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REVIEW

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Management of rickets: the new horizons for the pediatrician

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Abstract
Rickets is a major public health concern globally. It results from impaired mineralization of the growing bone at its growth plate associated with abnormal calcium and phosphate metabolism. Among different classifications, nutritional deficiency is the commonest variety, and the genetic form of rickets has also been identified frequently in this genomic era. Treatment and management of rickets should be targeted as per type along with the pathogenesis of development of this condition. Management differs for each form of rickets and therapy requires distinct treatment, monitoring and follow-up schedule according to the pattern of response to therapy. The objective of this review is to summarize the treatment and management of different types of rickets in the light of recent guidelines and relevant literature.

Keywords Vitamin D, Nutritional rickets, Refractory rickets, Management, Children

Introduction

Rickets is a disease of growing bone resulting from alteration of calcium and phosphate homeostasis causing impaired apoptosis of hypertrophied chondrocytes in the metaphyseal growth plate [1]. Nutritional rickets is a global health problem and discussed widely with non-communicable diseases now a days. It is more prevalent in low and middle-income countries, particularly in the Indian sub-continent, Africa and Middle East [2]. Rickets is mainly caused by deficiency and impaired metabolism of vitamin D, calcium and phosphate among children [3]. The prevalence of genetic causes has also increased over the recent era with the discovery of novel genes. Treatment of rickets should be targeted on the pathogenesis, which is strictly connected with the type of rickets [4]. There are two principal types of rickets which have been conventionally referred to as calcipenic and phosphopenic rickets [5]. Calcipenic rickets is mainly due to calcium and vitamin D deficiency as well as abnormality of vitamin D metabolism and function at its site of action [6]. Phosphopenic rickets can be sub-divided into two forms based on excessive renal phosphate wasting and reduced dietary intake. Excess renal loss of phosphate may either be mediated through excess fibroblast growth factor-23 (FGF23) or renal tubular defect [7]. The testing of vitamin D status and use of its supplement has increased substantially in recent years [8]. Treatment of rickets with vitamin D and oral calcium supplementation is the common practice in low-resource settings now a days. Despite strict adherence to this regime, if rickets fails to heal; refractory rickets must be considered. These forms of rickets are again subdivided into hypophosphatemic rickets and vitamin D-dependent rickets (VDDR) [7]. The discovery of a phosphaturic hormone, FGF23 together with detection of underlying genetic defects in many hereditary forms of rickets provide a landscape of understanding the pathogenesis and type-specific diagnosis of rickets. Progress continue in the field of research,

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and perhaps a human monoclonal antibody to FGF23, Burosumab is the ultimate frontier in the management of rickets till date [9].

Diagnosis of refractory rickets is challenging due to the unavailability of genetic testing everywhere despite of its paramount importance. Till date, substantial variability exists regarding Optimal vitamin D dosing, duration of supplementation and status of vitamin D across different guidelines. Provision of calcium and vitamin D enriched food in appropriate quantity during the period of rapid growth (infancy, childhood and adolescent) would be the best preventive strategy of nutritional rickets in low resource settings, this crucial issue is poorly addressed by the parents and physician as well because of ignorance. Dietary management is also a neglected part in CKD-MBD as more attention has been paid to medication and other management of CKD. Disparity also exists in access to vitamin D supplementation due to public health implication barrier in resource limited countries.

With a view to highlighting the therapeutic approach to various forms of rickets based on recent relevant literature and current recommendations as well as to raise awareness regarding judicious use of vitamin D supplementation among pediatricians, this burning issue has been focused on in this review.

Methodology

This article focuses on different types of rickets, their treatment and prevention of rickets among pediatric age groups. Relevant literatures were searched independently by two authors from the Google Scholar and PubMed databases. More emphasis was given to recent studies to report the updated information regarding this topic. Although we did not grade the strength of our work, this review presents a brief, but specific therapeutic approaches to the various types of rickets in the light of current guidelines.

Treatment of different forms of rickets

It is necessary to differentiate between hypocalcemic rickets and hypophosphatemic rickets based on main biochemical findings which will guide to choose the initial treatment approach. The presence of elevated alkaline Phosphatase (ALP) activity is more relevant in hypocalcemic rickets than hypophosphatemic rickets [10]. Serum PTH level is either normal or mildly elevated, whereas secondary hyperparathyroidism is the most striking biochemical sign in hypocalcemic rickets. Hypocalcemia is evident in both the form of rickets, but may be normal in hypophosphatemic rickets. Hypophosphatemia can be found in both the types, which is due to secondary hyperparathyroidism in hypocalcemic rickets [4]. TmP/GFR is another tool to distinguish dietary phosphate deficiency from renal phosphate wasting [11].

The therapy of rickets is based on vitamin D and calcium supplementation along with phosphate when necessary. Both vitamin D and calcium supplementation are mandatory in case of malabsorption. Vitamin D may have a role in calcium deficiency. Vitamin D with calcium may not be needed always, rather increases the risk of nephrocalcinosis and kidney stones [12].

Nutritional rickets

The treatment of nutritional rickets comprises of intensive phase followed by a maintenance phase. There exists a wide range of recommendations.

The US Endocrine society recommends 2000 IU/day of cholecalciferol for all age groups in the intensive phase followed by 400–600 IU/day in the maintenance phase. The National Osteoporosis Society of the United Kingdom recommends 3000 IU in infants ˂6 months old, 6000 IU in 6 months to 12 years old and 10,000 IU in 12–18 years old of cholecalciferol per day in intensive phase followed by 400–600 IU/day in maintenance phase [13]. Optimal dose of vitamin D supplementation varies as per different guidelines (Table 1).

Vitamin D supplementation in the form of 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 [18].

Children with obesity and those are on treatment with anticonvulsants, glucocorticoids, and anti-retroviral medications may require higher doses of vitamin D to maintain their serum 25(OH)D concentrations in the sufficient range (as much as 6000 IU daily). Glucocorticoid inhibits vitamin- D at its receptor binding with retinoid X receptor (RXR), thereby inhibiting its absorption through the intestine. Anticonvulsants and anti-retroviral drugs enhance the catabolism of 25(OH)D into its inactive molecule [19]. Calcipenic nutritional rickets need calcium supplementation (Table 2).

Treatment of refractory rickets

When a child with suspected nutritional rickets exhibits no improvement with appropriate vitamin D therapy, a diagnosis of refractory rickets must be made [20]. Vitamin D refractory rickets are usually vitamin D dependent rickets including type 1 A,1B,2 A, 2B and type 3, FGF-23 dependent hypophosphatemic rickets including X linked, autosomal dominant, autosomal recessive (type 1,2, and 3) and FGF-23 independent hypophosphatemic rickets including tubulopathy like Fanconi syndrome, Dent disease, drug induced proximal tubulopathy [21]. Drug induced vitamin D deficiency may need 400–4000 IU of vitamin D supplementation [22].

Table 1 Different guidelines for vitamin D supplementation [14]

First Author & year	Title	Type	Vitamin D S Status cut-off Values considered	Vitamin D Toxicity level considered	Population	Vitamin D supplementation
Munns et al. 2016 [15]	Global Consensus Recommendations on prevention and management of nutritional rickets	Consensus statement from expert members of various international societies	Sufficiency, > 50 nmol/L Insufficiency,30–50 nmol/L Deficiency, < 30nmol/L	> 250nmol/L, with hypercalcemia, hypercalciuria, and suppressed PTH	Children And adults	Infants (0–12 months) 400 IU/day in the first year of life, Independent of their mode of feeding. Beyond 12 months of age 600 up to 2000IU/day (Minimum duration 12 weeks pregnant women 600 IU/d throughout pregnancy
Braegger et al., 2013 [16]	Vitamin D in the healthy European pediatric population	Consensus Statement from members of the ESPHGAN Committee of nutrition	Sufficiency > 50 nmol/L Severe deficiency < 25 nmol/L	No agreement on a vitamin D toxicity threshold"	Children	Infants (birth to 12 months) 400IU/day in the first year of life Beyond 12 months: > 600IU/day In children from identified risk groups
Saggese et al. 2018 [17]	Vitamin D in pediatric age: consensus of the Italian Pediatric Society and the Italian society of preventive and social paediatrics jointly with the Italian federation of pediatricians	Consensus Statement From national Pediatric societies in Italy	Sufficiency > 30 ng/ml (> 75 nmol/L) Insufficiency 20-29ng/ml (50–74 nmol /L) Deficiency < 20ng/ ml (< 50nmol/L) Severe deficiency < 10ng/ml (< 25nmol/L)	Not Reported	Children	preterm infants: weight > 1500 g: 400-800IU/day, Weight < 1500 g. : 200-400IU/day by enteral feeding 400IU/day in all newborn independent of the type of feeding subjects beyond 12 months of age: 600up to 1000 IU/day in children and adolescents with risk factor for Vitamin D deficiency.

ESPGHAN (European society of pediatric gastroenterology, nutrition and hepatology)

Table 2 Calcium treatment in patients with rickets with hypocalcemia [11]

Condition	Calcium Salts	Doses, mg/kg (ml/kg)	Mode of administration
Symptomatic Acute hypocalcemia	Gluconate 10% (10 ml ≈ 90 mg elemental calcium)	5–20 (0.5-2.0)	Intravenous slowly, over 10–15 min to avoid bradycardia; diluted in 0.9% sodium chloride or 5% dextrose
Asymptomatic hypocalcemia or normocalcemia	Carbonate (40% of elemental calcium) Citrate (21% of elemental calcium)	30–75 **5 years old**: 500 mg/day **10 years old**: 1000 mg/day	Oral route, divided into 2–3 doses daily

Vitamin D-dependent rickets (VDDR)

VDDR has been broadly classified into three categories– VDDR type 1 (VDDR1), VDDR type 2 (VDDR2) and VDDR type 3 (VDDR3). VDDR1 again subdivided into VDDR type 1 A (VDDR1A) and VDDR type 1B (VDDR1B) caused by renal 1α-hydroxylase and hepatic 25-hydroxylase deficiency, respectively [4, 23]. VDDR2, currently termed as hereditary vitamin D resistant rickets [24] is caused by either mutation of vitamin D receptor gene (VDDR2A) or impaired interaction between vitamin D receptor and DNA (VDDR2B). VDDR3 results from genetic mutation leading to excessive inactivation of vitamin D metabolites [23].

Treatment of vitamin D-dependent rickets (VDDR)

In case of VDDR, treatment is based on the combination of vitamin D analogs and calcium (Table 3). The commonly used metabolite is calcitriol, which regulates the active transport of calcium from the intestine and suppresses the secretion of parathyroid hormone, and alfacalcidiol, which bypasses the need for renal activation. Calcitriol has a half-life of approximately 5–8 h; requiring at least 2–3 daily doses. In contrast, alfacalcidiol may be administered once a day as it has a longer half-life (approximately 24 h). Patients must be treated for a lifelong period in case of genetic vitamin D-dependent rickets with patient-tailored doses. The best treatment of VDDR1B is oral calcifediol as it bypasses the defect of hepatic 25-hydroxylation. Wide variability is noted regarding response to vitamin D therapy in VDDR2. Patients with VDDR2 without alopecia show a

Table 3 Maintenance treatment of vitamin D dependent rickets [4, 23]

Drug	VDDR1A	VDDR1B	VDDR2	VDDR3
Vitamin D	NI	Heterozygous 5000–10,000 IU/day Homozygous:600,000 every 3 months	LI	50,000/day
Calcifediol	NI	15–50 ug/day (preferred choice)	20–200 ug/day	50 to?
Alfacalcidol	10–100 ng/kg/day 0.5-3ug/day	0.5-3 ug/day (less effective)	10–400 ng/kg/day 5–60 ug/day	2 to?
Calcitriol	10–100 ng/kg/day 0.3-2 ug/day	0.3-2 ug/day (alternative choice)	10-400ng/kg/day 5-60ug/day	1 to?
Calcium salts (by oral route)	0.5–3 g/day	0.5–2 g/day	3–5 g/day 400–1400 mg/m^2/day (IV route)	?

NI, Not indicated; LI, little indicated

better response to treatment than patients having alopecia. About half of them with alopecia are refractory to high doses of active form of vitamin D [4, 25].

Some patients may need intravenous overnight calcium infusion for 12 h to maintain normocalcemia [23, 25]. The role of cinacalcet has also been found effective in these cases, encouraging its short-term use [26, 27].

Phosphopenic rickets

Classification of phosphopenic rickets

Phosphopenic or hypophosphatemic rickets include disorders that may be FGF23-dependent and FGF-23 independent forms (Fig. 1).

Hypophosphatemic rickets may be attributed to secondary hyperparathyroidism. This condition results from failure of organ involved in vitamin D metabolism, i.e. liver, kidney or intestine and inadequate supply of phosphate as occurs in malnutrition, prematurity, total parenteral nutrition, use of phosphate chelators [6].

There are some other rare form of FGF23 dependant rickets including genetic mutations of DMP1 (Dentin matrix protein 1) and ENPP1, which constitute less than 20% of hypophosphatemic rickets [28]. The latter is most important as current recommendations argue against treatment with anti-FGF23 antibody therapy [29].

Treatment of phosphopenic rickets

Conventional treatment of patients with FGF23-dependent hypophosphatemic rickets consists of inorganic oral phosphate salts combined with vitamin D active metabolites, such as calcitriol or alfacalcidol. Most of the data regarding the conventional treatment of hypophosphatemic rickets comes from the management of patients with X-linked hypophosphatemic rickets (XLH). The recommended starting and maintenance doses of inorganic phosphate and vitamin D active metabolites in patients with hypophosphatemic rickets are summarized in Table 4.

N.B. A progressive increase in the dose of phosphate and active vitamin D analogs is recommended. The treatment should be individualized and tailored according to the severity of the patient's condition and tolerability. The

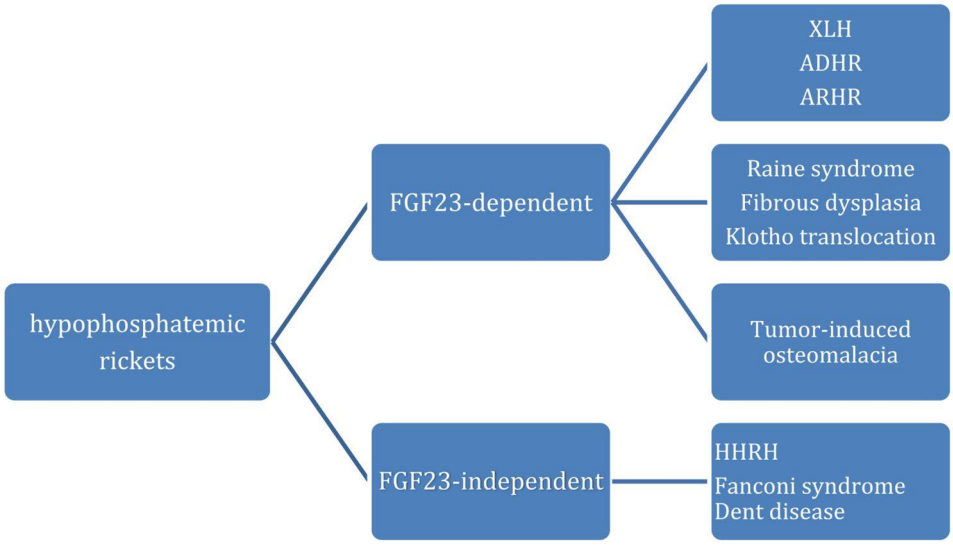

Fig. 1 classification of different forms of hypophosphatemic rickets [4]

Table 4 Starting and maintenance doses of inorganic phosphate and active vitamin D analogs in hypophosphatemic rickets [30–35]

	Newborn or before the development of clinical or radiological signs of rickets	Evidence of clinical or radiological signs of rickets
Starting Doses	Alfacalcidol,25-40ng/kg/day (0.8-1ug/day), once/day. Inorganic phosphate salts, 20–40 mg/kg/day, 4 to 6 intakes/daily	Alfacalcidol, 40–80 ng/kg/day (1-1.5 ug/kg) once/day. Calcitriol, 20–40 ng/kg/day, 2–3 times/day Inorganic phosphate salts, 40–60 mg/kg/day, 4 to 6 intakes/daily
Maintenance doses	Alfacalcidol,25–40 ng/kg/day (1–2 ug/day), once/day; calcitriol,20–30 ng/kg/day. 2–3 times/day. inorganic phosphate salts, 20–60 mg/kg/day. 4 to 6 intakes/ day	

two medications must be administered combinedly at a balanced dosage with careful monitoring.

Patients who respond poorly to conventional treatment or have significant side effects are candidates for therapy with Burosumab, a humanized IgG1 monoclonal antibody directed against the FGF23 hormone. Some patients with XLH have also been treated with growth hormone (GH) in combination with conventional treatment to improve growth although results are inconclusive [36].

In patients with autosomal dominant hypophosphatemic rickets (ADHR) and autosomal recessive hypophosphatemic rickets (ARHR), the dosages of phosphate supplements and vitamin D active metabolites may vary according to the severity of the disease and the response to treatment [4].

Monitoring and follow-up

Vitamin D deficiency

Therapeutic monitoring of treatment with vitamin D and calcium varies with the severity of rickets and response to therapy. Normalization of serum calcium and phosphate level.

usually occurs within 3 weeks of initiation of treatment [37], but it may be earlier (after 6–10 days of treatment) [38]. Serum parathyroid hormone (PTH) concentration falls within the normal range by normal feedback loop after restoration of serum Ca level. Serum 25(OH)D concentration rises rapidly and reaches its normal value after 4–6 weeks. Serum 1,25(OH)2D concentration increases rapidly after treatment that may remain elevated for 10 weeks [36]. Alkaline phosphatase activity declines progressively but may remain elevated for several months (3–6 months) depending on the severity of the vitamin D deficiency. Serum alkaline phosphatase level serves as a reliable and economic biochemical marker of activity of rickets and monitoring tool of therapeutic response [39].

Radiological examinations are useful to demonstrate the effectiveness of treatment with vitamin D in patients with nutritional rickets. The zone of provisional calcification at the end of the metaphyses is usually appeared within 3–4 weeks of treatment [38].

Clinical response pattern of nutritional rickets include improvements of symptoms like aches and pains disappear 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 [40].

Calcium deficiency

Radiological healing of the growth plate usually demonstrates after 3–6 months of calcium administration. It requires a longer time to improve the clinical signs than the biochemical alterations and radiological healing [41].

Vitamin D-dependent rickets

Response to therapy with active vitamin D metabolites (calcitriol or alfacalcidol) is usually faster. Radiological healing of rickets and normalization of the biochemical parameters occur within 7–9 weeks of therapy [42]. Strict adherence to long term treatment is of paramount importance. Serum concentrations of calcium, phosphate, PTH and urinary calcium excretion should be monitored routinely to see the response during the maintenance phase of therapy (at least every 4–6 months). Time interval may be shortened if hypocalcemia presents. Target should be made to keep serum calcium concentration in the low-normal range and PTH level below the upper limit of normal [43]. Urinary calcium excretion should be maintained below the normal limit for age and weight. Renal ultrasound should be performed every 1–2 years to detect nephrocalcinosis earlier and more frequently if there is evidence of hypercalciuria [23].

Hypophosphatemic rickets

Some recommendations for follow up of XLH patients who are receiving conventional treatment have been suggested (Table 5).

Treatment of hereditary hypophosphatemic rickets with hypercalciuria (HHRH)

Treatment includes supplementation of phosphate in a monitored way to avoid nephrocalcinosis. 1,25(OH)2 D is not recommended as it is high in HHRH. High fluid intake, avoidance of high salt and protein along with thiazide diuretics are useful in preventing nephrocalcinosis [44].

Table 5 Recommendations for the follow-up of patients with XLH rickets receiving conventional treatment [4, 25]

Clinical assessment	Timing
Clinical and auxological examination	< 5 years:1–3 months > 5 years: 3–6 months
Dental Examination	Every 6–12 months or based on clinical symptoms
Orthopedic examination	Every 12 months or based on clinical symptoms
Hearing test	>8 years or based on clinical symptoms
Biochemical parameters	
[a]Serum calcium, inorganic phosphate, creatinine, alkaline phosphatase, PTH	Every 3–6 months
Urinary calcium creatinine ratio, [b]TmP/GFR	Every 3–6 months in patients on active vitamin D or Burosumab treatment
Imaging examinations	
Radiographs of wrists, knees, standing lower limbs	Every 1–2 years or based on clinical signs
Renal ultrasonography	Every year
Fundoscopy and brain MRI	In the presence of craniosynostosis or skull shape malformation, headache, neurological symptoms or visual disturbances.
Quality of life	**Every year**

[a]Biochemical parameters including serum phosphate, ALP and TmP/GFR must be interpreted with age-specific normative value

[b]TmP/GFR is the maximum rate of tubular reabsorption of phosphate per glomerular filtration rate; calculated by entering the fasting urine and plasma concentrations (same unit) into following equation: TmP/GFR = $(Pp - \left(\frac{Up}{Ucr}\right) * Pcr)$ [25]

Age specific upper normal range of TmP/GFR: 2.2 (< 1 year), 1.4 (1–3 years), 1.1 (3–5 years), 0.8 (5–7 years), 0.7 (> 7 years)

Table 6 Classification of vitamin D status in children with CKD [51]

Sufficiency	> 75 nmol/L (> 30 ng/mL)
Insufficiency	50–75 nmol/L (20–30 ng/mL)
Deficiency	12–50 nmol/L (5–20 ng/mL)
Severe deficiency	< 12 nmol/L (< 5 ng/mL)

Table 7 Vitamin D supplementation in children with end stage renal disease (ESRD) [48]

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	> 75	400 IU/day	25(OH)D level at 6–12 months
> 1 year	> 75	1000/2000 IU/day (more in advanced CKD)	25(OH)D level at 6–12 months

Management of vitamin D deficiency in CKD-MBD

The therapeutic goal of pediatric CKD-MBD is to prevent or minimize complications in the growing skeleton, achieve adequate growth, and prevent vascular calcification by managing hyperphosphatemia, vitamin D deficiency, and secondary hyperparathyroidism [45, 46].

Vitamin D deficiency is common and often severe in children and adults with CKD. Treatment of vitamin D deficiency is important because vitamin D deficiency contributes to secondary hyperparathyroidism [47].

The European Society for Paediatric Nephrology (ESPN) CKD-MBD clinical practice guidelines suggest using native vitamin D (e.g., ergocalciferol and cholecalciferol) supplements to treat vitamin D insufficiency or deficiency in children with CKD G2-G5D, and to prevent or treat secondary hyperparathyroidism in children with CKD G2-G3 [48]. Active vitamin D analogs (e.g., alfacalcidol, calcitriol, paricalcitol, and doxercalciferol) should not be used to treat vitamin D deficiency [49]. Mega-dose vitamin D therapy is not recommended [50] (Tables 6 and 7).

Treatment of other forms of rickets

Fibrous dysplasia can cause hypophosphatemic rickets via secretion of excess of FGF23 in dysplastic tissue, resulting in some degree of phosphate wasting [52]. Management of fibrous dysplasia primarily focuses on non-rachitic complications as hypophosphatemia is less severe. Treatment with phosphate salt and active vitamin D therapy is considered when hypophosphatemic rickets develop. Failure to respond needs burosumab treatment. Bisphosphonates has limited role [25, 53].

Tumor-induced osteomalacia (TI0) may be solved by complete resection of the tumor. When tumor removal is not possible, conventional treatment of XLH should consider such as phosphate supplementation at a dose of 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 [54].

Phosphate supplements along with active metabolites of Vitamin D are suggested for the treatment of patients with hypophosphatemic rickets secondary to tubulopathies, Dent disease, Fanconi syndrome or other systemic diseases in association with the disease- specific treatments for each of them [55].

Vitamin D toxicity (VDT)

VDT is a rare, but serious clinical condition characterized by severe hypercalcemia, usually develops after excessive intake of vitamin-D megadose or its metabolite [56]. According to pediatric endocrine society, serum 25 (OH) D levels > 100 ng/ml (250 nmol/L) have been defined as hypervitaminosis D and > 150 ng/ml (375nmol/L) have been proposed to define vitamin-D intoxication [57]. According to a updated guideline in Poland (2023), VDT is defined as hypercalcemia, hypercalciuria and serum 25(OH)D concentration > 100ng/ml [58]. So, disparity is noted on VDT threshold amongst different guidelines. Priority must be given on laboratory reference value. There is delay in diagnosis of refractory rickets due to limited access to advance diagnostic facilities (i.e. genetic testing) in resource poor settings. Repeated treatment of mega dose of vitamin D leads to the risk of VDT. The long term effects of high dose vitamin D therapies require further investigations.

The clinical manifestations of VDT are primarily related to hypercalcemia, ranging from asymptomatic to severe life-threatening features [59]. Laboratory investigations reveal hypercalcemia and hypercalciuria. Nephrocalcinosis may be observed on renal ultrasonography. Treatment of toxicity includes discontinuing vitamin D, adequate hydration and management of hypercalcemia by calcitonin, steroid and hemodialysis with or without diuretics [60].

Prevention of rickets

Exclusively breast-fed infants consume an average of 750 ml of breast milk and ingest 10–40 IU (0.25 to 1 µg/day) of vitamin D daily. The vitamin D content is usually lower in mothers with dark skinned and on vitamin-D deficient diets. Breast-fed infants need to be exposed to sunlight 30 min/day while wearing a diaper to maintain 25(OH)D concentration at ˃ 20 ng/ml. Infant formula and orange juice in the United States is fortified to contain 40–100 IU (1-2.5 µgm/L) and 400 IU (10 µg) of vitamin D per liter respectively [61]. This rule should be made universal to all nations of the world. In case of light-skinned people, sufficient cutaneous vitamin D synthesis needs 10–15 min of sun exposure to the arm, legs, hands and face between 10.00 am to 3.00 pm during spring, summer and fall. Prolonged sun exposure results in a minimum serum 25(OH) D level of ˂80 ng/ml (200 nmol/L) [62]. Among Indian children, role of sunlight was found to be effective in improving vitamin D status who had a sunlight exposure of 17–30 min in infants and 30–45 min in older children over 15–40% of body surface area [63].

American Academy of Pediatrics (AAP) recommends universal supplementation of vitamin D 400IU per day throughout infancy regardless of mode of feeding (breast feeding or formula feeding). Infant can receive supplementation indirectly through breast milk from women who fortify their own milk by ingesting high doses of vitamin D (4000 to 6400 IU/day) [64]. AAP also recommends 1 L of vitamin-D fortified milk to all children beyond infancy. Unfortunately, only one-third of American children used to consume the recommended amount as per the 2022 report because only 30% o clinicians believe that recommendation [65]. 1 cup of milk contains 276 mg calcium as well as enough phosphate. The habit of drinking milk is very essential [22].

The food safety Standards Authority of India recommends milk fortification by using a fat soluble premix. Vitamin D supplementation with 400–600 IU/day is set as an estimated average requirement for Indian children. So, food fortification is a cost effective strategy of prevention of vitamin D deficiency in low resource settings [66].

Daily 4000 to 6000 IU (100–160 µg) of vitamin-D supplementation to lactating mothers is another strategy to improve vitamin D status in infant. Vitamin-D enriched foods are very little in number. Consumption of spinach, green vegetables, bread (wheat, brown), almonds rich in calcium can mitigate vitamin D deficiency [67].

Universal supplementation of vitamin-D during national immunization program to all infants and children can be an alternative option. More than 1100 foods are vitamin-D fortified in USA. Milk fortification in India has been found to be successful in school children. Education to all level of health workers, mass campaign in social media can be useful [67, 68]. All nation of the globe

can fortify their staple food with the recommended daily amount. Parliamentary legal approval of universal fortification of vitamin D may be helpful as per author's view.

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 [48].

Conclusion

Early diagnosis and institution of proper treatment are the main targets to avoid severe complications in later life. The differentiation among the varieties of rickets is an important step for definitive management. Although nutritional rickets is the commonest form, refractory patterns must be considered based on specific biochemical and radiographic findings along with special clinical features, so that appropriate treatment and monitoring can be instituted promptly in a timely- manner.

Abbreviations

IU	International unit
ESPGHAN	European society of pediatric gastroenterology, nutrition and hepatology
FGF23	Fibroblast growth factor-23
VDDR	Vitamin D-dependent rickets
RXR	Retinoid X receptor
ADHR	Autosomal dominant hypophosphatemic rickets
ARHR	Autosomal recessive hypophosphatemic rickets
CKD-MBD	Chronic kidney disease– mineral bone disease
NKF-KDOQI	National Kidney Foundation- Kidney Disease Outcomes Quality Initiative
TI0	Tumor-induced: osteomalacia
VDT	Vitamin D toxicity
ESRD	End stage renal disease
AAP	American Academy of Pediatrics

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Author contributions

Rummana Tazia Tonny was a major contributor in writing the manuscript. Ranjit Ranjan Roy made a substantial, direct and intellectual contribution to the work and approved it for publication.Tahmina Jesmin was actively involved in overall scrutiny of this review based on updated literature.Abdullah Al Mamun reviewed the manuscript.Nadira Sultana was actively involved in writing the manuscript and searching literature.

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Data availability

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Not applicable.

Consent for publication

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Competing interests

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