles VDDR1A, except its severity is variable with gene dosage; it appears to improve with age as the CYP enzyme matures by operation of the nonvitamin D mechanism. Treatment should be tailored according to the need (181).

Treatment of vitamin D dependent rickets type 2A (VDDR2A) or hereditary vitamin D resistance rickets (HVDRR) The starting dose of calcitriol is 2 mcg daily with 1000 mg of calcium to 30 mcg of calcitriol and 3 gm of calcium. A long-term infusion of calcium may be needed. Milder form of HVDRR without alopecia responds to high doses of calcitriol (4000-5000 IU). HVDDR with alopecia 50% will respond, rest 50% may be resistant. Responsive cases with alopecia may need 10 times higher doses than normal hair. Vitamin D refractory cases need large amounts of elemental calcium, 400-1400 mg/m2 daily. Cases with alopecia do not respond to treatment with vitamin D and calcium (44). The target is to increase 1-25$(OH)_2$D to 100 times higher than usual.

Therapy is monitored by Ca, Pi, ALP, creatinine,1-25$(OH)_2$D, PTH and urinary calcium creatinine ratio, and ocular calcification by eye examination. Symptomatic low Ca may need or should be treated with I/V calcium gluconate(1mg/Kg) and calcitriol IV/ PO (0.05ugm/kg/day). Continuous IV calcium drip may be needed, mostly 1000mg regularly. If the deformity is present, then orthopedic correction is advised (181).

Treatment of vitamin D-dependent rickets type 2B (VDDR 2B)- It is managed like VDDR 2A. It is a rare disease with presentations like VDDR1 and these children are short. These children are to be treated with lifelong doses (50000IU) of calcitriol (181).

Maintenance therapy depends on the response pattern of VDDR 2B- i) Some are responsive to cholecalciferol (D3), ergocalciferol (D2), and calcifediol 25(OH) ii) Some may need a high dose of 1-25$(OH)_2$D or 1 α (OH)D3, iii) A small subset will not respond to calciferol at any dose (18).

Maintenance may be lifelong depending upon need. Patients requiring higher doses should have daily calcium with 1000 mg elemental calcium per day. Nonresponsive to calciferol cases should be given 1000 mg intravenous elemental calcium daily infused over 12 hours for many months. Per oral calcium tolerance is 6 gm per day and in the absence of vitamin D, only 10 % of calcium is absorbed. At puberty, many children develop adaptation with increased calcium absorption, and hence many may maintain with modest oral calcium (190).

Vitamin D-dependent rickets type 3 (VDDR3) needs larger doses than nutritional rickets. Calcitriol is administered twice daily because of its short half-life of 4-6 hours. But calcifediol (25(OH)D) or calcidiol has a long half-life of 2-3 weeks, it can be given once daily (181).

Treatment of phosphopenic rickets

Phosphopenic rickets are to be treated with oral phosphate (Julie solution) at 4-6 doses per day and supplementation of vitamin D called conventional therapy. Normalization of serum alkaline phosphatase, calcium and phosphate, and parathyroid hormone indicates healing of rickets along with X-ray evidence. However, in severe phosphopenic XLH rickets treatment aiming to normalize phosphate would be dangerous because of phosphate-induced secondary hyperparathyroidism leading to a drop of phosphate level after each dose of oral phosphate. Similarly, PTH level

should be targeted 1 -2 times upper normal limit in CKD 2-5D to avoid phosphoturia and bone resistance. So, serum alkaline phosphatase level ideal is parameter to know XLH rickets control (130).

Conventional treatment of XLH is elemental phosphate orally at 20-60 mg/kg/day (0.7-2.0 mmol/kg/day) given 4-6 divided doses because of its short half-life. Vitamin D (calcitriol 10-80 ng/kg once daily or twice daily or alphacalcidiol 30-50 ng/kg once daily or twice daily) should be given along with phosphate (Pi). Empirical treatment with 0.5 µg daily of calciferol or 0.5 µg daily of alphacalcidiol in above 1-year children and subsequent days adjustment according to clinical and biochemical response is also an option (81). Evidence of response may be improvement of bone pain, deformity, gait, growth velocity of 1 standard deviation, dental abscess, and reduction of ALP to the upper normal limit in around one year. Early initiation of treatment & longer duration of treatment have better outcomes (81). Phosphaturia, phosphate and FGF-23 levels remain as such and are not guide of improvement and should not be tested (81). Long term improvement with vitamin D and phosphate may raise PTH and may cause secondary hyperparathyroidism. Hence serum calcium, PTH, urinary phosphate, serum creatinine and renal ultrasonography should be done (81). Phosphate in oral form is rapidly eliminated in urine and hence give at 4-6 times per day and always with calcitriol. Phosphate absorption is better in capsule and tablet form than liquid. Phosphate supplementation increases its serum level and decreases calcium level, thereby causes secondary hyperparathyroidism, which increases phosphate excretion, and autonomous tertiary hyperparathyroidism because PTH typically increases calcium and decreases phosphate.

Hyperparathyroidism can cause hypercalcemia, hypertension, and renal impairment. Phosphate in higher dose (> 80 mg/kg/day) may cause disease, discomfort, and secondary hyperparathyroidism. Calcitriol or alphacalcidiol doses should be adjusted to keep PTH level within normal range to avoid hypercalciuria, nephrocalcinosis. Rigid control of PTH may be unsafe because PTH itself causes phosphaturia and aggravation of symptoms. In raised PTH state vitamin D dosage should be increased and phosphate dosage need to be decreased. Vitamin D dosage need to be decreased if hypercalciuria develops. Age-appropriate calcium must ensured, at least 500 mg in above 1 year old child (191).

Conventional treatment should be continued until adult height is obtained. The European XLH guideline recommends burosumab treatment in XLH if the disease is non-responsive to conventional therapy, has complications in conventional treatment, or has non-adherence to conventional treatment and has radiological evidence of overt bone disease. Active disease must be confirmed by hypophosphatemia one week before burosumab therapy (192).

Contraception must be ensured in childbearing age of girls. Burosumab should not be given in severe renal function impairment and normal phosphate state and never along with conventional treatment.

The starting dose of burosumab is 0.8 mg/kg every 2 weeks, increasing 0.4 mg/kg to 0.8 mg/kg at 2- 4 weeks, maximum 2 mg/kg (adult dose is 1 mg/kg, maximum 90 mg given subcutaneously). Burosumab is recommended for > 12 months by US Food and Drug Administration (FDA), and >6 months by the European Medicine Agency (EMA) for XLH. It is expensive but more effective and has high safety profile. Fifty percent of XLH patients may have short stature despite adequate burosumab and conventional therapy. Two weekly burosumab is found superior to 4 weekly regimens in term of phosphate & radiological normalization (146)

Half-life of burosumab is 10 days and peak serum concentration occurs at 7-11 days. Thereby, fasting serum phosphate (Pi) and burosumab dose titration are done to measure drug responsiveness after that period (81).

Recombinant growth hormone therapy may be considered keeping in mind about its guarded result.

Fifty percent of XLH patient may have significant bowing of legs requiring corrective osteotomy and epiphysiodesis which should be considered only after metabolic control of disease to avoid recurrence. Osteotomies are performed by pediatric orthopedician in later childhood or at attainment of adult height. On the other hand, epiphysiodesis is performed at least 2-3 years before the end of skeletal growth.

Dental abscess due to poorly mineralized dentin, periodontitis and loss of deciduous and permanent tooth is common. Pulp necrosis features like colour change, swelling, pain, fistula, cellulitis, and abscess need an x-ray, pediatric dental surgeon treatment, and optimum vitamin D, calcium, oral phosphate or burosumab treatment. Prognosis of XLH is good.(193)

Less aggressive treatment may be needed with only calcitriol. Short stature may persist into adulthood. Surgical treatment is reserved for severe bowing, tibial torsion, or pathological fractures.

Neurosurgical consultation, fundoscopy and MRI are needed for symptomatic patients with intracranial hypertension, craniosynostosis, Chiari type 1 malformation (81).

Treatment of ADHR: Autosomal dominant hypophosphophenic rickets (ADHR) due to FGF-23 gene mutation is also identical to XLH, ADHR is often mild disease and may undergo spontaneous remission (146)

Treatment of hereditary hypophosphatemic rickets with hypercalciuria (HHRH) includes supplementation of phosphate in monitored way to avoid nephrocalcinosis. Vitamin 1-25(OH)2 D is not recommended as it is high in HHRH. High fluid intake, avoidance of high salt, protein and thiazide diuretic are useful to prevent nephrocalcinosis (194). Endogenous calcitriol levels are elevated and the addition of exogenous calcitriol may be harmful. Thus, plasma calcitriol and urinary Ca excretion should be measured before initiating therapy.

SLC34A3 gene mutation encoding NaPi-2C transporter causes chronic Pi wasting leading to suppression, calcitriol and PTH and consequent calcium absorption in the gut and its secondary effect as hypercalciuria, the hall mark of HHRH, responsible for progressive renal failure (195).

Management of CKD-MBD

For the management of CKD-MBD, KDIGO 2009 does not recommend the use of cholecalciferol over ergocalciferol but European Renal Best Practice Group 2010 recommended cholecalciferol or other 25(OH)D analog. Calcifediol (25-hydroxyvitamin D3) requires 1-α hydroxylation, is a derivative of vitamin D, and is approved by the Food and Drug Administration (FDA) for adults. Pharmaceutical-grade products of vitamin D3 are available while those for vitamin D2 are limited. Megadose therapy of vitamin D is not recommended for CKD-MBD. CKD has reduced urinary calcium excretion and hence is more prone to hypercalcemia, nephrocalcinosis and renal impairment. Hence European Society of Pediatric Nephrology- Chronic Kidney Disease Mineral and Bone Disorders and dialysis working group recommends not to use stoss therapy in CKD-MBD. Vitamin D toxicity may appear at its level >150 nmol/l and 25(OH)D > 250 nmol/l is associated with reduced PTH levels(196).

Ergocalciferol (D2) or cholecalciferol (D3) therapy improves biological endpoints including PTH in CKD. Ergocalciferol treatment for 3 months

in an intensive fashion elevates 25(OH)D to the normal range and 60 % of children continue to have normal levels in maintenance therapy. But higher doses may be required for CKD stages 3-4 and even a repeat course of intensive vitamin D replacement therapy may be needed. Vitamin D has a positive rule in the management of anemia of chronic kidney disease (CKD), enhances response, reduces of proteinuria, and attenuates of CKD progression (158).

Table 10 Vit-D deficiency level in CKD-MBD (172)

	European Renal Best Practice (2010)	NKF-KDOQI (2003)
Deficiency	<30 nmol/L	<37.5 nmol/L Severe deficiency- <12.5 nmol/L
Insufficiency	30-75 nmol/L	40-75 nmol/L

Table 11 Vitamin D supplementation in children with ESRD or dialysis (197)

Age	25(OH) D level (nmol/L)	Daily dose	Monitoring
Intensive replacement therapy			
<1 year	<12	600 IU/day	Serum Ca and urinary Ca levels at 1-3 months 25(OH)D after 3 months
> 1 year	12-50	8000 IU/day	Serum Ca and urinary Ca levels at 1-3 months 25(OH)D after 3 months
	50-75	4000 IU/day	Serum Ca and urinary Ca levels at 1-3 months 25(OH)D after 3 months
Maintenance therapy			
<1 year > 1 year	>75 >75	400 IU/day 1000-2000 IU/day (more in advanced CKD)	25(OH)D level at 6-12 months 25(OH)D level at 6-12 months

nmol/L = ng/ml/2.5, 25(OH)D < 75 nmol/L: needs intensive replacement therapy

There is risk of vitamin D toxicity in CKD-MBD evidenced by hypercalcemia, hypercalciuria and nephrocalcinosis. Hence it needs to be monitored and addressed. High dose monthly 1,25 (OH)D has been found to leave an acute elevation of $1,25(OH)_2D$, which in presence of hypocalcemia may be catabolic to bone.

Healthy children has symptomatic vitamin D toxicity at levels more than 500 nmol/L. The third National Health and Nutrition Examination Survey (NHANE III) report of the general well adult population shows reverse J-shaped association between serum 25(OH)D and all-cause mortality and more death at serum 25(OH)D levels above 120 nmol/L. (196)

Babies born to vitamin D deficient mother treated with a bolus of 50,000 IU has similar 25(OH)D level at 3-4 months as daily dose of 400 IU.

All types of vitamins dependent and most of phosphoturic rickets are genetic disease, hence they need to be treated as refractory, difficult rickets. Cinacalcet is a calcimimetic can be used in XLH after discontinuation of $1\text{-}25(OH)_2D$ and phosphate. Paricalcitriol is 1, $25(OH)_2D$ analogue which can also be used in cinacalcet intolerance and nonresponse. Failure to all medical treatment may need to choose parathyroidectomy (88).

The calcimimetic agent, cinacalcet, reduces PTH secretion and hence reduces phosphate. It may allow a lower vitamin D & phosphate dose in XLH, minimizing toxicities like hypercalciuria,

Treatment of fibrous dysplasia is phosphate salt and active vitamin D therapy, failure to respond needs burosumab treatment. Bisphosphonates has limited role in fibrous dysplasia (192).

Tumor induced osteomalacia (TI0) needs complete resection of tumor, which may need resection followed by phosphate 15-30 mg/kg/day in 4-6 divided doses and calcitriol or alphacalcidiol at 15-60 ng/kg/day; doses should be adjusted as per clinical and biochemical state & presence of side effects. Alternatively, burosumab can be used in the dosage of 0.4 mg/kg body weight subcutaneously every 2 weeks, dosage may need to be increased upto 2 mg/kg/day (maximum 180 mg) (186)

Vitamin D toxicity - Excess of vitamin D therapy may lead to intoxication and the upper limit of intake is 1000 IU in <1yr age, 2000 IU in >1yr age.

European Paediatric Nephrology group recommends stopping cholecalciferol (D3) and ergocalciferol (D2) supplements at serum 25(OH)D levels of ≥120 nmol/L but to define symptomatic toxicity serum 25(OH)D levels more than 250 nmol/L with hypercalcemia, hypercalciuria and suppressed PTH (198). Toxicities are:

(1) GIT- Anorexia, nausea, vomiting, irritability, constipation, pancreatitis, decrease gastrointestinal tract transit time interval.

(2) Cardiac-Arrhythmia

(3) CNS- Depression, psychosis, hallucination, coma

(4) Renal- Polydipsia, and polyuria. hypertension secondary to hypercalcemia, increased Na, renal failure.

(5) Dehydration and arrhythmia the cause of death

Laboratory investigations reveal hypercalcemia and hypercalciuria. Nephrocalcinosis may be observed on renal ultrasonography. Treatment of toxicity includes discontinuing vitamin D, hydration, and managing hypercalcemia by calcitonin, steroid, and hemodialysis, with or without diuretics (199).

PREVENTION OF RICKETS:

Breast milk has 15-60 international (IU) units /L (0.4-1.2 µg/L) even in vitamin D-sufficient mothers. Exclusively breast-fed infants consuming an average of 750 ml of breast milk ingest 10-40 IU (0.25 to 1 µg/day) of vitamin D in the absence of sun exposure or supplement. The vitamin D content is usually lower in mothers with dark skin or on deficient maternal diets. Most breast-fed infants need to be exposed to sunlight 30 minutes/week while wearing a diaper to maintain 25(OH)D concentration at > 20 ng/ml. Infant formula in the United States is fortified to contain 40-100 IU (1-2.5 µgm/L) and orange juice is fortified to contain 400 IU (10µg) of vitamin D per liter (81,107). This rule should be made universal to all nations of the world. In person with light pigmentation sufficient cutaneous vitamin D synthesis needs 10-15 minutes of sun exposure to the arm, legs or hands, arms, or face between 10.00 am to 3.00 pm during spring, summer, and fall. South Asian ancestry with pigmented skin requires 3 times longer sun exposure than that of light skin pigmentation, and peoples of African ancestry need 6 to 10 times

than that of light skin to produce adequate vitamin D (24)Prolonged sun exposure results in a minimum serum 25(OH) D level of <80 ng/ml (200 nmol/L) (165).

American Academy of Pediatrics (AAP) recommends 1 liter of vitamin D-fortified milk to all children above one-year-old. Despite its recommendation, only one-third of American children consumed the recommended amount as per the 2022 report because only 30 % of clinicians believe that recommendation (200).

Supplementation to lactating mothers 4000 to 6000 IU (100-160 µg) daily is another strategy to improve vitamin D status in infant. Vitamin D supplementation to pregnant women may help. Nearly 45% of children and adolescents across Europe have vitamin D insufficiency or deficiency because of non-adherence and non-consumption of adequate fortified milk, consumption of foods rich in vitamin D such as fatty fish, hardboiled egg, yoghurt, margarine. Unfortunately, very little amounts of foods are vitamin D enriched. Consumption of spinach, green vegetables, bread (wheat, brown) almonds rich in calcium can mitigate vitamin D deficiency (201).

Recommended daily allowance (RDA) must be ensured to all ages which include 0 to 1 year 400 IU & 1 to 70 yr 600 IU, pregnant and lactating women 600 IU and above 71 years 800 IU. 1 cup milk contains 276 mg calcium, milk also has enough phosphate, so habit of drinking milk is essential (59).

Universal supplementation of vitamin to all infants and children can be an option. It can be supplemented at immunization point. More than 1100 foods are fortified in USA, milk fortification in India has been found to be successful in school children. Education to all levels of health worker, mass campaign in social media can be useful (202,203). All nation of the globe can fortify their staple food with recommended daily amount. Parliamentary legal approval of universal fortification of vitamin D may be helpful.

For every 40 IU of vitamin D ingested over 4 to 5 month increases 25(OH)D by 0.70nmol/L. Maternal 25 (OH)D level of >80 nmol/LL is recommended for fetal and neonatal wellbeing. All preterm on enteral feedings of 150-160 ml/kg/day of fortified human milk or preterm formula should be provided calcium of 150-220 mg/kg/day,

phosphorus of 90-140 mg/kg/day and vitamin D of 300-400 IU daily (81)

CKD-MBD prevention can be ensured by optimum CKD nutrition with concomitant daily or monthly oral D2 or D3 supplementation, keeping normal 25(OH)D and calcium. Higher doses of ergocalciferol and repeat course of intensive replacement treatment may be needed.

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