Indian Academy of Pediatrics Revised (2021) Guidelines on Prevention and Treatment of Vitamin D Deficiency and Rickets

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ABSTRACT

Justification: The emerging literature on prevalence of vitamin D deficiency in India, prevention and treatment strategies of rickets, and extra skeletal benefits of vitamin D suggest the need for revising the existing guidelines for prevention and treatment of vitamin D deficiency in India.

Objectives: To review the emerging literature on vitamin D prevalence and need for universal vitamin D supplementation. To suggest optimum vitamin D therapy for treatment of asymptomatic and symptomatic vitamin D deficiency, and rickets. To evaluate the extra-skeletal health benefits of vitamin D in children.

Process: A National consultative committee was formed that comprised of clinicians, epidemiologists, endocrinologists, and nutritionists. The Committee conducted deliberations on different aspects of vitamin D deficiency and rickets through ten online meetings between March and September _____, 2011. A draft guideline was formulated, which was reviewed and approved by all Committee members.

Recommendations: The group reiterates the serum 25-hydroxy vitamin D cutoffs proposed for vitamin D deficiency, insufficiency, and sufficiency as <12 ng/mL, 12–20 ng/mL and >20 ng/mL, respectively. Vitamin D toxicity is defined as serum 25OHD >100 ng/mL with hypercalcemia and/or hypercalciuria. Vitamin D supplementation in doses of 400 IU/day is recommended during infancy; however, the estimated average requirement in older children and adolescents (400-600 IU/day, respectively) should be met from diet and natural sources like sunlight. Rickets and vitamin D deficiency should be treated with oral cholecalciferol, preferably in a daily dosing schedule (2000 IU below 1 year of age and 3000 IU in older children) for 12 weeks. If compliance to daily dosing cannot be ensured, intermittent regimens may be prescribed for children above 6 months of age. Universal vitamin D supplementation is not recommended in childhood pneumonia, diarrhea, tuberculosis, HIV and non-infectious conditions like asthma, atopic dermatitis, and developmental disorders. Serum 25-hydroxy vitamin D level of >20 ng/mL should be maintained in children with conditions at high-risk for vitamin deficiency, like nephrotic syndrome, chronic liver disease, chronic renal failure, and intake of anticonvulsants or glucocorticoids.

Keywords: *Cholecalciferol, Infections, Recommendations, Sunlight, Vitamin D supplementation.*

Vitamin D deficiency (VDD) has been reported as an emerging problem globally over the last decade. It remains a significant problem even in tropical countries, despite sunlight abundant [1]. The implications of VDD are believed by many to extend beyond skeletal manifestations to effects on infections, cancers, autoimmune diseases, and mental health conditions [2]. Global Consensus Guidelines prevention and treatment of VDD and nutritional rickets in childhood were released in 2016 [3]. The Indian equinox with apparent abundant sun light in most parts of the country, darker skin color with high melanin content, different socio-cultural factors and genetic variations [4] suggested the need for a guideline relevant to the Indian context; which were released by the Indian Academy of Pediatrics (IAP) in the year 2017 [5].

The Comprehensive National Nutrition Survey (CNNS), by the Ministry of Health and Family Welfare, Government of India involving about 35,000 children aged between 1 to 19 years from all over India, was conducted in 2016-18 [6]. Prevalence of vitamin D deficiency defined as serum 25OHD < 12 ng/mL was found to be 14% among children aged 1-4 years, 18% among school age children (5-9 years) and 24% among adolescents (10-19 years) [6], which was below the proportions reported in hospital and community-based studies from India. Gender disparity was observed to be most wide in adolescents with 34% of girls having deficiency as against 14% of boys. Thus, a need was felt to revisit the earlier recommendations.

OBJECTIVES

The present guidelines re-examine the role of vitamin D supplementation during infancy and childhood in the light of population data on prevalence of vitamin D deficiency. The present guidelines also summarize the recommendations on sunlight exposure for Indian children, and the optimum dosage, schedule, and duration of vitamin D therapy, relevant as per Indian literature. The present guideline is proposed to be used general pratioteness, pediatricians, and epidemiologists working in child health.

PROCESS

A group of experts were invited under the IAP Action Plan in March, 2020, which consisted of faculty from medical colleges, pediatric practitioners, office bearers of Indian Academy of Pediatrics, and external experts with experience in nutritional epidemiology and clinical research (**Annexure 1**). Six sub-committees were constituted to conduct detailed narrative reviews on the following topics: (*i*). Vitamin D deficiency- problem assessment; (*ii*). Preventive strategy- maternal and infant supplementation; (*iii*) Preventive strategy- natural dietary and sunlight; (*iv*) Treatment of VDD and rickets; (v) Role of vitamin D in extraskeletal health- infections, and (*vi*) Role of vitamin D in extra-skeletal health - non-infective conditions.

Data were gathered through semi-structured search strategy with respect to the study question of each respective section. The search was performed on Pub Med and MEDLINE electronic databases.

The initial draft recommendations were discussed with supporting evidence as prepared by the writing committee through emails. The recommendations were then deliberated upon during 10 successive online

meetings (March to September 2021). Delphi technique was used to arrive at a consensus after discussions which helped formulate the final recommendations. An external peer-review was invited by an International expert who provided critical inputs for revising the manuscript.

The level of evidence of each recommendation was graded from 1-5 as per the Oxford Centre for Evidence-Based Medicine (OCEBM) classification [7]. The draft guidelines were circulated for approval to all the members of the Committee for suggestions, if any and final approval.

RECOMMENDATIONS

The Global Consensus Guidelines and earlier IAP Guidelines have classified vitamin D deficiency, insufficiency, and sufficiency as serum 25-hydroxy vitamin D levels as <12 ng/mL, ≥12-20 ng/mL and >20 ng/mL, respectively [3]. The Group observed that there is a dearth of robust scientific evidence to conclude if these cut-off levels of serum 25(OH)D are valid, especially for skeletal outcomes. Most available Indian studies had used variable cutoffs of 5-20 ng/mL for defining low serum 25(OH)D levels and adverse clinical outcomes [8-35]. Studies have demonstrated an inverse relation between serum parathyroid hormone (PTH) and vitamin D levels, but have not agreed on the inflection point of 25(OH)D level at which PTH begins to rise [36,37]. Most studies were observational and measured only association, thus lacked data on causality, on false positives for adverse skeletal outcomes, inflection point for increase in PTH levels, and correlation of 25(OH)D levels with bone markers and bone histomorphometry. Other confounders like inflammation and adiposity have not been accounted during estimation of burden of VDD in CNNS survey. The Group agreed that in the absence of valid serum 25(OH)D cutoffs, a level of <12 ng/mL may be endorsed as the definition of VDD in concurrence with the earlier guidelines [3,5] and as per the cut-off used in the CNNS survey [6]. Serum 25(OH)D >20 ng/mL is considered as desirable/sufficient to provide a buffer for periods of stress, exigency, and seasonal patterns.

The burden of vitamin D deficiency in India shows a marked variation in prevalence across different studies. The prevalence is confounded by factors like age, concomitant calcium deficiency, study setting (community or hospital), study participants (healthy or diseased), geographical location (as per latitude of the area), and sociocultural factors (dressing pattern, dietary intake) [6,32,33,35].

Vitamin D Toxicity

Also, as the therapeutic indications of vitamin D supplementation increased over the last decade, the possibility of vitamin D intoxication remained an area of concern. The Group felt the need to define urinary excretion cutoffs in addition to serum 25(OH)D levels alone for definition of vitamin D intoxication. The serum 25(OH)D cutoff of >100 ng/mL with associated hypercalcemia and/or hypercalciuria defines vitamin D toxicity. Serum levels between 50-100 ng/mL are unusual without supplementation and should alert the physician to avoid further vitamin D supplementation.

Estimation of vitamin D

Automated immunoassay is the most common method utilized by the laboratories world-over [38]. It is simple to use, requires low sample volume and is relatively inexpensive. The major drawback is that it utilizes polyclonal antibodies which in turn get affected by changes in body protein concentrations. Immunoassays, however, cannot differentiate between the two forms of vitamin D, notably 25(OH)D2 and 25(OH)D3. The concentration of 25(OH)D2 is relatively more in infants and so the estimation of 25(OH)D levels by immunoassay may not be a reliable method during infancy [39]. Another inherent specificity issue with assays utilizing antibodies is cross-reactivity with other vitamin D metabolites; most notably vitamin 24,25(OH)2D3 which constitutes about 10-15% of the total 25(OH)D concentration [40]. These shortcomings can be overcome by utilizing the liquid chromatographic methods either LC-UV or LC-MS/MS [41].

Consensus Statements and Recommendations

1.1 Definition and diagnosis: Classification of Vitamin D status in children should be based on serum 25(OH)D levels and defined as deficiency <12 ng/mL, Insufficiency: 12–20 ng/mL, and sufficiency >20 ng/mL [**LOE** 2].

1.2 Hypervitaminosis and vitamin D toxicity: Diagnosis of vitamin D toxicity can be made in the presence of serum 25(OH)D levels >100 ng/mL with hypercalcemia* and/or, hypercalciuria;** levels between 50-100 ng/mL should be viewed with caution. Serum PTH levels will be suppressed in cases with vitamin D toxicity [**LOE** 3].

The normal upper limit for serum calcium: birth to 3 mo: 11.3 mg/dL; 3-6 mo: 11.2 mg/dL; 6 to 12 mo: 11.3 mg/dL; 1 to 3 y: 11.1 mg/dL; 4 to 18 y: 10.7 mg/dL. The normal limits for urine spot calcium: creatinine ratios by age: Up to 6 mo: < 0.8; 6-12 mo: < 0.6; ≥ 24 months: < 0.2; OR 24-hour urinary calcium excretion >4 mg/kg/day.

1.3 Prevalence of Vitamin D Deficiency

1.3.1 Population-based studies measuring serum 25(OH)D remain the best method of estimation of the burden of vitamin D deficiency [**LOE** 2].

1.3.2 The prevalence of Vitamin D deficiency is variable across different parts of India based on geographic location, age group and sociocultural and demographic factors [**LOE** 2]. National representative data on VDD are not available for infants under 1 year of age. Hospital and community-based studies (using cut offs of 10-20 ng/mL) have reported vitamin D deficiency in infancy to range from 22-92 % [**LOE** 3]. Prevalence in older children and adolescents range between 14-24% as per CNNS data.

1.4 Estimation of vitamin D levels

1.4.1 Serum 25(OH)D level should be estimated for all clinical purpose where assessment of vitamin D status is required [**LOE** 5].

1.4.2 Vitamin D levels are best measured with liquid chromatography coupled to ultra

violet (LC- UV) or tandem-mass spectrometry (LC-MS/MS) [**LOE** 2]. Where LC-UV/LC-MS/MS are unavailable, automated immunoassay may be used [**LOE** 2]

Vitamin D Supplementation for VDD Prevention

The Group noted that the cutoff for vitamin D deficiency in pregnant women at less than 20 ng/mL is higher than that for children (<12 ng/mL) in view of physiological role of vitamin D in fertility and conception [42], however there is not enough evidence for 20 ng/mL to be used as a cutoff for the same. The pooled prevalence of low vitamin D levels (≤20 ng/mL) in pregnant women from India was reported as >30%, which seemed as a major public health concern [43]. However, the higher cutoff of defining VDD in pregnancy appears to be the reason for high prevalence.

The World Health Organization (WHO) has provided guidelines on the role of dietary interventions for improving pregnancy outcomes, which did not recommend routine vitamin D supplementation in pregnancy [44,45]. WHO also recommends that the required vitamin D needs should be met by sunlight exposure and dietary intake; the amount of time needed in the sun is *however,* not known and depends on many variables [44]. An adequate dietary calcium intake should be encouraged during pregnancy. Calcium should be supplemented in dose of 1200 mg daily in all pregnant and lactating women [46] or in higher doses of 1.5 to 2 grams to improve outcomes for pre-eclampsia in those with low dietary intake [42,47].

The ethical dilemma of stigmatization during pregnancy with nutritional deficiency, unnecessary diagnostic testing and public health concerns like cost-effectiveness and equitable distribution; *vis-à-vis* significant clinical benefits of universal antenatal vitamin D supplementation need to be further explored.

The impact of vitamin D supplementation on other neonatal outcomes was investigated in another systematic review of studies from developing countries. A significant association of maternal VDD (≤20 ng/mL) was seen with low birth weight (LBW), small for gestational age and preterm birth (1 study). There was no association on NICU admission, head circumference or neonatal deaths/ stillbirth (four trials, 1884 women; RR: 0.59, 95% CI: 0.28 to 1.22) [48]. Similar conclusions were observed in other systematic reviews [49,50]. As per a recent Cochrane review, maternal vitamin D supplementation showed a reduction in incidence of LBW without any effect on preterm birth, whereas the combination of vitamin D and calcium though reduced the risk of LBW but showed an increased risk for preterm birth [51].Similar positive effect of maternal vitamin D supplementation on birth length and birth weight without any reduction in incidence of SGA and preterm births was observed in another meta-analysis [52]. The recent WHO recommendations for nutritional interventions in pregnancy (2020) concluded little or no effect of vitamin D versus placebo on risk of preterm birth (eight trials, 2938 women; RR: 0.78, 95% CI: 0.48 to 1.27), little or no difference on risk of still birth (four trials, 1884 women; RR: 0.59, 95% CI: 0.28 to 1.22), unclear benefit on low birth weight and neonatal mortality. The administration of calcium with vitamin D or no vitamin D and calcium also didn't conclude any significant effect on LBW, neonatal mortality and preterm birth [45].

The available data on prevalence of VDD in infancy mandating routine vitamin D supplementation were reviewed. As mentioned in section 1, the burden of deficiency was highly variable across different studies, with limited literature on impact of routine vitamin D supplementation. However, among different age-groups, infants were considered at higher propensity for VDD as breast milk is a poor source of vitamin D and options of complementary feeding are usually not fortified or rich in vitamin D [53]. The national vitamin D supplementation program providing 400 IU daily to children between 0-3 years showed a decline in prevalence of nutritional rickets in Turkey [54]. A dose of 400 IU daily was found beneficial to achieve serum 25(OH)D levels >20 ng/mL and for prevention of rickets in infants [55-58]. The administration of doses higher than 400 IU did not achieve any significant benefits in bone mineral content or bone markers, and a risk of hypervitaminosis was observed with doses of 1600 IU per day [57,58]. A few randomized controlled trials have shown inferior effect of dose of 400 IU than 800 IU in prevention of VDD in preterm babies [59-63].

Vitamin D supplementation in under-five age group of children was associated with mild improvement in linear growth (mean difference 0.66, 95% CI -0.37 to 1.68) 3 studies, 240 participants, without any significant effect on length/ height Z-scores [64]. Adolescence appears a vulnerable age for manifesting the effects of vitamin D and calcium deficiency as it is the period of maximum bone mass accrual. The prevalence of VDD was higher in adolescents (girls>boys) than other age-groups in the recent CNNS survey [6]. The Committee opined that the estimated average requirements (EAR) of vitamin D and calcium during adolescence should be met with sunshine and dietary intake without the need of universal vitamin D supplementation (see later). This further refutes the need to screen apparently healthy children for vitamin D deficiency.

A few children may remain at high-risk with their underlying disease states where routine requirements of vitamin D may not be met by natural sources. Such children should receive pharmacological supplementation (minimum 400 IU daily) for prevention of VDD. Routine supplementation with vitamin D was therefore considered as an effective strategy for prevention of vitamin D deficiency in infants and high-risk children.

Consensus Statements and Recommendations

2.1 Maternal supplementation

2.1.1**.** Maternal vitamin D status has no bearing on anthropometry outcomes and bone density of the offspring in infancy but may be associated with maternal and neonatal biochemical vitamin D deficiency and neonatal hypocalcemia if the deficiency is severe (**LOE** 1).

2.1.2 Maternal vitamin D supplementation may improve biochemical vitamin D deficiency in neonates and hypocalcemia in infancy, without any conclusive benefit for other fetal and neonatal outcomes, including neonatal infections, small for gestational age, preterm birth, congenital anomalies, large for gestational age, and fetal/neonatal mortality (**LOE** 1).

2.1.3 Universal vitamin D supplementation is not recommended during pregnancy (**LOE1**).

2.1.4 Routine calcium supplementation should be ensured during pregnancy for optimizing maternal and neonatal health outcomes including skeletal health [**LOE** 1].

2.2 Infant and childhood supplementation

2.2.1We recommend routine vitamin D supplementation in infancy (0-1 years of age) in doses of 400 IU/ day. Doses above 400 IU do not offer any additional skeletal benefit during childhood. Higher doses such as 1600 IU daily or above can result in toxicity (**LOE2**).

2.2.2 A dose of 400 IU/day is safe in preterm babies. Doses of 800 IU/day can achieve desired biochemical levels faster, but the level of evidence and safety data are not enough to make a separate dosing recommendation for preterm babies [**LOE** 3].

2.2.3 Routine vitamin D supplementation is not recommended during childhood and adolescence. Estimated average requirement (EAR) of vitamin D (400-600 IU/day) should be met from sunlight and dietary sources to prevent VDD in these age-groups.

2.2.4 We recommend routine vitamin D supplementation (minimum 400 IU daily) in children with underlying high-risk conditions (**Box I**). Routine screening of apparently healthy children for vitamin D deficiency is not recommended. [**LOE** 5]. Asymptomatic children should be screened only if they are at risk for vitamin D deficiency (e.g., children receiving long term anticonvulsants or glucocorticoids; chronic kidney disease, malabsorption states, children with disabilities, chronic inflammatory diseases, etc) [**LOE** 5].

Box I High-Risk Conditions Requiring Routine Vitamin D Supplementation

- Non-ambulatory states like cerebral palsy, neuromuscular disorders
- Chronic kidney disease
- Chronic liver disease
- Malabsorption syndromes
- Long-term use of glucocorticoids, antiepileptic drugs, ketoconazole
- Endocrine disorders like hyperparathyroidism
- Disorders with extensive cutaneous involvement

Sunlight and Diet for VDD Prevention

3.1 Sunlight: Background

The primary source of vitamin D is endogenous conversion of 7-dehydrocholesterol into previtamin D3 with the help of ultraviolet-B rays (UV-B) of sunlight (wavelength:290 -315nm), which further undergoes isomerization into vitamin D3 (cholecalciferol) by sunlight. This conversion is linear in first 30 min after which there is a non-linear rate of conversion which peaks within 8 hours and is responsible for conversion of 80% of previtamin D3 into cholecalciferol [65]. However, usually only 10-15% of 7-dehydrocholesterol in the skin converts into previtamin D3. Cholecalciferol is converted to active vitamin D3 after successive hydroxylations occurring in

liver and kidney, respectively. The previtamin D3 and cholecalciferol later get converted into inert metabolites like lumisterol and tachysterol with a ceiling effect after prolonged duration of sunlight exposure, which prevents development of vitamin D toxicity [66]. The increments in serum 25(OH)D are achieved with every increase in UV irradiance till peak of 55 nmol/L (22 ng/mL) after which the levels get saturated possibly by the photoisomerization of previtamin D [66,67]. The rise in vitamin D production is higher in those with low baseline serum 25(OH)D levels, and plateaus with constant UVB dosing.

The amount of cutaneous biosynthesis of vitamin D depends on both host and environmental factors. Among the environmental factors, latitude, pollution, cloud cover and intensity of UV irradiance influence vitamin D production [65, 68-70]. The UV irradiance should be received directly by skin and not filtered through surfaces like glass in windowpanes which can itself absorb UVR. The host factors which determine vitamin D synthesis are age, skin melanin content, single nucleotide polymorphisms in melanin gene, body surface area exposed (clothing), lifestyle and use of sun-barrier measures including topical creams and sunscreens [69,71]. Fitzpatrick skin type is used to classify skin types from I to VI based on their melanin content, where I is the lightest. Indian skin types have higher melanin content than Caucasians and are usually classified as IV or V [72].

VDD remains a significant public health concern even in tropical countries [73]. Studies have found a positive correlation between sunlight exposure and vitamin D production in skin, both from temperate countries as well as India [25,74]. Age is an important host factor which affects this association as the amount of 7-dehyrocholesterol is constant till old age when it begins to decline [75]. The body surface area (BSA) is also greater for similar exposed body parts in infants and younger children than adolescents or adults. Therefore, young adults demonstrate higher vitamin D levels than older subjects after exposure to the same amount of solar radiation [76]. A rough estimation of BSA for children approximates face, forearms, hands, lower legs and feet to 7-10%, 8%, 4%, 8-12% and 8% BSA, respectively making a cumulative score of approximately 40% in young children (<5 y). The same area in an adolescent or adult would be approximately 30% [77,78].

Sunlight doses have been measured as 'minimal erythema dose (MED)' which is defined as dose of UVR required to produce barely perceptible erythema. UV-B MED in skin type IV and V varies from 40-60 to 60-90 mJ/cm^2 (= 400-600 J/m2) which is almost three times the lighter skin type (type I and II) [72]. However, as MED would vary significantly with skin pigmentation, a unit of standard erythemal dose (SED) is commonly used. It is the erythemally weighted radiant UVR equivalent to 100 J/m^2 solar UV index. SED does not rely on erythema and is independent of skin type. One SED is equal to 0.5 times the MED for type I skin [66]. Doses equivalent to MED induce skin damage and may be harmful, instead sub-erythemal doses have shown to be more effective in cutaneous vitamin D production [66]. Also, frequent small UVB dosing were found more efficacious in increasing serum 25(OH)D levels than single large exposures. This could be explored as a feasible option in Indian settings to utilize natural sunlight exposure.

Studies conducted in different ethnic and geographical locations suggest variable duration of sunlight exposure to achieve sufficient serum 25(OH)D levels. The increase in serum 25(OH)D is higher in summer than winter months[16,31,79-82].A review suggested 30-45 min of daily sunlight exposure over 12%-18% of BSA as sufficient to maintain vitamin D levels in the Indian population [83].Data available from few other Indian studies in infants, children and adults have been extrapolated to suggest an optimal duration of sunlight exposure, though the rise in serum 25(OH)D may be unpredictable with the underlying host and environmental factors [28,84-86]. This guideline does not endorse artificial UV sources for vitamin D production in children. At present safety data for skin cancers with sunlight exposure in Indian children is unknown [87,88].

Systematic reviews based on adult studies have also shown that serum vitamin D level increases after both, sunlight and vitamin D supplementation; however, the rise is higher and more predictable with vitamin D supplementation than sunlight [89-92]. The rise in serum 25(OH)D was less after long-term sunlight exposure and artificial UVB source than natural sunlight [89]. Compliance to supplementation and sunlight remains a major confounder in estimating the efficacy in natural settings.

3.2 Diet: Background

Among the dietary sources, Vitamin D3 (cholecalciferol) is mainly obtained from animal source like fish, liver, cod liver oil and eggs while vitamin D2 (ergocalciferol) is found in plants, especially mushrooms [93]. The content of vitamin D in Indian foodstuffs can be approximately estimated according to the Indian food composition tables (IFCT), 2017 [94]. There is minimal amount of natural vitamin D in milk (5-40 IU/L) and milk products like cheese and butter (30 IU/100g), which contribute minimally to the RDA [95]. The consumption of skimmed or low-fat milk with reduced fat content of 0.1% and 1% further reduces the amount of vitamin D. Unfortified whole milk, toned milk and full cream milk have higher fat content (>3%) with vitamin D levels between 0.2 –0.6 µg/L (8-24 IU/L) [96]. Egg yolk contains variable amount of vitamin D (27-40 IU/egg) and may not be a rich source of vitamin Cooking of animal products like boiling eggs, pasteurization of milk, baking and heating meat does not cause significant vitamin D loss. Among fishes, fatty fish like salmon, tuna, mackerel have higher vitamin D content with maximum content in fish liver (1200 µg/kg) than non-fatty fish [96].

Data from CNNS report showed that most (54-56%) children in India consumed vegetarian diets without eggs with higher prevalence of vitamin D deficiency in vegetarians than non-vegetarians [6]. Among the non-vegetarian sources, oily fish, or cod liver oil*d*. are unlikely to meet the RDA of vitamin D in amounts likely consumed by children. Data from other developed countries showed low median intake of vitamin D at less than 10 µg/day (400 IU/day) in children and adults [97-101].

Both, vitamin D and calcium intake are crucial for optimal bone health. In the absence of calcium, bone mineralization may remain poor even with replete vitamin D intakes. The major sources for calcium intake in Indian diets are dairy coarse cereals like ragi, whole legumes like chickpea and green vegetables [13,102]. The

nutritional trend in India by National Nutrition Monitoring Bureau (NNMB) from 1975 to 2017 showed that only 37% households in India had daily consumption of >70% RDA of calcium with 44% households having <50% RDA consumption [103]. Likewise, guidelines for Indian children recommend increase in RDA of calcium to 500 mg/day in infancy, 600 mg/day in 1-9 yr old and 800 mg/day in adolescents [46]. However, the dietary insufficiency was substantially overestimated in these publications because: (i) NNMB primarily sampled the underprivileged, resulting in a bias for national projections; and (ii) the estimates used the dated Nutritional Requirements for Indians with the Recommended Dietary Allowance (RDA) metric for comparison, which is intended to meet the requirements of 97.5% of the individuals. The updated Nutritional Requirements for Indians, recently published by the Indian Council of Medical Research, use the appropriate metric for comparison, namely the Estimated Average Requirements (EAR), reflecting the average intakes of the populations (needs of half of the population), which are substantially lower than the RDA. The EAR was calculated to meet serum 25(OH)D levels of 40 nmol/L (midpoint between 30-50 nmol/L). The Writing Committee did not have access to the NNMB raw data to provide dietary estimates. Statistical analysis reported an EAR of approximately 400 IU/day in children and 600 IU/day in adolescents (as obtained from natural resources) as sufficient to meet the desired serum vitamin D level [104]. Similar data were not sufficiently available for infancy, suggesting continuing with a recommendation of 400 IU/day as EAR (***details in section 2***).

Consensus Statements and Recommendations

3.1 Sunlight

3.1.1 Sunlight exposure increases serum 25(OH)D levels and is recommended for children and adolescents across all regions of India to prevent vitamin D deficiency (serum 25(OH)D<12 ng/mL) (**LOE** 2).

3.1.2 A daily sunlight exposure of 17-30 min in infants and 30-45 min in older children over 15-40% body surface area is recommended at least five times a week during noon (11AM-3PM) for preventing vitamin D deficiency across different regions and seasons (**LOE** 3.)

3.1.3 Daily application of sunscreens decreases serum vitamin D levels and are not recommended for routine use in children (**LOE** 3)

3.1.4 The rise in serum 25(OH)D is marginally higher with vitamin D supplementation than sunlight in adults (**LOE** 1). Evidence is not enough to recommend superiority or inferiority of vitamin D supplementation over sunlight exposure in preventing vitamin D deficiency in children (LOE 5)

3.1.5 The risk of skin cancers with prolonged sunlight exposure in Indian pediatric population is unknown (**LOE** 3)

3.2 Diet

3.2.1 An adequate intake of calcium should be ensured during childhood to meet the dietary requirements. The calcium demand can be met from both dairy and non-dairy (cereal, vegetables etc.) sources (LOE 5).

3.2.2 Foods rich in vitamin D may not contribute sufficiently to meet the vitamin D requirements, however, their intake should be encouraged for consumption as part of a balanced diet within the usual dietary practices (vegetarian or non-vegetarian) (LOE 5).

Treatment of Rickets and VDD

Background

Symptoms of vitamin D deficiency in children include nutritional rickets, hypocalcemic seizures, tetany, hypocalcemic dilated cardiomyopathy, bony deformities and osteomalacia [3]. There is evidence that all children with nutritional rickets be treated for vitamin D deficiency, irrespective of serum 25(OH)D levels since they are at increased risk of deformities, muscle weakness and fractures [3,105].

Asymptomatic individuals may be screened if they are at risk for vitamin D deficiency (e.g., children receiving long term anticonvulsants or glucocorticoids; chronic kidney disease, malabsorption states, children with disabilities, chronic inflammatory diseases, etc) [42]. Currently, there is not enough evidence to recommend screening for vitamin D deficiency in healthy population and asymptomatic individuals who are not at risk [106]. The treatment of isolated biochemical derangements in serum vitamin D levels (that do not correlate clinically) is unclear. However, incidentally detected serum 25(OH)D level of less than 12 ng/mL in healthy children should be treated to prevent development of clinical features related to vitamin D deficiency. There is also evidence that children with symptomatic vitamin D deficiency (serum 25(OH)D $\leq$ 20 ng/mL) without rickets, but with clinical features e.g., hypocalcemic seizures, tetany, hypocalcemic dilated cardiomyopathy, should be treated as for vitamin D deficiency [42].

Both, daily as well as intermittent regimes are efficacious in the management of nutritional rickets [107-115]. Daily doses are more physiological than bolus doses. Lower doses of vitamin D (up to 2000 IU/day) have been shown to heal rickets in infancy [107,108,116]. However, there is not enough evidence to suggest that intermittent bolus doses of vitamin D are safe in infancy and childhood [110,111]. In some situations, therapy with large cumulative doses spread over a few weeks or months may be more feasible if it is felt that there might be issues with compliance with daily vitamin D therapy. Thus, although daily regimens are preferred, vitamin D dose recommendations for both treatment options, daily as well as bolus regimens is a practical and feasible approach [3]. Bolus doses may be administered at interval of 2-4 weeks comparable to the equivalent daily dose to decrease the risk of hypervitaminosis.

Based on the available evidence [3, 107-115], we recommend daily treatment as the first line of management. The issue of safety of bolus regimens in doses equivalent to those used in daily regimes need to be established in well-powered randomized controlled trials in the future, especially in infants.

Oral treatment is the preferred form of vitamin D administration, which more rapidly restores serum 25(OH)D levels than intramuscular (IM) treatment [117,118]. Parenteral administration of mega doses of vitamin D (> 300,000 IU) is not recommended. When single large doses are used, vitamin D3 appears to be preferable

compared to D2 because the former has a longer half-life [119]. Vitamin D3 is reported to be better than vitamin D2 to raise serum 25(OH)D levels (mean difference 15.69, 95%CI: 9.46 to 21.93 nmol/L) with average dose per day being a significant predictor, irrespective of the participant demographics, baseline vitamin D levels, total dose, and vehicle of supplementation [120].

Vitamin D oral doses are packaged in India in maximum of 60,000 IU per unit, unlike other developed countries which package as 50,000 IU per unit. Studies have shown comparable efficacy of lower doses of vitamin D, suggesting a feasible dosing regimen of five doses of 60,000 IU for cumulative 300,000 IU. There are no randomized controlled trials on the optimal duration of daily treatment for nutritional rickets in children. Most studies and expert opinion, recommend optimal healing in nutritional rickets after 12 weeks of daily therapy [107,108, 121-125].

Healthcare providers should be aware of the various vitamin D preparations available in India and counsel patients regarding both desirable doses and variability among formulations. Most preparations available in the Indian market contain vitamin D3 [126]. Unsupervised intake of alfacalcidiol and calcitriol, which are not recommended for vitamin D deficiency and nutritional rickets, could result in adverse effects including toxicity. Calcitriol has been used in children with hypocalcemic seizures, along with intravenous calcium gluconate administration in initial treatment to augment clinical improvement.

Oral calcium supplementation (dose 50-75 mg per kg per day to maximum of 500 mg) should be routinely prescribed in combination with vitamin D while treating vitamin D deficiency [121,127,128]. Oral calcium is supplemented frequently as calcium carbonate in children. Preparations with calcium phosphate should be used in younger children and infants who have low phosphate levels to prevent phosphate sequestration with calcium carbonate.

Monitoring during therapy

There is insufficient literature to guide the frequency of testing in children receiving vitamin D therapy nutritional therapy or vitamin D deficiency. There are no randomized trials specifically regarding this issue. In this situation, one may infer that to assess response to therapy as well as to detect toxicity, serum calcium, phosphate, alkaline phosphatase, serum 25 (OH)D levels should be performed at 12 weeks after vitamin D therapy [110,111,114]. Some children may require longer treatment duration for normalization of alkaline phosphatase [129].

We suggest that in a child with rickets, radiographs should be performed at 4 weeks and 12 weeks after vitamin D therapy to look for evidence of healing. The earliest sign of healing would be evident on a radiograph by 4 weeks. an absence of radiological line of healing should alert towards an underlying non-nutritional cause of rickets. If complete radiological healing and normalization of biochemical parameters is not attained in rickets by 12 weeks, therapeutic doses of vitamin D and calcium should be continued. At the same time, the child should be assessed for refractory rickets as per flowchart shown in **Figure 1**. Maintenance dose of vitamin D should be

started once complete healing has been achieved. Urine calcium: creatinine ratio and renal ultrasonogram should be done when there is hypercalcemia or hypervitaminosis D.

Recommendations

4.1. Recommendations regarding Indications for treatment (Figure 1)

4.1.1 Children with nutritional rickets should be treated for vitamin D deficiency and monitored for therapeutic response (**LOE** 2); (Figure **1 and Table I**).

4.1.2 Children with clinical pointers towards non-nutritional rickets, should undergo evaluation for etiology of rickets including assessment of serum 25(OH)D levels and parathyroid hormone (**Figure 1**) (**LOE** 5).

4.1.3 Children with other symptoms attributable to vitamin D deficiency (e.g., hypocalcemic seizures, tetany, hypocalcemic dilated cardiomyopathy) AND having serum 25(OH)D level $\leq$ 20 ng/mL should also be treated for vitamin D deficiency (**LOE** 2).

4.1.4 Incidentally detected low serum 25(OH)D level < 12 ng/mL in healthy children or $\leq$20 ng/mL in those at high-risk should be treated (**LOE** 5), as per protocol for nutritional rickets.

4.2. Recommendations regarding dose, regimes, and duration of vitamin D therapy

4.2.1 We recommend daily treatment as the first line of management (**LOE** 2). The safety of intermittent bolus doses of vitamin D is not established, especially in infancy. The issue of safety of regimens involving administration of bolus intermittent doses need to be established in well-powered randomized controlled trials in the future, especially for infants (**LOE** 5).

4.2.2 Vitamin D (2000 IU/day) is recommended for treatment of nutritional rickets and symptomatic vitamin D deficiency in infants, 3000 IU/day or its equivalent in weekly/monthly bolus doses may be given in children older than 1 year (**LOE** 2). (**Table I)**

4.2.3 We recommend that the above therapy be given for a minimum of 12 weeks (**LOE** 2). Some children may require a longer treatment duration for normalization of alkaline phosphatase and serum 25(OH)D levels (LOE5)

4.2.4 There is paucity of information regarding the role of lower dose of vitamin D (less than 2000 IU/day) for treatment of rickets (**LOE** 3)

4.2.5 Calcium intake of 50-75 mg/kg/day (not exceeding 500 mg/day) must be ensured either through diet or supplementation in combination with vitamin D (**LOE** 1).

4.3 Different formulations of vitamin D

4.3.1 Oral treatment with vitamin D is recommended, which more rapidly restores serum 25(OH)D levels and is safer than intramuscular (IM) treatment (LOE 1). We suggest that intramuscular route is to be used only when absorption of oral dose is doubtful e.g., in malabsorption states (LOE 5)

4.3.2 When intermittent bolus doses are used, vitamin D3 is more efficacious than vitamin D2 in improving vitamin D status. For daily treatment, vitamin D3 is only marginally better than vitamin D2 in improving vitamin D status (LOE 1).

4.3.3 Health care providers should be aware of the various vitamin D preparations available in India and counsel patients regarding both desirable doses and variability among formulations (LOE 5).

4.3.4 Alfa-calcidiol (1-hydroxycholecalciferol) and calcitriol are not recommended for management of nutritional rickets and vitamin D deficiency (LOE 5).

4.4 **Monitoring during treatment with vitamin D for nutritional rickets**

4.4.1 Radiographs should be obtained at 4 weeks and 12 weeks after vitamin D therapy in rickets to look for evidence of healing (LOE 3).

4.4.2 Serum calcium, phosphate, alkaline phosphatase, serum 25 (OH)D levels should be performed at 12 weeks after vitamin D therapy to measure response and toxicity (LOE 3).

4.4.3 If complete radiological healing and normalization of biochemical parameters (serum 25(OH)D >20-50 ng/mL) is not attained in rickets by 12 weeks, therapeutic doses of vitamin D and calcium should be continued. Maintenance dose of vitamin D should be started once complete healing has been achieved (LOE 5).

4.4.4 Urine calcium: creatinine ratio and renal ultrasonogram should be done when there is hypercalcemia or hypervitaminosis D (as mentioned in section 1) (LOE 5).

Extraskeletal Health- Infections

5.1 Vitamin D and Pneumonia

There is mounting evidence that vitamin D has an immune-modulating effect and helps in intensifying innate immunity [130]. Many observational studies and systematic reviews have suggested an association between vitamin D deficiency and acute lower respiratory tract infection (ALRTI), however, the same biological effect of vitamin D has not been well documented by experimental studies and systematic reviews of RCTs [131-137].

5.2 Vitamin D and Tuberculosis

Growing evidence suggests the immunomodulatory effect of vitamin D in tuberculosis (TB). The exact mechanism of action of vitamin D as an immune regulator is not fully understood [138]. The possible mechanism through which vitamin D helps in preventing *Mycobacterium tuberculosis* (MTB) infection is through the binding of the active form of vitamin D (1,25[OH]2D3) to VDR. There are many observational studies on the association of vitamin D deficiency and TB in adults, with limited literature in children. A meta-analysis of five clinical trials in which one study addressed the pediatric population, found no evidence of a beneficial effect of vitamin D in the treatment of TB [139]. A systematic review and meta-analysis of eight clinical trials with 1787

patients with active pulmonary TB reported that vitamin D has beneficial effects in improving sputum smear and culture conversion. However, the authors did not present results for the subgroup of children [140].

5.3 Vitamin D and HIV

Vitamin D deficiency in HIV leads to decreased innate and adaptive immune response, increase inflammation, and increases the susceptibility of infection due to alteration of monocyte and T cell function [141]. Observational studies in adults and children have reported a low level of vitamin D in HIV-infected children [142-144]. A systematic review, which included thirty studies out of which two were undertaken in children, concluded significant heterogeneity in included studies and the need for further controlled studies to establish a relationship between vitamin D and HIV and infection [145]. There is a paucity of literature on the therapeutic effect of vitamin D on HIV infection in children [146,147].

5.4 Vitamin D and Diarrhea

Early studies in infants and children have shown lower levels of vitamin D in children hospitalized with diarrhea than healthy controls, suggesting the role of vitamin D in childhood diarrhea. Lower levels of S.25 (OH)D were also associated with higher risk of diarrhea with bacteria producing enterotoxins (ETEC) unlike those which had invasive or cytotoxic properties [148]. Most observational and interventional studies have shown association of vitamin D status with number of episodes and severity of diarrhea. However, no causality with VDD or therapeutic efficacy of vitamin D could be established in acute diarrhea in normal-weight or underweight children [26, 31, 149-151]. A recent meta-analysis [135] did not show benefit of vitamin D supplementation in childhood diarrhea with data from two trials.

Consensus Statements and Recommendations:

5.1.1 Vitamin D levels are lower in children with pneumonia, and a lower level of vitamin D may be associated with higher incidence and severity of pneumonia (**LOE** 1).

5.1.2 There is no beneficial role of routine vitamin D supplementation in the treatment of pneumonia in children (**LOE** 1).

5.2 Vitamin D levels are significantly lower in children with tuberculosis (**LOE** 1). There is no advantage of routine vitamin D supplementation in childhood tuberculosis (**LOE** 1).

5.3 An association has been demonstrated between vitamin D deficiency and HIV infection in children (**LOE** 3). The therapeutic effect of vitamin D supplementation in pediatric HIV is not established. (**LOE** 2)

5.4.1 Vitamin D levels show poor correlation with incidence and severity of acute diarrhea (**LOE**2)

5.4.2 Vitamin D supplementation is not beneficial in acute childhood diarrhea (**LOE** 1)

Extra-Skeletal Health (Non-Infectious Conditions)

6.1 Vitamin D and Asthma

Numerous observational studies had suggested that a low level of vitamin D is associated with an increased risk of asthma in children [152-154]. A systematic review and meta-analysis of twenty-seven studies, out of which eighteen studies included children, indicated a positive correlation of vitamin D and lung functions in both adults and children with asthma [155]. Although epidemiological studies showed a low level of vitamin D level in children with asthma, several meta-analyses on vitamin D supplementation in asthma in children reveal conflicting or limited evidence for protection against exacerbations [156-159].

6.2 Vitamin D and Obesity

Various hypotheses have been proposed to explain possible link of vitamin D level with obesity and metabolic syndrome. Most reviews indicate marginal and insignificant effect, if at all, on few parameters like abdominal obesity, arterial stiffness, and insulin secretion [160-164]. Systematic reviews of intervention studies with vitamin D supplementation in obese adolescents have failed to demonstrate any utility over insulin action [165-167].

6.3Vitamin D, Atopy, and Skin Conditions

Vitamin D shows effects on keratinocyte proliferation and differentiation, suppression of inflammatory responses, expression of antibacterial peptides, maintenance of integrity of the permeability barrier, production of cathelicidin and suppression of IgE mediated cutaneous reactions [168]. Incidence of AD was higher among specific vitamin D receptor polymorphism type [169]. However, reasonable number of studies either refuting any such association or even indicating reverse association make it difficult to draw clear conclusions. [170-173].

6.4 Vitamin D and Nephrotic Syndrome

Vitamin D deficiency has been established at different types and stages of various form of nephrotic syndromes, further compounded by the ongoing disturbances in the biochemical *milieu* where there is a loss of vitamin D binding globulin with proteinuria. Patients also exhibit osteoblast suppression and osteoclast induction which further compromise the bone health in these patients. Metabolic bone health may be further compromised with the frequent use of high dose corticosteroids [174-175]. The supplementation of vitamin D is indicated primarily for restoration of the bone health in these patients, which is documented in various studies as improvement in biochemical and radiological parameters of bone health [176,177] and is recommended by international and national guidelines [178,179].

6.5 Vitamin D and Childhood Developmental Disorders

Maternal vitamin D level and supplementation may affect the foetal brain development as well as the neurodevelopmental outcomes of the offspring [180]. The neuroprotective effect of vitamin D is believed to be secondary to its influences on neuronal calcium homeostasis, release of neuromediators, production of

neurotrophins and protection from oxidative damage [181]. Among the various neurodevelopmental disorders affected by vitamin D status, attention deficit hyperactivity disorders (ADHD) and autistic spectral disorders (ASD) have been studied among children. Several studies indicate higher incidence of vitamin D deficiency among children affected with ADHD or ASD [182,183]. There is some evidence that optimal vitamin D status is associated with better symptomatology in these children and is advised to be maintained with supplementation [184,185].

Consensus Statements and Recommendations:

6.1 Vitamin D levels are lower in children with asthma, which may be associated with reduced lung function and asthma exacerbation in children. **(LOE 1).** Despite that,vitamin D supplementation in children with asthma has not proven to be beneficial **(LOE 1).**

6.2.1 Vitamin D status is associated with obesity and parameters indicating glycemic handling. **(LOE 2)**

6.2.2 Routine vitamin D supplementation is not recommended in obese children and adolescents for weight and metabolic outcomes (**LOE** 1)

6.2.3 Vitamin D levels should be maintained in sufficiency range (>20 ng/mL) in children with obesity and metabolic syndrome. The precise dosing amount and frequency cannot be generalized for these patients **(LOE 3)**.

6.3.1 An association between vitamin D status and pathophysiology and clinical presentation in atopic dermatitis is known. **(LOE 3)**

6.3.2 Routine supplementation of vitamin D in children with atopic dermatitis is not recommended as supplementation showing improvement in atopic dermatits is not proven (**LOE** 2).

6.4.1 Routine vitamin D and calcium supplementation is recommended in children with nephrotic syndrome to maintain serum 25(OH)D levels above 20 ng/mL (**LOE** 3).

6.4.2 Serum 25(OH)D concentrations may be monitored annually in children with nephrotic syndrome (**LOE** 4)

6.5.1Literature indicates higher incidence of vitamin D deficiency among children with ADHD and ASD. **(LOE 2).**

6.5.2 The direct therapeutic role of vitamin D in ADHD and ASD is not supported by literature. It is advisable to maintain optimal vitamin D status in these disorders. **(LOE 2)**

CONCLUSIONS

The present guidelines endorse the earlier classification for vitamin D deficiency, insufficiency, and sufficiency as serum 25-hydroxy vitamin D levels as <12 ng/mL, ≥12-20 ng/mL and >20 ng/mL, respectively. Oral vitamin D supplementation in dosage of 400 IU/day should be continued during infancy. The estimated average requirement of vitamin D of 400 IU/day in childhood and 600 IU/day in adolescents should be met from dietary sources and sunlight. Sunlight exposure is recommended for all ages, the exact duration and body surface area however, will differ on host and environmental factors. Oral cholecalciferol with calcium carbonate should be used for treating vitamin D deficiency and rickets in a dose not exceeding 300,000 units across different ages.

Daily vitamin D therapy is more physiological than bolus doses, though the Indian experience with daily vitamin D therapy is limited. The Committee suggest treatment of incidentally detected low serum 25(OH)D level < 12 ng/mL in healthy children or ≤20 ng/mL in those at high-risk. Vitamin D supplementation only shows an association with common childhood infections and extraskeletal diseases, not sufficient to mandate routine vitamin D supplementation in children with these conditions.

The committee noted the lack of robust scientific evidence to objectively conclude few aspects of prevention and management of vitamin D deficiency in childhood, and further proposed areas for future research (**Box II**).

Box II Areas for Future Research

- Representative survey to estimate prevalence of VDD in infants.
- Population-based studies to explore association of vitamin D deficiency and sufficiency with parathyroid hormone, skeletal and non-skeletal outcomes.
- Predicting response to controlled sunlight exposure in different ages.
- Role of sunlight versus routine vitamin D supplementation.
- Safety of bolus regimens needs to be established in well-powered randomized controlled trials for treatment of nutritional rickets, especially for infants.
- Efficacy of doses of vitamin D lower than 2000 IU/day for treatment of nutritional rickets.
- The optimal time points for monitoring treatment during treatment for nutritional rickets
- The functional benefit of treatment of isolated biochemical derangements in serum vitamin D levels (that do not correlate clinically).

Contributors: All authors were part of the National Consultative Committee (*Annexure* 1) that formulated these Guidelines. PG, BJP, GVB: conceived the design and prepared the agenda. AA, TG,AD,SK,JPG,KA,BKB: reviewed the literature for each section in detail and wrote the first draft of the respective sections. VK,VLB,RK,AS,HPS,PK,SB,HBM: moderated the draft recommendations of each respective section and provided critical inputs. DS, AK, RKM were invited experts who provided critical inputs for revision and participated in discussions and manuscript editing. CM: provided external review and critical inputs of the draft recommendations which were incorporated in the successive revisions. HPS, AK, DS, PK,PG provided their inputs in the guidelines. All authors approved the final version and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Annexure 1: List of Participants

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Table I Doses for Management of Vitamin D Deficiency or Nutritional Rickets in Children

Age	***Daily dose for 12 wk[a]***	***Alternative intermittent dose regimen[b]***	***Maintenance dose (daily)[c]***
<6 mo	2000	NA	400
6-12 mo	2000	Equivalent of 2000 IU/day may be given on a monthly or weekly basis	400
>12 mo	3000	60000 IU fortnightly (after every 2 weeks) x 5 doses	600

[a]Reassess response after 12 weeks. Ensure daily calcium intake of 50-75 mg/kg/day, not exceeding 500 mg/day. [b]In certain situations, if compliance is not good, intermittent regimens may be prescribed (in children above 6 months of age only). [c]Ensure daily intake of recommended dose through supplementation or dietary sources. Optimum duration of maintenance vitamin D therapy is not known at present

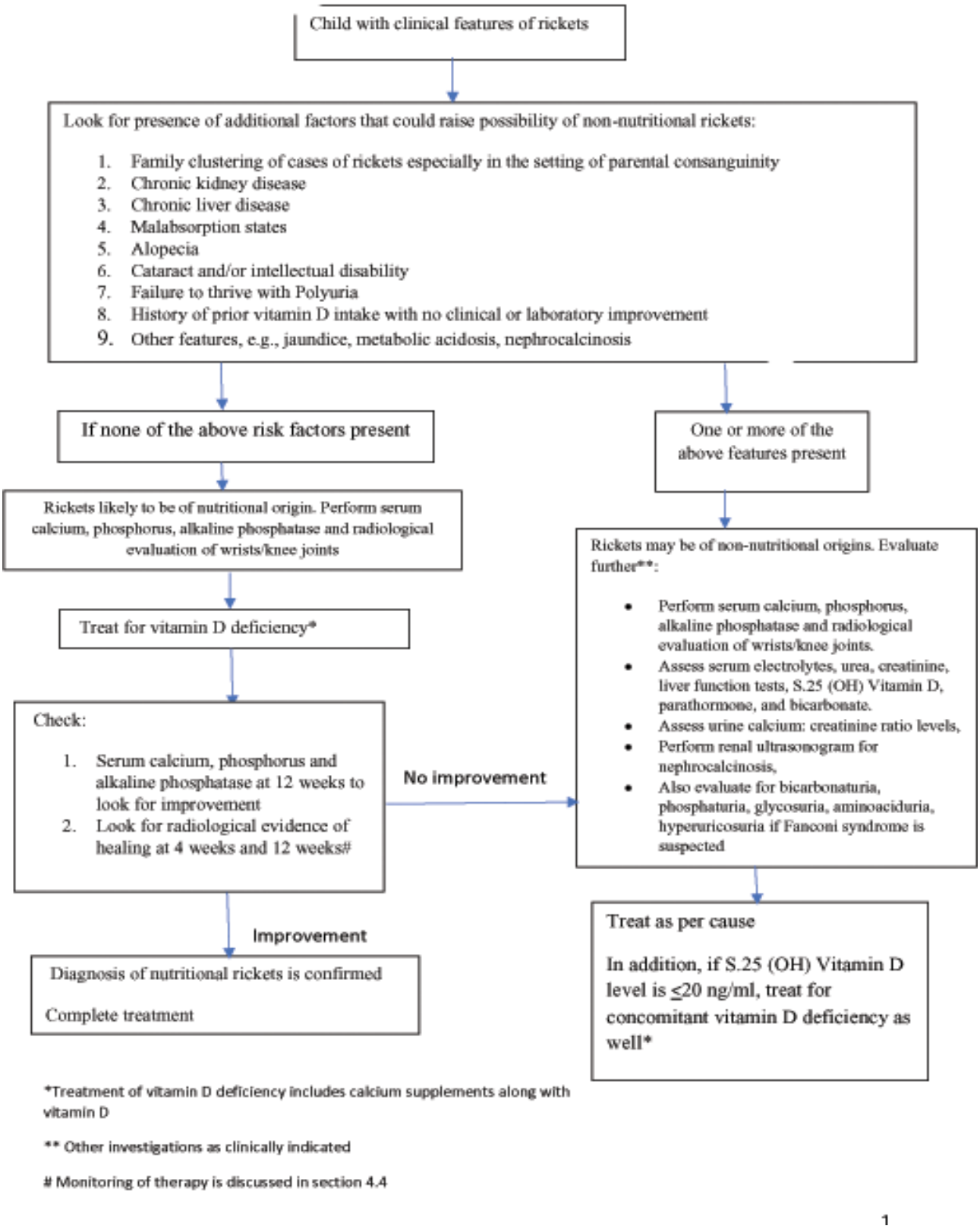

Fig. 1 Algorithm for evaluation of rickets.