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Review

An Update on the Biochemical Staging of Nutritional Rickets: A Comprehensive Review

Hüseyin Anıl Korkmaz [1,2]

[1] Department of Pediatrics, Division of Pediatric Endocrinology, İzmir Faculty of Medicine, University of Health Sciences, İzmir 35210, Türkiye; hanilkorkmaz@gmail.com; Tel.: +90-232-411-60-00

[2] Division of Pediatric Endocrinology, Department of Pediatrics, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, İsmet Kaptan Mahallesi, Sezer Doğan Sokak No:11, Konak, İzmir 35210, Türkiye

Abstract

Nutritional rickets remains a significant global public health concern affecting infants and young children in regions with limited sunlight exposure or inadequate dietary vitamin D and calcium. This review revisits the biochemical staging system applicable to severe combined vitamin D and calcium deficiency. We propose that the classical three-stage model may be supplemented by recognition of a Nutritional Pseudohypoparathyroidism/PTH Resistance Variant—characterized by profound hypocalcemia, paradoxically normal or elevated serum phosphate, and markedly elevated parathyroid hormone (PTH)—reflecting acquired renal PTH resistance. Hypomagnesemia must be excluded before this designation is applied, as it constitutes a reversible and mechanistically distinct cause of functional PTH resistance. This phenotype is reversible with treatment and requires prospective validation. Evidence-based treatment strategies for each stage are summarized.

Keywords: nutritional rickets; vitamin D deficiency; calcium deficiency; parathyroid hormone resistance; PTH resistance variant; biochemical staging; hypocalcemia; hyperphosphatemia; pseudohypoparathyroidism; inactivating PTH/PTHrP signalling disorders (iPPSD)

1. Introduction

Rickets is a metabolic bone disease characterized by impaired skeletal mineralization, resulting in bone softening, deformities, and growth disturbances [1]. It predominantly affects infants and young children during periods of rapid skeletal growth and most commonly results from vitamin D or calcium deficiency [1,2]. Despite being preventable, nutritional rickets remains a significant global public health concern [3].

Diagnosis relies on clinical symptoms, biochemical markers, and radiological findings [1,4]. Hypophosphatemia may occur in skeletal rickets because low calcium intake leads to secondary hyperparathyroidism, causing phosphorus excretion and deficiency (Figure 1) [5,6]. Severe hypocalcemia may produce serious neuromuscular and cardiac complications [7].

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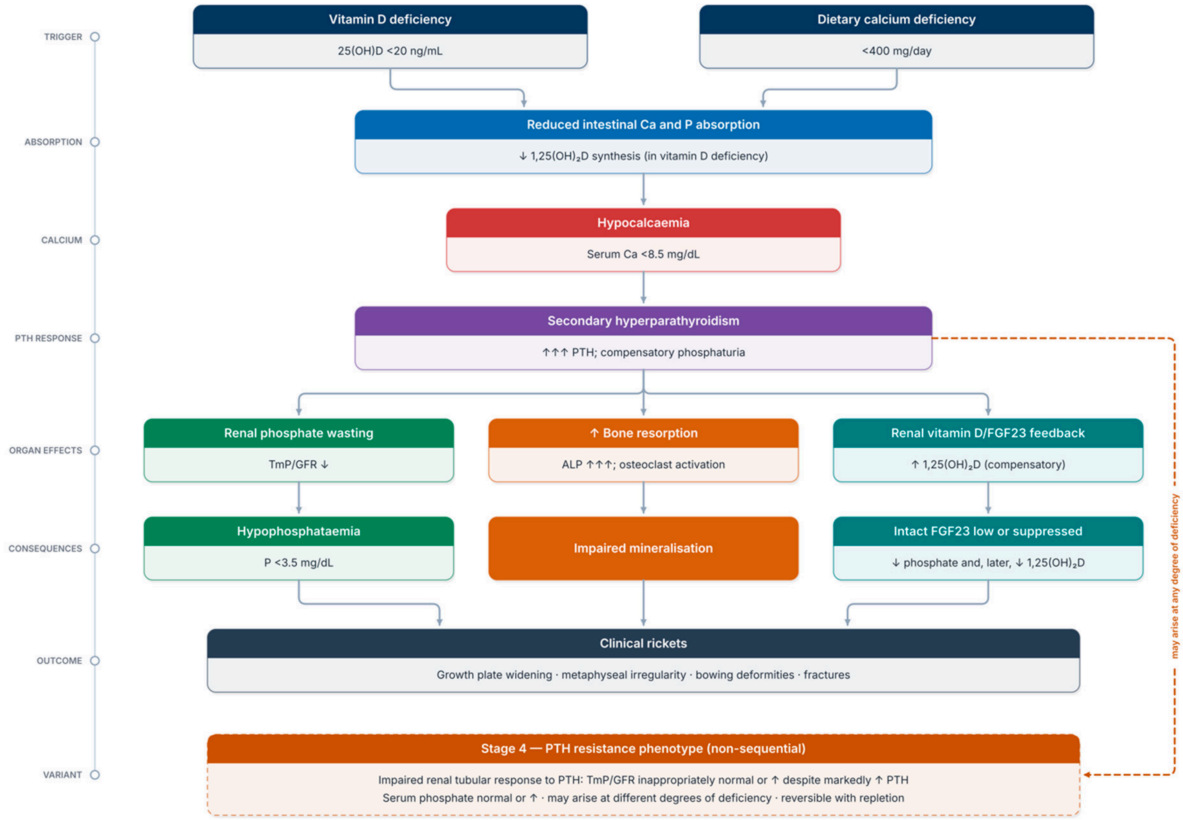


Figure 1. Pathophysiology of nutritional rickets. Vitamin D and/or dietary calcium deficiency leads to hypocalcemia and secondary hyperparathyroidism, with downstream effects on renal phosphate handling and bone remodeling that culminate in clinical rickets [8]. In one Bangladeshi cohort, intact FGF23 was undetectable in many children with nutritional rickets [9]. The provisional Stage 4 (PTH resistance) phenotype is shown as a non-sequential variant that may arise at different degrees of deficiency (the authors' proposal). In nutritional rickets, TmP/GFR is reduced and serum phosphate may also be low in association with secondary hyperparathyroidism [10]. Abbreviations: $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; Ca, calcium; FGF23, fibroblast growth factor 23; P, phosphate; PTH, parathyroid hormone; TmP/GFR, tubular maximum reabsorption of phosphate corrected for glomerular filtration rate.

Clinical manifestations of rickets are diverse and age-dependent, including rachitic rosary, craniotabes, delayed fontanel closure, frontal bossing, thoracic deformities, Harrison's groove, and lower limb deformities, with additional extra-skeletal manifestations documented in older children and adolescents [11,12].

Biochemical staging of nutritional rickets has been described [13]; a review by Korkmaz provides an updated analysis of its biochemical findings.

This review revisits the three-stage biochemical classification of nutritional rickets [13] and summarizes evidence-based management for each stage. In addition, it discusses a biochemical phenotype described in case reports of vitamin D deficiency, in which PTH resistance resolves with repletion: hypocalcemia with normal or elevated serum phosphate despite markedly elevated PTH [14,15]. For convenience, this phenotype is designated "Stage 4." I propose the designation as a provisional category. It is not part of the three-stage sufficient/insufficient/deficient status framework of the Global Consensus [8,16], and its thresholds have not been prospectively validated. It is intended to help clinicians recognize this pattern and distinguish it from pseudohypoparathyroidism, and to provide a common definition for future studies. It is not intended to change the treatment recommended by those guidelines.

2. Pathophysiology of Nutritional Rickets

2.1. Vitamin D Metabolism and Calcium Homeostasis

Vitamin D is central to calcium and phosphate homeostasis and skeletal mineralization [17], undergoing two hydroxylation steps: first to form 25-hydroxyvitamin D [25(OH)D] in the liver [18], the best indicator of vitamin D status [19], then in the kidney to form 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], which is the biologically active hormone responsible for maintaining calcium and phosphorus homeostasis (Figure 1) [20,21].

A key function of 1,25$(OH)_2$D is to enhance intestinal calcium and phosphate absorption [21]. Vitamin D deficiency triggers compensatory parathyroid hormone (PTH) secretion, which restores serum calcium through increased renal reabsorption and bone resorption [21,22] and upregulates 1α-hydroxylase expression [23]. PTH simultaneously promotes renal phosphate excretion, causing phosphorus loss into the urine and low serum phosphorus (Figure 1) [21].

2.2. The Central Role of Hypophosphatemia

Hypophosphatemia is regarded as the common denominator of all forms of rickets [24]. Normal serum phosphate is essential for growth plate maturation [25]; its depletion disrupts chondrocyte maturation and apoptosis, producing an accumulation of hypertrophic chondrocytes and widening of the growth plate (Figure 1) [24,26].

The 2024 SIEDP position statement (Baroncelli et al.) addresses the diagnosis and management of rickets [10].

Fibroblast growth factor 23 (FGF23), synthesized by osteoblasts and osteocytes, promotes renal phosphaturia and suppresses 1,25$(OH)_2$D synthesis [27]. In progressive vitamin D deficiency, rising PTH decreases phosphate reabsorption in the kidney, causing phosphate wasting [21].

2.3. Calcium Deficiency Rickets

Calcium deficiency rickets can present with normal 25(OH)D levels when dietary calcium is restricted [24]. Low dietary calcium supply triggers secondary hyperparathyroidism, which maintains serum calcium at the cost of phosphate wasting and hypophosphatemia [8]—illustrating that calcium deficiency can cause rickets independently of vitamin D status [5].

2.4. Radiographic Assessment and Its Relationship to Biochemical Staging

The Rickets Severity Score (RSS), a 10-point system with demonstrated inter- and intraobserver reliability [28], developed by Thacher et al., quantifies metaphyseal fraying and cupping at the wrist and knee [24,28]; this score moderately correlates with alkaline phosphatase [28].

2.5. Pathophysiology of Acquired PTH Resistance in Nutritional Rickets

This review highlights an unusual biochemical phenotype: severe hypocalcemia with impaired phosphaturic response to PTH, as described by Rao et al. in adult patients; this phenotype resembles pseudohypoparathyroidism type II [29]. The inactivating PTH/PTH-related peptide (PTHrP) signaling disorders (iPPSD) classification has been proposed as a novel nomenclature for pseudohypoparathyroidism and related disorders [30]. This acquired PTH resistance, observed in severe hypocalcemia due to vitamin D depletion, resembles this defect [29], and this dissociation between the effect of PTH on phosphate reabsorption and cyclic adenosine monophosphate (cAMP) generation can be a consequence of hypocalcemia [29].

First, severe vitamin D deficiency (25(OH)D ≤ 10 nM) reduces circulating $1,25(OH)_2D$ levels because the substrate concentration is insufficient to maintain them despite secondary hyperparathyroidism [31]. Since $1,25(OH)_2D$ upregulates PTH/PTHrP receptor expression at both mRNA and protein levels in immortalized renal distal tubular cells [32], its deficiency may blunt the phosphaturic response [33]—analogous to pseudohypoparathyroidism type II, where cAMP generation is preserved but the downstream phosphaturic effect is blunted [29,34]. Evidence that the phosphaturic response to PTH is impaired in hypocalcemic states [29] supports this analogy, and the effect of endogenous PTH on phosphate reabsorption varies with plasma calcium levels [29].

Second, chronically low serum calcium induces parathyroid cell hypertrophy and only a moderate increase in parathyroid cell number, alongside a large increase in PTH gene expression per cell, in animal models [35].

Third, coexisting hypomagnesemia is a plausible contributor to functional PTH resistance; magnesium may impair cAMP generation and skeletal PTH responses [36]. Critically, hypomagnesemia induces functional hypoparathyroidism, characterized by inappropriately low or normal PTH despite hypocalcemia; Rude et al. attribute this condition to both impaired PTH secretion and end-organ resistance to PTH [37]. Correction of hypomagnesemia can lead to resolution of PTH refractoriness and normalization of serum calcium [38]. PTH resistance in disorders such as those mimicking pseudohypoparathyroidism is defined by the absence of vitamin D deficiency and the presence of normal magnesium levels and renal function [39].

Rao et al. reported that, in these patients, this PTH resistance was acquired and reversible with correction of hypocalcemia [29].

Intact FGF23 was undetectable in 88% of children with nutritional rickets in one Bangladeshi cohort [9]: active vitamin D directly stimulates FGF23 expression in osteocytes via a vitamin D response element [40]. In vitamin D-deficient rickets, serum FGF23 helps distinguish the condition from hypophosphatemic rickets [41]. Critically, suppressed FGF23 and elevated PTH co-occur in rats fed a low-calcium and low-vitamin D diet [42]: PTH secretion rises in response to hypocalcemia [43], whereas the PTH response is altered in a rat model of secondary hyperparathyroidism associated with vitamin D deficiency [44]; FGF23 suppression has been reported in children with nutritional rickets [9]. Reduced 1,25-dihydroxyvitamin D levels result in decreased expression of NaPi-IIb in the intestine, which leads to reduced phosphate absorption [45]. However, the calcium-dependent regulation of FGF23 has been documented mainly in rodent and genetically modified mouse studies [46]; pediatric evidence—notably the toddler cohort of Khadilkar et al. [47]—suggests that low dietary calcium intake is associated with PTH resistance.

FGF23 suppression in nutritional rickets must be distinguished from the FGF23 excess of genetic phosphate-wasting disorders [24]. In nutritional rickets, low plasma phosphate may be associated with decreased FGF23 production [9]. By contrast, X-linked hypophosphatemia (XLH), autosomal dominant hypophosphatemic rickets (ADHR), and autosomal recessive hypophosphatemic rickets (ARHR) all feature hypophosphatemia as a biochemical hallmark of excess FGF23 [48]. Measurement of intact FGF23 is therefore a key discriminating biomarker [24,49]: suppressed values support nutritional rickets, while elevated values direct investigation toward genetic phosphate-wasting disorders [24,50].

Variability of FGF23 findings in nutritional rickets. Published findings in nutritional rickets are not uniform, and several factors account for this. First, the assay matters: C-terminal assays detect both the intact hormone and its cleavage fragments, whereas intact assays detect only the biologically active molecule [51]. Second, iron deficiency anaemia, which coexisted with nutritional rickets in nearly half of affected children in one Pakistani cross-sectional study [52], increases FGF23 production, as described below [53,54]. Third,

the predominant aetiology matters. In calcium-deficiency rickets, $1,25(OH)_2D$ is generally elevated [55,56] and may stimulate FGF23 [40]. C-terminal FGF23 was elevated in Gambian children with putative calcium-deficiency rickets [57]; at 5-year follow-up, circulating FGF23 was elevated in 19% of those with a history of rickets-like bone deformities [58], and poor iron status predicted the elevated C-terminal values [57]. By contrast, in rural Bangladeshi children with low-calcium-intake rickets, intact FGF23 was undetectable in 88% of participants in the rickets group (Group A), and low plasma calcium was suggested as a possible cause of the low intact FGF23 [9]. Fourth, phosphate and $1,25(OH)_2D$ stimulate FGF23 secretion, so values may depend on phosphate and vitamin D status at the time of sampling [59–61]. Finally, age-specific reference intervals further affect interpretation [62]. In practice, a low intact FGF23 has been reported in nutritional rickets [9], whereas low-normal values in the setting of hypophosphataemia still indicate FGF23 excess [63]. An elevated value, particularly on a C-terminal assay, should be interpreted with iron deficiency considered as a possible alternative cause [64,65].

Concurrent iron deficiency is a relevant factor, as iron status has been inversely associated with FGF23 in Gambian children [66]. In the genetic disorder autosomal dominant hypophosphatemic rickets (ADHR), iron deficiency stimulates FGF23 transcription in knock-in mice [67] and increases intact FGF23 concentrations in patients [68]. Clinicians should therefore consider serum ferritin when interpreting FGF23 measured with Immutopics assays, as low ferritin may alter results and complicate assessment [69]. In healthy individuals, iron deficiency increases C-terminal FGF23 while intact FGF23 remains normal, reflecting increased cleavage of newly synthesized FGF23 that generates C-terminal fragments detected by C-terminal assays in addition to the active intact hormone [51,53,70].

Strength and nature of the supporting evidence. The evidence supporting a PTH resistance phenotype in nutritional rickets is of three kinds, and these should be distinguished. First, the mechanistic evidence, namely the dissociation between PTH-induced nephrogenous cAMP generation and the phosphaturic response, derives principally from adults with hypocalcaemic osteomalacia [29]; however, that study concludes that the dissociation is nonspecific and can be a consequence of hypocalcaemia. Additional evidence comes from experimental models showing reduced PTH-binding capacity and PTH-stimulated adenylyl cyclase activity in vitamin D deficiency [71]. Second, direct paediatric clinical evidence includes individual case reports in infants [40–44,72,73] and a small number of studies, including one reporting that low dietary calcium intake is associated with PTH resistance in toddlers [47]. Third, a report of two young adults given formal PTH infusion (Ellsworth–Howard) testing suggests that the defect may be type I-like (blunted cAMP response) or type II-like (preserved cAMP, absent phosphaturia) [14], indicating that the phenotype may not be mechanistically uniform. The key studies are summarised in (Section 3.4).

3. Biochemical Staging of Nutritional Rickets

The proposed framework retains the classical three-stage system [13] while introducing a PTH resistance variant. Table 1 summarises approximate biochemical values and clinical features for each stage. The values shown must be interpreted alongside clinical and radiographic assessment. Stage 4 is a provisional, non-sequential category (Sections 1 and 3.4).

Table 1. Biochemical staging of nutritional rickets: classical Stages 1–3 and the provisional, non-sequential Stage 4 (PTH resistance phenotype).

Parameter	Stage 1 (Early/Subclinical)	Stage 2 (Classic Rickets)	Stage 3 (Severe/Late)	Stage 4 * (PTH Resistance Phenotype)
25(OH)D (ng/mL)	<20 [74]	<10 [75]	<5 [56,76]	Usually not deficient, since PTH resistance is described in the absence of vitamin D deficiency [39]
Serum calcium	Low [77]	Normal or low [78]	Hypocalcaemia (<8.5 mg/dL) [79]	↓ [39]
Serum phosphate	Normal–low [21,77]	↓ (low-normal to low) [21]	↓ [12]	↑ [39]
Serum magnesium	Normal (single untreated case report in vitamin D-resistant rickets) [80]	Normal (single untreated case report) [80]	Normal (single untreated case report) [80]	Normal (required for the PTH resistance definition) [39]
PTH	Normal–↑ [81]	↑↑ [24]	Persistently elevated [19]	At or above the upper limit of normal [39]
ALP	Normal–↑ [82]	↑↑ [24]	↑↑↑ (up to 2000 IU/L in calcipenic rickets) [11]	Not established
$1,25(OH)_2D$	Normal–↑ [21]	Normal–↑ [21]	↓↓ [10]	Not established
FGF23 (intact) ‡	Normal [83]	Normal–↓ [9,50]	↓ (low or undetectable in nutritional rickets) [50]	Not established
Urinary Ca/Cr	Normal–↓ [24]	↓ [24]	↓ [24]	↓ [84]
TmP/GFR †	Normal	↓ [24]	↓ [24]	Normal–↑ (based on a single case report) [85]
Radiographic findings	Normal–mild changes [24]	Metaphyseal irregularity [86]	Classic rickets; growth plate widening [86]	As in Stage 3, with osteopenia [87]
Clinical features	Asymptomatic or latent hypocalcaemia possible [88]	Bone pain, deformity [89]	Hypocalcaemic seizures, tetany [78]	Heart failure reported with profound hypocalcaemia in a single case report [90]
Relation to other stages	Sequential	Sequential	Sequential	Not sequential; PTH resistance is defined in the absence of vitamin D deficiency [39]

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; ALP, alkaline phosphatase; Ca/Cr, calcium-to-creatinine ratio; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; TmP/GFR, tubular maximum reabsorption of phosphate corrected for glomerular filtration rate. Symbols: ↑, elevated; ↓, reduced; the number of arrows indicates the degree of abnormality. * Provisional category; non-sequential phenotype (Section 3.4). Supporting evidence in Table 2; limitations in Section 5.6.

Critical differential: hypomagnesaemia. Severe magnesium deficiency can produce hypocalcaemia through impaired PTH secretion and end-organ PTH resistance [37]. In hypomagnesaemic hypocalcaemia, PTH is typically low or inappropriately normal [91]. Serum magnesium should therefore be measured when hypocalcaemia is evaluated to exclude functional hypoparathyroidism [92]. Magnesium repletion raises serum PTH within one day, whereas serum calcium normalises only after about four days [37].

Early-phase discriminators versus VDDR1A (CYP27B1): at initial biochemical evaluation, before confirmatory $1,25(OH)_2D$ assay results or CYP27B1 sequencing results are available, two features distinguish Stage 4 from vitamin D-dependent rickets type 1A (VDDR1A): (i) VDDR1A preserves normal or elevated 25(OH)D [93]; (ii) serum phosphate rises during magnesium depletion (reported in a single hypomagnesaemic patient) [94] (PTH's phosphaturic action appears impaired [95]), whereas VDDR1A presents with hypophosphataemia [93] (secondary hyperparathyroidism plausibly contributes to phosphate wasting) [93,96]. Calcitriol offers advantages for VDDR1A because it replaces the deficient hormone and acts rapidly [93].

† TmP/GFR values are given relative to age-specific reference intervals [50,97]. PTH acts on the proximal tubule to internalize sodium-phosphate cotransporters, reducing

TmP/GFR and serum phosphate [98,99]. In calcipenic rickets with a markedly raised PTH concentration, TmP/GFR would be expected to be reduced [24]. TmP/GFR and serum phosphate are generally similar when expressed in the same units [50]. In phosphorus-deprived rats, PTH had a diminished action on renal phosphate transport, which was interpreted as renal resistance to PTH [100]. A normal TmP/GFR with low serum phosphate indicates renal phosphate conservation, for example due to inadequate dietary intake or malabsorption [50]. TmP/GFR is independent of GFR at least down to about 40 mL/min [101]. TmP/GFR can be calculated from paired fasting blood and urine samples [101].

‡ FGF23 values refer to intact FGF23. It is often low or undetectable in nutritional rickets [9] and falls after treatment [102]. Elevated values, particularly with C-terminal assays, have been reported in the presence of iron deficiency [54] (Section 2.5). In ADHR, an elevated FGF23 may warrant assessment of iron status, because iron deficiency can raise intact FGF23 concentrations [68].

3.1. Stage 1: Early/Subclinical Stage

Biochemical Profile: The early phase of vitamin D deficiency is characterized by deficient 25(OH)D levels, typically with normal serum calcium levels, although PTH may begin to rise as a compensatory mechanism and 1,25$(OH)_2$D levels may be normal or elevated because secondary hyperparathyroidism stimulates renal 1α-hydroxylase activity [21,103].

Pathophysiology: Declining 25(OH)D can reduce intestinal calcium absorption, mainly when concentrations are very low [31,104], prompting increased PTH secretion, which stimulates renal 1α-hydroxylase to enhance the conversion of 25(OH)D to 1,25$(OH)_2$D [4,105,106]. These compensatory mechanisms help maintain serum calcium levels within normal limits [4,104].

Clinical Caveat—Risk of overdiagnosis in Stage 1: Normal 25(OH)D levels do not exclude nutritional rickets, because rickets can develop with low dietary calcium intake even without overt vitamin D deficiency; therefore, 25(OH)D must be interpreted together with dietary calcium history and other biochemical parameters [4,24].

Furthermore, the 2024 meta-analysis by Leyvraz et al. [107] suggests that a serum 25(OH)D threshold of around 28 nmol/L or higher would represent a low risk of nutritional rickets for the majority of children with an adequate calcium intake.

Clinical Features: Stage 1 may present with non-specific lower limb pain or proximal myopathy in adolescents [88]. Radiographic changes are uncommon in infants and toddlers with vitamin D deficiency [108].

Management: Nutritional rickets should be suspected in high-risk children with characteristic clinical signs and abnormal biochemistry, and treatment with vitamin D and calcium is required [2]. Therapy consists of vitamin D supplementation, and adequate dietary calcium intake or supplementation should be ensured [2].

3.2. Stage 2: Compensated Stage

Biochemical Profile: Stage 2 is characterized by normal serum calcium, low-normal or low fasting serum phosphorus levels, and elevated alkaline phosphatase (ALP) levels [21]. Secondary hyperparathyroidism stimulates the kidneys to produce 1,25$(OH)_2$D, and thus, 1,25$(OH)_2$D levels are normal or often elevated [21].

Pathophysiology: Progressive vitamin D deficiency intensifies PTH secretion to maintain normocalcemia through enhanced renal calcium reabsorption and bone resorption, while PTH simultaneously increases renal phosphate excretion and causes hypophosphatemia [21].

Clinical Features: Children with vitamin D deficiency may present with age-dependent features, including hypocalcemic seizures in young infants and skeletal signs such as leg bow-

ing and delayed walking in toddlers [109]. Radiographs may show metaphyseal changes characteristic of rickets [88]. Hypocalcemic symptoms generally appear in later stages of vitamin D deficiency when compensatory mechanisms fail to sustain normocalcemia [8].

Management: Treatment of nutritional rickets requires vitamin D and calcium supplementation to address both deficiencies [56], with a common regimen of 2000 IU/day of vitamin D and 500 mg/day of elemental calcium [4]. Maintenance supplementation (at least 400 IU/day up to 1 year and 600 IU/day from 1 to 18 years) should follow completion of the treatment course, once healing of rickets is confirmed [88].

3.3. Stage 3: Decompensation

Biochemical Profile: The final stage of nutritional rickets represents decompensated disease characterized by severe vitamin D deficiency, inhibited 1,25$(OH)_2$D synthesis, impaired calcium and phosphorus absorption, and persistent elevation of PTH and alkaline phosphatase [19].

Pathophysiology: The compensatory mechanisms that maintained normocalcemia in Stage 2 are exhausted [8]. Severely depleted 25(OH)D limits 1,25$(OH)_2$D production [31], and skeletal calcium mobilization can no longer maintain serum calcium [110]. Hypocalcemia at this stage reflects the exhaustion of skeletal calcium stores [21], and hypophosphatemia impairs skeletal mineralization [111].

Clinical Features: Nutritional rickets presents with florid skeletal deformities—bowing of long bones, rachitic rosary, Harrison's groove, frontal bossing, and delayed fontanel closure [76]. Hypocalcemic complications, including tetany, seizures, or laryngospasm, may occur [88]. Growth retardation and developmental delays can occur in children with nutritional rickets [89].

Management: Nutritional rickets requires treatment with calcium and vitamin D supplementation [112]. Severe, symptomatic hypocalcemia may necessitate intravenous calcium administration [10].

3.4. Stage 4: Nutritional Pseudohypoparathyroidism/PTH Resistance Variant

Biochemical Profile: In Stage 4, severe vitamin D deficiency is associated with reduced calcium absorption and elevated PTH and alkaline phosphatase [31]. Renal PTH unresponsiveness in vitamin D deficiency can produce a biochemical profile mimicking pseudohypoparathyroidism type II [113]. In 6 of 8 adults with severe hypocalcemia from vitamin D depletion, nephrogenous cAMP excretion was increased while TmP/GFR remained normal [29]. The effect of endogenous PTH on phosphate reabsorption varies with plasma calcium level [29].

Age-specific reference intervals are needed in pediatric endocrinology, as normative serum calcium values differ across developmental stages [114,115]. Laboratories should establish these intervals [116].

Pathophysiology: The exact pathogenesis of parathyroid hormone resistance in vitamin D deficiency that mimics pseudohypoparathyroidism type II remains unclear [113]. In severe vitamin D deficiency, renal PTH resistance may develop, producing a biochemical pattern resembling pseudohypoparathyroidism type II [15]. Concurrent hypomagnesemia should be considered, as severe magnesium depletion can cause hypocalcemia and PTH unresponsiveness [38].

Relationship to Stages 1–3. Stage 4 does not represent a progression from Stage 3. It is best regarded as an independent biochemical phenotype that may be superimposed on vitamin D and/or calcium deficiency to varying degrees. It has been described in an infant with vitamin D deficiency rickets and normal tubular phosphate reabsorption, mimicking PHP type II [117] and in toddlers, in whom low calcium intake from limited

dairy may contribute [118]. What defines Stage 4 is a qualitative alteration in renal tubular responsiveness to PTH, so that serum phosphate is elevated rather than low despite elevated PTH [15,113], not a greater quantitative severity of deficiency. In adults, this pattern was observed in hypocalcemic but not normocalcemic osteomalacia [29]. The numerical label is retained for convenience and should be read as "PTH resistance phenotype", not as a fourth sequential step.

Operational definition. For research and reporting purposes, Stage 4 should be assigned only when all of the following are present under an author-proposed framework adapted from the consensus definition of PTH resistance [39], which excludes vitamin D deficiency, so criterion (4) is an extension of that definition: (1) hypocalcemia relative to age-specific reference intervals; (2) serum phosphate within or above the age-specific reference range, with inappropriately normal or elevated TmP/GFR; (3) markedly elevated PTH; (4) evidence of nutritional deficiency, i.e., low 25(OH)D and/or documented low dietary calcium intake; (5) normal serum magnesium and renal function for age; and (6) absence of features of Albright hereditary osteodystrophy. The designation is illustrated when criterion (7)—biochemical improvement after nutritional repletion—has been reported in an infant with low calcium intake [119]. Molecular evaluation at the GNAS locus is recommended for suspected PHP [39].

Table 2 summarises the key studies on which the Stage 4 construct is based. Three observations merit emphasis. First, in a paediatric report, PTH resistance was considered on the basis of the biochemical constellation (hypocalcaemia, hyperphosphataemia and elevated PTH) [120]; Ellsworth–Howard testing has been reported in young adults [14] and in paediatric case histories [121]. Second, a paediatric case report describes biochemical normalisation after nutritional repletion within two months [119]. Third, the phenotype has been described in a child with 25(OH)D of 23.2 ng/mL [119] and in toddlers with low dietary calcium intake [47], which suggests that severe calcium deficiency may mimic its biochemical pattern [119].

Table 2. Key studies supporting the provisional Stage 4 (PTH resistance phenotype) in nutritional deficiency.

Study [Ref.]	Population	n	Primary Biochemical Findings	Method Used to Infer/Confirm PTH Resistance	Reversibility After Treatment
			Paediatric clinical evidence		
Srivastava & Alon, 2002 [122]	Patients with stage I vitamin D-deficiency rickets	2	Biochemical pattern resembling PHP type II [122]	Clinical–biochemical; both initially diagnosed as PHP type II	Reclassified as stage I vitamin D-deficiency rickets [122]
Khadilkar et al., 2009 [47]	Underprivileged toddlers, low dietary calcium (India)	Not reported in cited excerpt	Low dietary calcium intake was associated with PTH resistance [47]	Not described in cited excerpt	Reversal with oral calcium supplementation is stated in the study title but is not confirmed by the cited abstract excerpt, which only reports the association with low dietary calcium
Akın et al., 2010 [117]	Infant on phenobarbital with inadequate vitamin D intake (Turkey)	1	Hypocalcaemia, hyperphosphataemia, low 25(OH)D, ↑ PTH [117,120]	Normal TRP despite hyperphosphataemia (PHP II-like) [117]	Normalisation of Ca, P, ALP and PTH with vitamin D + oral Ca [117]

Table 2. *Cont.*

Study [Ref.]	Population	n	Primary Biochemical Findings	Method Used to Infer/Confirm PTH Resistance	Reversibility After Treatment
Lee et al., 2020 [119]	11-month-old girl with a seizure (Korea)	1	Ca 5.7 mg/dL, P 5.9 mg/dL, PTH 484 pg/mL, 25(OH)D 23.2 ng/mL, $1,25(OH)_2D$ 12.8 pg/mL [119]	Biochemical pattern; no AHO; GNAS methylation analysis normal [119]	All parameters normal after 2 months of oral Ca + vitamin D [119]
Shieh & Álvarez, 2022 [113]	Adolescent boy with seizures and vertebral compression fractures	1	Hypocalcaemia, hyperphosphataemia, ↑ ALP, ↑ PTH, deficient 25(OH)D [113]	Biochemical pattern (PHP II-like)	Rapid improvement with IV calcium and vitamin D [113]
Adult and young-adult clinical evidence					
Rao et al., 1985 [29]	Adults with hypocalcaemic osteomalacia due to vitamin D depletion; 13 patients with normocalcaemic osteomalacia as a comparison group	8	In 6/8: raised nephrogenous cAMP with normal TmP/GFR [29]	NcAMP–TmP/GFR relationship (dissociation = PHP II-like)	Normal relationship restored in all 6 after vitamin D + calcium [29]
Seki et al., 2010 [14]	Young adults with dietary vitamin D deficiency	2	Severe hypocalcaemia, normophosphataemia, markedly ↑ PTH, 25(OH)D < 5 ng/mL [14]	Ellsworth–Howard test: no phosphaturic response in both; cAMP blunted in one (PHP I-like), normal in one (PHP II-like) [14]	Resolved with calcium ± vitamin D and diet correction [14]
Sastry et al., 2022 [15]	Patients with restrictive eating disorders	2	Severe vitamin D deficiency with hyperphosphataemia and ↑ PTH [15]	Biochemical pattern	Resolved; calcitriol required in addition to Ca + cholecalciferol [15]
Experimental evidence					
Turner et al., 1995 [44]	Rats on a vitamin D-deficient diet	—	Secondary hyperparathyroidism; increased renal PTH/PTHrP receptor mRNA	PTH-stimulated adenylyl cyclase in renal membranes	Studied after correction with vitamin D or calcium/lactose
Sneddon et al., 1998 [32]	Renal tubular cell models	—	$1,25(OH)_2D$ upregulates PTH/PTHrP receptor expression	Receptor mRNA/protein	Not applicable

Abbreviations: AHO, Albright hereditary osteodystrophy; ALP, alkaline phosphatase; NcAMP, nephrogenous cyclic AMP; PHP, pseudohypoparathyroidism; TmP/GFR, tubular maximum reabsorption of phosphate per glomerular filtration rate; TRP, tubular reabsorption of phosphate. Magnesium status was not reported in all cases. Hypomagnesemia-induced PTH resistance [37,38] is a distinct cause and is not included.

Diets characterized by very low calcium intake lead to decreased ionized calcium and secondary hyperparathyroidism [21], and this is a recognized mechanism contributing to the biochemical profile in this proposed phenotype. This variant may emerge in populations with low dietary calcium intake, consistent with established links between such dietary deficiencies and the development of rickets [5]. Future epidemiological studies of this phenotype should systematically assess dietary composition and regional Ca:P ratios.

Severe dietary calcium deficiency could mimic laboratory findings of pseudohypoparathyroidism [119]. However, consensus statements for pseudohypoparathyroidism suggest considering vitamin D deficiency or resistance as a differential diagnosis for hypocalcemia with elevated PTH [39].

Clinical Features: Children with severe nutritional rickets may present with hypocalcemia and symptoms such as seizures, tetany, or laryngospasm [8,78,88]. The biochemical profile can mimic pseudohypoparathyroidism, with hypocalcemia and markedly elevated PTH [119]. However, severe nutritional rickets may be distinguished from genetic pseudohypoparathyroidism (iPPSD) given a history of inadequate vitamin D and calcium intake [24] and the absence of a GNAS methylation defect in one reported case [119]; a rapid biochemical response to targeted nutritional rehabilitation was also reported in a patient [123].

Differential Diagnosis: Vitamin D-deficiency rickets and pseudohypoparathyroidism can mimic each other clinically and biochemically, and distinguishing between them is difficult [122]. The 2018 International Consensus Statement by Mantovani et al. provides the reference framework for defining clinical PTH resistance, characterized by the association of hypocalcemia, hyperphosphatemia, and elevated PTH in the absence of vitamin D deficiency and with normal magnesium levels and renal function [39]. A conference abstract describes a patient with severe nutritional calcium deficiency whose biochemical abnormalities resolved with nutritional repletion and in whom no GNAS methylation defect was identified [119].

- Dietary history: Patients with severe nutritional rickets may have a history of low dietary calcium intake after weaning [118].
- 25(OH)D levels: Deficiency (a level below about 12 ng/mL supports the diagnosis) may be present in nutritional rickets, but normal levels do not exclude it [24]; normal calcifediol levels are expected in suspected pseudohypoparathyroidism (after excluding concurrent vitamin D deficiency) [39], although levels are elevated in some subgroups [124].
- $1,25(OH)_2D$ levels: Some small pseudohypoparathyroidism studies have reported low levels in a few patients [124,125].
- Response to treatment: Patients with severe nutritional rickets show normalization of serum calcium and phosphate with vitamin D and calcium supplementation, usually within about 3 weeks [10]; patients with pseudohypoparathyroidism have been treated with vitamin D metabolites to correct hypocalcemia [126].
- Urinary cAMP excretion is markedly elevated in rachitic children, correlating with PTH levels [127]; the urinary cAMP response to PTH is blunted in pseudohypoparathyroidism [128].
- Mutations in GNAS or related genes are found in pseudohypoparathyroidism [129,130].

Hypomagnesemia: Severe magnesium deficiency causes functional hypoparathyroidism with a biochemical phenotype characterized by hypocalcemia and target-organ resistance to PTH [37]. Hypomagnesemic PTH resistance resolves with magnesium repletion [38]. Serum magnesium should be measured in children with persistent hypocalcemia or a poor response to calcium treatment [131,132], as hypomagnesemia can cause a similar biochemical phenotype and, if untreated, may lead to persistent, refractory hypocalcemia that cannot be resolved with calcium or vitamin D supplementation alone [91].

The tubular maximum reabsorption of phosphate per glomerular filtration rate (TmP/GFR) is reduced in nutritional rickets, reflecting phosphate loss due to secondary hyperparathyroidism [10,99]; TmP/GFR is characteristically suppressed in genetic phosphate-wasting disorders such as XLH [50]. TmP/GFR values must be interpreted using age-matched pediatric reference intervals, as values decline progressively during puberty before stabilizing in adulthood [97]. TmP/GFR should be calculated from paired fasting blood and urine samples rather than inferred from the percentage tubular reabsorption of phosphate, which does not account for the filtered phosphate load [24,101].

Another differential diagnosis for nutritional rickets is vitamin D-dependent rickets type 1B (VDDR1B) [24] caused by loss-of-function mutations in CYP2R1 (encoding 25-hydroxylase) [75]. VDDR1B presents with very low 25(OH)D concentrations [133], and calcifediol (25-hydroxyvitamin D) therapy has been reported to restore vitamin D and mineral homeostasis by bypassing the enzymatic defect [75].

Recommended biochemical investigations include serum 25(OH)D, PTH, alkaline phosphatase, calcium, and phosphorus levels [88].

Management: Nutritional rickets requires vitamin D and calcium supplementation [8]. Patients with symptomatic hypocalcemia, such as tetany, convulsions, or dilated cardiomyopathy, should receive intravenous calcium gluconate until serum calcium normalizes [10]. With appropriate treatment, PTH levels usually fall into the normal range, and serum calcium and phosphate normalize, typically within about 3 weeks [10].

4. Evidence-Based Treatment Strategies

Management of nutritional rickets involves strategies tailored to patient age and clinical setting, such as the use of high-dose (stoss) therapy in resource-limited settings (Figure 2) [8]. The following recommendations are based on global consensus guidelines [8].

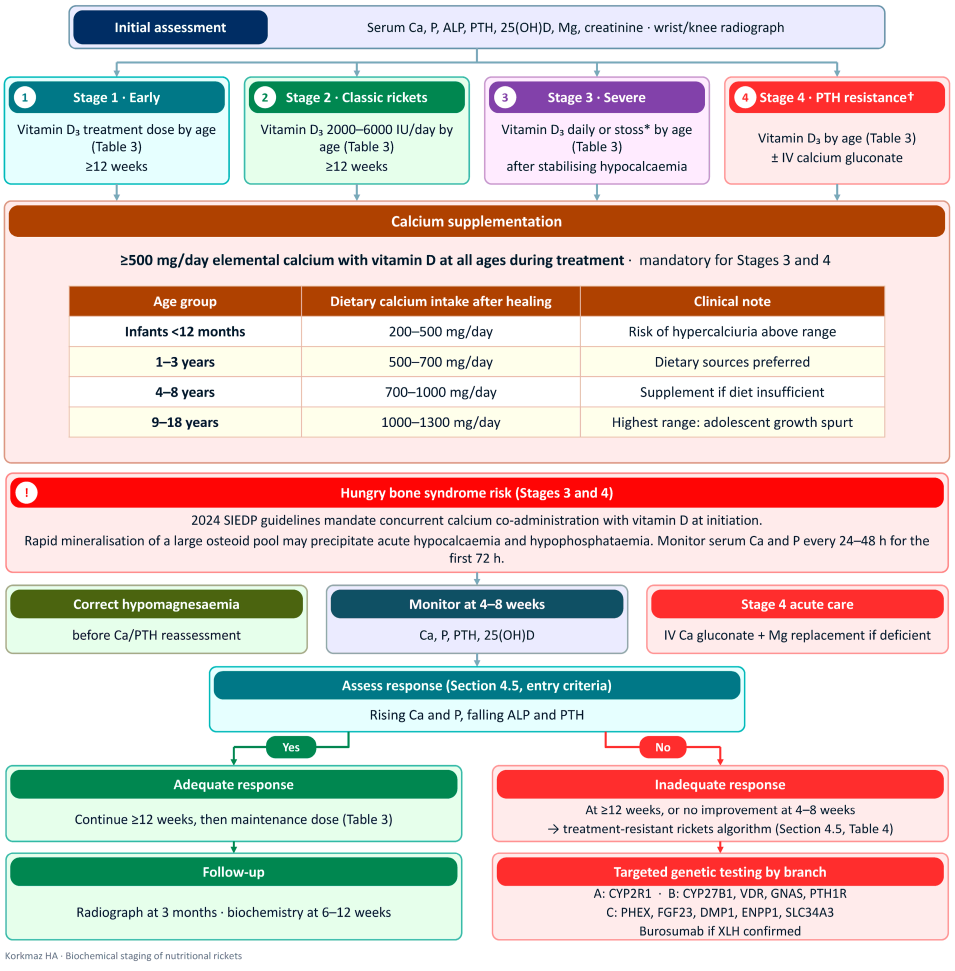


Figure 2. Evidence-based treatment algorithm for nutritional rickets. * 50 IU (1250 µg) at 3–12 months, 150,000 IU (3750 µg) at >12 months–12 years, 300,000 IU (7500 µg) at >12 years; not recommended below 3 months [8,76]. † Stage 4 (PTH resistance phenotype): provisional, non-sequential category; see Sections 1, 3.4 and 5.6. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; Ca, calcium; FGF23, fibroblast growth factor 23; IV, intravenous; Mg, magnesium; P, phosphate; PTH, parathyroid hormone; XLH, X-linked hypophosphatemia [49,134].

4.1. General Principles

Vitamin D Formulations: Both cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) are effective for treating nutritional rickets when given as daily therapy [8]. However, for single high-dose (stoss) therapy, vitamin D3 is preferred due to its longer half-life [8].

Route of Administration: Oral administration is preferred over parenteral (stoss) administration, as oral therapy restores 25(OH)D levels more rapidly [8]. Intramuscular administration may be preferred in patients with intestinal malabsorptive diseases who cannot take oral vitamin D [135].

Calcium Supplementation: All children with nutritional rickets should receive calcium supplementation in addition to vitamin D, with a recommended minimum dose of 500 mg calcium/day [8]. Urinary calcium monitoring (spot urine calcium-to-creatinine ratio) is used to screen for hypercalciuria during vitamin D analog treatment of hypophosphatemic rickets [136]. Calcium can be provided through dietary sources (milk, dairy products, fortified foods) or oral supplements [137].

Duration of Treatment: Vitamin D treatment should continue for 3–4 months, with reassessment of biochemical markers and radiographic findings to evaluate healing [10]. Some children may require longer courses [88].

Dosing: Age-specific treatment and maintenance doses of vitamin D are summarized in Table 3. The stage-specific recommendations in Section 4.2 refer to this table.

Table 3. Vitamin D treatment doses for nutritional rickets, by age (adapted from the Global Consensus Recommendations [8]).

Age	Daily Dose for 3 Months [10]	Single-Dose Alternative (Stoss) [10]	Maintenance Daily Dose [10]
<3 months	2000 IU (50 µg)	Not recommended	400 IU (10 µg)
3–12 months	2000 IU (50 µg)	50,000 IU (1250 µg)	400 IU (10 µg)
>12 months to 12 years	3000–6000 IU (75–150 µg)	150,000 IU (3750 µg)	600 IU (15 µg)
>12 years	6000 IU (150 µg)	300,000 IU (7500 µg)	600 IU (15 µg)

Conversion: 1 µg cholecalciferol = 40 IU (IU ÷ 40 = µg) [138]. A routine intake of 500 mg/day of elemental calcium from diet or supplements should accompany vitamin D regardless of age [10]. Response should be reassessed after 3 months, and some children require a longer course [10,139]. Single doses above 300,000 IU are not recommended because of the risk of hypercalcaemia and hypercalciuria [88]. After healing, maintenance supplementation of at least 400 IU (10 µg)/day in the first year of life and at least 600 IU (15 µg)/day thereafter is recommended [88]; the Italian consensus recommends a range up to 1000 IU (25 µg)/day [88].

Monitoring: In a prospective study, baseline assessment included serum calcium, phosphate, ALP, 25(OH)D and radiographs of wrists and knees, with follow-up monitoring at 6-week intervals up to 24 weeks to evaluate clinical, radiological and biochemical markers [140]. In routine practice, the biochemical response is monitored every 4 weeks during the first 3 months (serum calcium, phosphate, ALP and PTH) and serum 25(OH)D is assessed every 3–4 months [10].

4.2. Stage-Specific Treatment Recommendations

4.2.1. Stage 1 (Early/Subclinical)

Vitamin D Dosing:

- Infants <12 months treated for hypovitaminosis D: 2000 IU (50 µg) daily for a minimum of 3 months [88].
- Children 1–12 years: 3000–6000 IU (75–150 µg) daily for a minimum of 3 months [88], or a single dose (in resource-limited settings) of 150,000 IU (3750 µg) [8]. Age-adjusted

dosing note: Infants aged 3–12 months should receive 2000 IU (50 µg) daily for 3 months [10]; a single dose (in resource-limited settings) of 50,000 IU (1250 µg) may be considered for infants aged 3–12 months [8]; single-dose therapy is described for infants older than 3 months [8]. The administration of a single large dose of vitamin D > 300,000 IU is not recommended because it may pose a high risk of vitamin D intoxication with hypercalciuria and hypercalcemia [88]. Adolescents >12 years follow a 6000 IU daily protocol for a minimum of 3 months [88]. The dosage of adjunctive calcitriol should be titrated according to serum calcium concentrations; urinary calcium excretion should be monitored regularly (at least every 4–6 months) and kept below the upper limit of normal for age and weight [10].

Calcium Supplementation: Patients should obtain a minimum of 500 mg/day of elemental calcium from dietary or supplemental sources [8]. Monitor urinary calcium excretion regularly (at least every 4–6 months) to maintain it below the upper limit of normal for age and weight [10].

Monitoring: 25(OH)D deficiency is commonly defined as a level below 20 ng/mL in general vitamin D guidance [74], whereas the rickets-specific global consensus uses a lower threshold of 12 ng/mL [88].

Maintenance: After rickets has healed, transition to age-appropriate maintenance supplementation (400–1000 IU/day in the first year of life and 600–1000 IU/day from 1 to 18 years) [88].

- Infants <1 year: 400–1000 IU (10–25 µg) vitamin D daily [135].
- Children 1–18 years: 600–1000 IU (15–25 µg) vitamin D daily [88,135].

4.2.2. Stage 2 (Compensated)

Vitamin D Dosing:

- Infants <3 months: 2000 IU (50 µg) daily for a minimum of 3 months; single-dose therapy is an option for infants older than 3 months in resource-limited settings [8,10].
- Infants 3–12 months: 2000 IU (50 µg) daily for 3 months, or a single dose (in resource-limited settings) of 50,000 IU (1250 µg) [8,88].
- Children 1–12 years: 3000–6000 IU (75–150 µg) daily for a minimum of 3 months, or a single dose (in resource-limited settings) of 150,000 IU (3750 µg) [8,88].
- Adolescents >12 years: 6000 IU (150 µg) daily for a minimum of 3 months, or a single dose of 300,000 IU (7500 µg) [8,88].

Calcium Supplementation: Provide at least 500 mg elemental calcium daily [4,8].

Monitoring: Treatment progress is monitored using relevant biochemical parameters [10], and radiological healing and biochemical markers are evaluated at 3 months [10].

Maintenance: Continue vitamin D supplementation after rickets has healed according to age guidelines [88] and meet the minimum daily calcium requirement in at-risk individuals [8].

4.2.3. Stage 3 (Decompensated)

Acute Management of Severe Hypocalcaemia: Administer intravenous calcium gluconate (10% solution, 5–20 mg/kg [0.5–2.0 mL] slowly over 10–15 min with cardiac monitoring) for symptomatic acute hypocalcaemia [10].

Vitamin D Dosing: Start as for Stage 2, by age (Table 3), once acute hypocalcaemia has been stabilised, with concurrent calcium to prevent hungry bone syndrome [10,88].

Calcium Supplementation: 30–75 mg/kg/day of elemental calcium in divided doses [10]. Monitoring is tailored to the severity of rickets and response to therapy [10]. Calcium

supplementation is important to prevent 'hungry bone syndrome'—hypocalcaemia caused by increased bone mineralisation as PTH levels normalise [88].

Monitoring: Monitor serum calcium and phosphate concentrations, as normalisation usually occurs within 3 weeks; also monitor alkaline phosphatase and PTH [10]. Radiographic signs of healing usually appear within 3–4 weeks of treatment initiation [141].

Maintenance: After healing of rickets, vitamin D supplementation should continue [88].

4.2.4. Stage 4: Nutritional Pseudohypoparathyroidism/PTH Resistance Variant

Acute Management: Severe symptomatic hypocalcaemia requires immediate correction, which might include intravenous administration of calcium salts according to general guidelines for the management of acute hypocalcaemia in hypoparathyroidism [39].

- Intravenous calcium gluconate: 10% solution, 5–20 mg/kg (0.5–2.0 mL) administered slowly over 10–15 min to avoid bradycardia with electrocardiographic monitoring [10].
- In a single-centre cohort of patients with vitamin D-dependent rickets type II, a daily intravenous calcium infusion (1500 mg/m^2/day over 10–12 h) was continued until calcium and phosphate levels normalised [142].

Vitamin D Dosing: Pharmacologic doses of vitamin D aggressively treat vitamin D deficiency and quickly correct serum calcium and phosphorus levels [21].

- Age-appropriate doses as in Table 3: 2000 IU (50 µg) daily if <12 months, 3000–6000 IU (75–150 µg) daily if >12 months to 12 years, or 6000 IU (150 µg) daily if >12 years, for at least 3 months, or the corresponding single dose from 3 months of age [8,88].

Calcium Supplementation:

- Regularly assess serum alkaline phosphatase activity as it is a reliable and economical biochemical marker for monitoring the effectiveness of treatment [10].
- Serum PTH concentrations usually fall within the normal range as normocalcemia is restored [10].
- Radiographic healing is usually evident within 3–6 months, depending on the severity of the deficiency [21].

Expected Response:

- Serum calcium normalization usually occurs within 3 weeks, but it may also be evident after only 6–10 days of treatment [10].
- PTH levels typically normalize within 1–2 months of treatment [21].

Radiographic changes may take 3–6 months to resolve after adequate treatment [143]. Failure to respond to native vitamin D and calcium treatment should prompt reconsideration of the diagnosis [24]. Maintenance involves vitamin D supplementation to prevent the recurrence of nutritional vitamin D deficiency rickets [10].

4.3. Evidence from Randomized Controlled Trials

Multiple randomized controlled trials have evaluated treatment strategies for nutritional rickets, including comparisons of vitamin D, calcium, and combination therapy [144–147]. Thacher et al. [148] reported that Nigerian children with rickets responded better to calcium alone or calcium combined with vitamin D than to vitamin D alone [146]. However, low-certainty evidence suggests that vitamin D plus calcium, or calcium alone, may improve healing in children with nutritional rickets compared to vitamin D alone [149]. A subsequent trial by the same group found that in nutritional rickets, daily calcium supplementation of 1000 mg or 2000 mg produced more rapid radiographic healing than 500 mg [139]. These findings underscore the importance of addressing both vitamin D and calcium deficiencies [150].

Daily versus intermittent dosing: A trial has compared daily vitamin D supplementation with a single high-dose (stoss) therapy [151]. Saluja et al. [152] found that low-dose depot vitamin D3 (60,000 IU for infants, 150,000 IU for children) was as effective as daily dosing (2000–4000 IU) for treating nutritional rickets. Mittal et al. [153] demonstrated that a single oral dose of 90,000 IU is safe and effective for healing rickets. Daily dosing carries a lower risk of vitamin D toxicity than large single doses do, although compliance and cost remain major concerns for its routine use [154].

Cochrane Review: A systematic review by Chibuzor et al. [149] concluded, with low-certainty evidence, that calcium alone or the combination of vitamin D and calcium improves healing in children with nutritional rickets compared with vitamin D alone.

4.4. Special Considerations

Calcium-Deficiency Rickets: In children with nutritional calcium-deficiency rickets, calcium supplementation (1000 mg daily) is recommended until healing is complete [10].

Compliance and Follow-Up: Intermittent bolus dosing may be effective in patients with poor compliance [10].

Prevention: Universal vitamin D supplementation for infants (400 IU/day during the first year of life) and dietary or supplemental vitamin D intake (at least 600 IU/day thereafter) are recommended to prevent nutritional rickets in immigrant children from dark-skinned ethnic risk groups [89]. Pregnant and lactating women should receive adequate vitamin D supplementation (600 IU [15 µg]/day, or 1000–2000 IU [25–50 µg]/day for women with risk factors) [88]. Vitamin D transfer to the fetus was lower in women with obesity and baseline insufficiency receiving 10 µg/day than in women receiving 20 µg/day [155], and its secretion into breast milk rises with high-dose maternal supplementation [156].

4.5. Diagnostic Algorithm for Suspected Treatment-Resistant Rickets

The algorithm is applied in sequence. Steps 1 and 2 apply to every child. Step 3 assigns the child to one of three biochemical branches (Steps 4–6), and only the branch that matches the child's biochemistry is followed. Genetic testing (Step 7) is targeted according to the branch (Table 4).

Entry criteria: The algorithm applies when, after at least 12 weeks of verified treatment (Table 3), radiological healing may still be incomplete [157]. Serum calcium and phosphate usually normalise within about 3 weeks of adequate treatment [10], so no biochemical improvement warrants earlier entry into the algorithm. It is also appropriate when atypical features are present from the outset, such as a positive family history, which can identify affected children within the first weeks of life [158], normal 25(OH)D at diagnosis [159], or the Stage 4 pattern (Section 3.4).

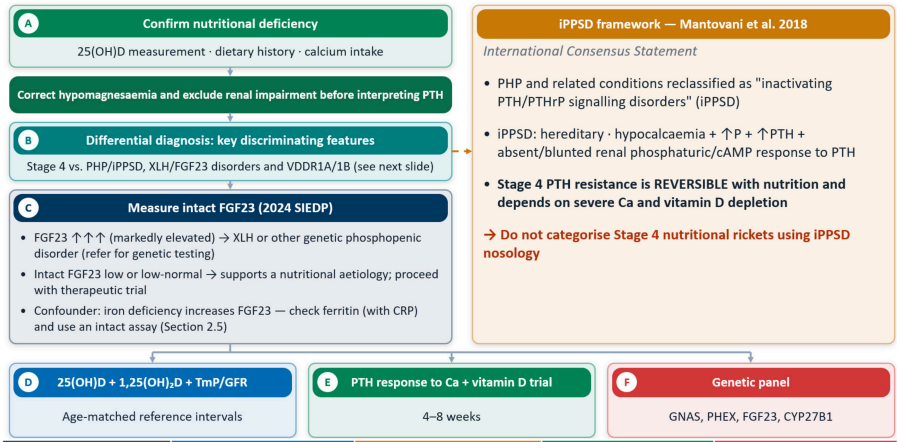
Step 1: Verify adherence, dose and calcium intake (all children). Confirm that the child has taken an age-appropriate dose of cholecalciferol for at least 3 months: 2000 IU (50 µg) daily if aged <12 months; 3000–6000 IU (75–150 µg) daily if aged >12 months to 12 years; and 6000 IU (150 µg) daily if aged >12 years [88]. From 3 months of age, a single high-dose regimen is acceptable in resource-limited settings [8]. Confirm also that the child has received at least 500 mg/day of elemental calcium [8]. If adherence or dosing was inadequate, correct it and repeat the course before proceeding.

Step 2: Core re-evaluation (all children). Measure serum calcium, phosphate, ALP, PTH, 25(OH)D, magnesium and creatinine, and obtain paired morning urine for calcium/creatinine ratio and TmP/GFR [99]. Hypomagnesaemia should be corrected [160] and renal impairment excluded before the remaining results are interpreted [63], because PTH resistance is only defined when magnesium and renal function are normal [39].

Step 3: Assign the biochemical branch (all children). Based on Step 2: Branch A if 25(OH)D remains low despite verified adherence; Branch B if 25(OH)D is adequate and elevated PTH predominates [161]; Branch C if 25(OH)D is adequate and hypophosphataemia with reduced TmP/GFR predominates [162], with normal or near-normal calcium.

Step 4: Branch A, persistently low 25(OH)D. (4a) Screen for malabsorption when indicated by poor growth, chronic diarrhoea or other gastrointestinal symptoms [163,164], using tissue transglutaminase IgA with total IgA for coeliac disease [165], a common malabsorptive condition in children [163]; Crohn's disease, pancreatic insufficiency and short bowel syndrome should also be considered [166,167]. Review drugs that accelerate vitamin D catabolism, such as enzyme-inducing antiepileptic drugs [168]. (4b) If malabsorption and drug effects are excluded, suspect VDDR1B (CYP2R1). This disorder presents with very low 25(OH)D and normal or high $1,25(OH)_2D$ [133] and responds to calcifediol [112], which bypasses the 25-hydroxylation defect; mutations identified by CYP2R1 sequencing support the diagnosis [133,169].

Step 5: Branch B, adequate 25(OH)D with hypocalcaemia and elevated PTH. Measure $1,25(OH)_2D$ [170]. (5a) Low or inappropriately normal $1,25(OH)_2D$ suggests VDDR1A (CYP27B1) [171], which is treated with calcitriol or alfacalcidol [172,173]. (5b) Markedly elevated $1,25(OH)_2D$ suggests hereditary vitamin D resistance (VDDR2, VDR) [174]. (5c) Elevated serum phosphate with PTH at or above the upper limit of normal and normal calcifediol suggests PTH resistance [39]. Once magnesium and renal function have been confirmed to be normal (Step 2), a nutritional cause (Stage 4) is supported if the pattern resolves with repletion [99,123]. If it persists, pseudohypoparathyroidism should be evaluated by GNAS locus analysis [39], and PTH1R mutations, which underlie related disorders, should also be considered [175]. Figure 3 summarises this differential diagnosis.



Feature	Stage 4 (nutritional)	PHP/iPPSD	XLH/FGF23 disorders	VDDR1A/1B
25(OH)D	Usually <10 ng/mL	Normal (may have co-deficiency)	Normal	Very low (1B) or normal (1A) ◆
Serum phosphate	Normal–↑ (for age)	↑ (PTH resistance)	↓↓↓	↓ ◆
$1,25(OH)_2D$	↓↓↓	Low–normal	↓ (regulatory)	↓↓↓ (1A); normal–↑ (1B)
Response to vitamin D + Ca	Full recovery (4–8 weeks)	Incomplete; PTH persists	No phosphate normalisation	Partial (1B); none (1A)
Genetics	None	GNAS/PRKAR1A (+ methylation)	PHEX/DMP1/FGF23/ENPP1	CYP27B1 (1A); CYP2R1 (1B)
FGF23 (intact)	Not established	Normal	↑↑↑	Normal
TmP/GFR†	Inappropriately normal–↑ (relative to PTH)	Normal–↑ (PTH resistance blunts phosphaturia)	↓↓↓	Normal–↓
Reversibility	Reversible with nutrition	Not reversible without treatment	Not reversible (genetic)	Reversible with active vitamin D/calcifediol

Figure 3. Differential diagnostic algorithm for Stage 4 nutritional rickets. The figure expands Step 5 (Branch B) of the algorithm in Section 4.5; boxes A–F indicate the sequence of evaluation. † The markedly raised PTH is expected to lower TmP/GFR through renal phosphate wasting [99]. In

pseudohypoparathyroidism, a small 1976 case series reported that the impaired renal phosphaturic response to PTH was not corrected by vitamin D2 treatment [125]. In XLH and other FGF23-mediated disorders, TmP/GFR is reduced with hypophosphataemia [50,101]. Values should be calculated from paired serum and second-morning urine samples taken at the same time and interpreted against age-specific reference intervals, which are highest in infancy and decline until adulthood [24]. The arrows indicate whether serum levels are low or high. Abbreviations: ALP, alkaline phosphatase; FGF23, fibroblast growth factor 23; PHP/iPPSD, pseudohypoparathyroidism/inactivating PTH/PTHrP signalling disorder; PTH, parathyroid hormone; TmP/GFR, tubular maximum reabsorption of phosphate corrected for glomerular filtration rate; VDDR, vitamin D-dependent rickets; XLH, X-linked hypophosphataemia [39].

Step 6: Branch C, adequate 25(OH)D with hypophosphataemia and reduced TmP/GFR. (6a) Assess iron status and inflammation, which regulate FGF23 [64,176]. This should be done before FGF23 is interpreted (Section 2.5), because iron deficiency seems to raise FGF23 production and processing [45,54,177]. (6b) Measure intact FGF23 [49,134]. An elevated or inappropriately normal value in the presence of hypophosphataemia is consistent with an FGF23-mediated disorder (XLH, ADHR, ARHR or, rarely, tumour-induced osteomalacia) [24,178]. A low value points to FGF23-independent phosphate wasting, such as hereditary hypophosphataemic rickets with hypercalciuria (SLC34A3) or renal Fanconi syndrome [10,24,179]. (6c) If iron deficiency is confirmed, give oral iron (which normalised FGF23 and phosphate in a small pilot study of iron-deficient ADHR patients [68]) and repeat the FGF23 and phosphate measurements after iron repletion, as a single reported case showed biochemical improvement after ferritin normalisation [180].

Step 7: Targeted genetic evaluation. Genetic testing is guided by the clinical branch, with candidate genes listed for each disorder [10]. A broader next-generation sequencing panel is indicated when FGF23-mediated and non-FGF23-mediated hypophosphataemia are difficult to distinguish [181]. When XLH is confirmed, burosumab is considered first-line targeted therapy for symptomatic children [182].

Table 4. Stepwise evaluation of suspected treatment-resistant rickets: sequence, criteria for application and key tests.

Step	Applies to	Key Tests	Outcome/Next Step
Entry	Children who fail to respond to oral calcium and vitamin D treatment [24] or who have atypical features [86]	Ca, P, ALP, PTH; radiograph	Proceed to Step 1
1	All	Adherence, dose (Table 3), calcium intake	Inadequate → correct and repeat course; adequate → Step 2
2	All	Ca, P, ALP, PTH, 25(OH)D, Mg, creatinine; urine Ca/Cr and TmP/GFR	Exclude metabolic acidosis and renal disease → Step 3 [24]
3	All	Interpretation of Step 2	Assign Branch A, B or C
4 (A)	Low 25(OH)D despite adherence	Coeliac serology (tTG-IgA + total IgA) if indicated [165]; drug review; calcifediol trial [75]	Malabsorption (e.g., coeliac disease [183]) or VDDR1B (CYP2R1) [78,133,184]

Table 4. *Cont.*

Step	Applies to	Key Tests	Outcome/Next Step
5 (B)	Adequate 25(OH)D; hypocalcaemia, ↑ PTH [10,185]	1,25$(OH)_2$D; phosphate and TmP/GFR	VDDR1A or VDDR2 [10]
6 (C)	Adequate 25(OH)D; hypophosphataemia, ↓ TmP/GFR	Ferritin + CRP (± transferrin saturation, FBC), then intact FGF23 [134]	FGF23-mediated vs. FGF23-independent phosphate wasting [49,134]; iron repletion and retest if iron deficient (suggested by a small ADHR pilot trial) [68]
7	According to the branch	Targeted gene panel [186]	Molecular diagnosis; targeted therapy

Iron studies are mandatory only in Step 6 and whenever an elevated FGF23 result is being interpreted; elsewhere they are at the clinician's discretion. Abbreviations: CRP, C-reactive protein; FBC, full blood count; tTG-IgA, tissue transglutaminase IgA; other abbreviations as in Tables 1 and 2. ↑: high blood parathyroid hormone levels, ↓: low TmP/GFR.

5. Discussion

This review revisits the classical three-stage biochemical classification system for nutritional rickets [13] and proposes the recognition of an uncommon PTH resistance phenotype as a potential additional stage (designated "Stage 4" for clinical utility). The following sections discuss the clinical implications, limitations, and future directions of this proposed framework.

5.1. Clinical Utility of the Proposed Framework

Clinical utility of Stages 1–3. The classical three stages enable clinicians to relate a single set of biochemical results to the physiological state of compensation. Stage 1 indicates deficiency, and because elevated ALP is the most sensitive biochemical feature of active rickets, its absence makes active rickets unlikely [4]. Stage 2 identifies phosphate-driven mineralisation failure while calcium is still maintained [8,21]. Stage 3 identifies decompensation with a risk of hypocalcaemic seizures, tetany and cardiomyopathy and therefore indicates the need for parenteral calcium and protection against hungry bone syndrome [8,10,88,187]. Staging also sets expectations for monitoring: calcium and phosphate normalisation within about 3 weeks [10] and radiographic healing over 3–6 months [21].

Clinical utility of the Stage 4 designation. The value of recognising the PTH resistance phenotype is mainly diagnostic and protective. First, it prevents premature labelling of a reversible nutritional disorder as pseudohypoparathyroidism/iPPSD. This misclassification has occurred in reported paediatric cases [122] and may lead to unnecessary further evaluation for other forms of pseudohypoparathyroidism [113]. Second, it makes the measurement of serum magnesium, renal function and 25(OH)D an explicit prerequisite before PTH resistance is diagnosed [39]. Third, it identifies patients with severe hypocalcaemia who merit close cardiac monitoring during repletion [188], and in whom calcitriol may occasionally be required in addition to calcium and cholecalciferol to overcome PTH resistance [15]. Fourth, it provides a practical rule: when this pattern does not resolve after adequate nutritional repletion (in vitamin D-deficiency rickets, PTH typically normalises within one to two months of treatment [21]), it should prompt GNAS/iPPSD and PTH1R evaluation [189].

Research utility. A shared operational definition (Section 3.4) would allow researchers to report cases consistently and pool them in registries. This would make it possible to estimate

the frequency of the phenotype, to define age-specific phosphate and TmP/GFR thresholds and to establish whether its main driver is vitamin D deficiency, calcium deficiency or the degree of hypocalcaemia. The limitations of the framework are discussed in Section 5.6.

5.2. Pathophysiological Insights and Research Gaps

The staging framework highlights key pathophysiological concepts. Hypophosphataemia is a final common pathway of rickets [93], and secondary hyperparathyroidism can maintain serum calcium at the expense of phosphate wasting [21]. A final stage of vitamin D deficiency is characterised by the marked inhibition of $1,25(OH)_2D$ synthesis [19]. The contributions of $1,25(OH)_2D$ deficiency and PTH receptor downregulation (described in chronic kidney disease) [190] to the impaired phosphaturic response require further clarification. Future priorities include (a) prospective studies defining the prevalence and risk factors for the PTH resistance phenotype; (b) mechanistic characterisation of renal tubular PTH responsiveness before and after treatment; and (c) determination of whether biochemical stages represent a sequential natural history or a spectrum of presentations.

5.3. Differential Diagnosis: Stage 4 Versus Pseudohypoparathyroidism (iPPSD)

Because their biochemical profiles overlap, distinguishing vitamin D-deficiency rickets from inactivating PTH/PTHrP signalling disorders (iPPSD) is important (Figure 3) [14,117]. Four features are most helpful. A key distinguishing feature is reversibility: nutritional rickets resolves with vitamin D and calcium treatment, whereas pseudohypoparathyroidism is an inherited disorder whose renal PTH resistance is not corrected by vitamin D treatment [117,125,191]. Vitamin D status is also informative. Clinical PTH resistance in iPPSD is defined as hypocalcaemia, hyperphosphataemia and elevated PTH in the absence of vitamin D deficiency, with normal magnesium and renal function [39], whereas 25(OH)D is usually low in Stage 4 [192]. In addition, features of Albright hereditary osteodystrophy (short stature, round facies, brachydactyly and subcutaneous ossifications) are characteristic of pseudohypoparathyroidism type Ia [193]. Finally, a history of low dietary calcium intake after weaning supports a nutritional aetiology [118].

Iron deficiency is associated with markedly elevated C-terminal FGF23 with normal intact FGF23 [54], so check serum ferritin (with C-reactive protein) before interpreting an elevated FGF23, because iron deficiency and inflammation both raise FGF23 production [194], and use an intact FGF23 assay (Section 2.5).

◆ VDDR1A early-phase discriminators (vs. Stage 4 at initial evaluation): 25(OH)D is normal or elevated in VDDR1A [93]. Serum phosphate may be low in Stage 4 as well, because secondary hyperparathyroidism drives renal phosphate wasting [134,195], and it is low in VDDR1A [196]. Apply these features before the active vitamin D metabolite is measured or CYP27B1 sequencing results are available; calcitriol replaces the deficient hormone and acts rapidly [93].

Validation: the three-stage biochemical classification was derived from data on children with nutritional rickets [13].

In practice, clinical and biochemical features alone do not establish aetiology [86], and children with non-nutritional rickets often respond poorly to vitamin D and calcium [86], so this pattern should raise suspicion of non-nutritional rickets [86]. In that case, genetic and epigenetic testing for pseudohypoparathyroidism is indicated to confirm the diagnosis [39]. Urinary calcium should be monitored during high-dose repletion because hypercalciuria is the main toxicity that limits vitamin D analog dosing [136]. Three factors can confound interpretation: (i) hypomagnesaemia, whose correction can restore PTH secretion within minutes and serum calcium over several days [37]; (ii) iron deficiency, which can raise cFGF23 [54] (iron repletion can lower cFGF23 [51]), and ferric carboxymaltose, which

can raise intact FGF23 [65]; and (iii) hypoalbuminaemia, which may complicate interpretation of bone turnover markers in patients with secondary hyperparathyroidism on haemodialysis [197].

Within the pseudohypoparathyroidism spectrum, PHP-Ib typically presents without features of Albright hereditary osteodystrophy [198] and with a blunted urinary cAMP response to PTH [199], whereas PHP-II shows a preserved cAMP response but an absent phosphaturic response [200,201]. PHP-II can therefore resemble vitamin D deficiency rickets [117]. Two features distinguish PHP-II from vitamin D deficiency rickets: vitamin D status, which is generally expected to be normal in PHP because the consensus diagnostic criteria assume normal calcifediol and no vitamin D deficiency [39] but is decreased in vitamin D deficiency rickets [117]; rapid biochemical normalisation with vitamin D and calcium, which occurs in nutritional rickets [21,202]. Measuring renal function helps exclude renal failure, which also raises serum phosphate [196]. In children with persistent hypophosphataemia, nutritional causes must also be distinguished from phosphate-wasting disorders such as XLH, characterised by elevated FGF23, and Fanconi syndrome, characterised by renal tubular phosphate transport defects [50,63,203,204]. Measurement of PTH and FGF23 helps to separate PTH-driven from FGF23-driven phosphate wasting [203].

5.3.1. PTH1R Variants and Hypomagnesaemia as Mimics

Loss-of-function variants in PTH1R, which encodes the PTH/PTHrP receptor type 1 [205,206], have been reported to produce hypocalcaemia, hyperphosphataemia and elevated PTH in a family with a homozygous variant, a profile reminiscent of pseudohypoparathyroidism [206]. The phenotypic spectrum is broad. It ranges from Blomstrand chondrodysplasia and Eiken syndrome, caused by recessive variants [207,208], to nonsyndromic failure of tooth eruption caused by heterozygous variants [209], and heterozygous variants with incomplete penetrance have also been described [210]. When the biochemical profile strongly suggests pseudohypoparathyroidism, analysis of the GNAS locus is recommended first [39,211]. If the clinical presentation does not point to a specific gene, a panel covering genes of the PTH/PTHrP signalling pathway may be performed [39]. Hypomagnesaemia is a further, readily reversible mimic [212]. Magnesium deficiency impairs PTH secretion and peripheral responsiveness, producing functional hypoparathyroidism that improves with magnesium repletion [37]. It should be suspected in children with poor intake, malabsorption or renal magnesium wasting [213–215].

5.3.2. Vitamin D-Dependent Rickets Types 1A and 1B

Vitamin D-dependent rickets types 1A and 1B are monogenic mimics of nutritional rickets [133,173,216]. VDDR1A, caused by CYP27B1 variants, presents with normal or elevated 25(OH)D but low 1,25$(OH)_2$D; this pattern is a biochemical clue, although its clinical features overlap with nutritional rickets [159,174,217]. It requires treatment with calcitriol or alfacalcidol [75,173]. VDDR1B, caused by CYP2R1 variants, results in very low 25(OH)D and can therefore be confused with nutritional vitamin D deficiency [218]. Patients with VDDR1B usually respond to calcifediol [12].

5.4. Global Perspectives and Calcium-Deficiency Rickets

While countries in Asia and the Middle East are most often affected by nutritional vitamin D deficiency [5], calcium deficiency plays a major role in areas with low dietary calcium intake, particularly in Africa and parts of Asia [219,220], and rickets manifests on a spectrum ranging from isolated vitamin D deficiency to isolated calcium deficiency [219], underscoring the importance of assessing both vitamin D and calcium status when evaluating children with rickets.

5.5. Prevention Strategies

Given that nutritional rickets is a preventable condition [3], public health strategies should focus on:

1. Universal Vitamin D Supplementation: Infants should receive approximately 400 IU of vitamin D daily, and children over 12 months should receive approximately 600 IU daily [4,5].
2. Maternal Supplementation: Pregnant and lactating women should receive adequate vitamin D supplementation (600 IU daily or 1000–2000 IU daily for women with risk factors) [88] to support vitamin D transfer into breast milk during lactation, although the reviewed studies found that substantially higher doses than the recommended intake were needed to achieve sufficient transfer [221].
3. Food Fortification: Fortification of staple foods with vitamin D is a strategy to reduce the prevalence of vitamin D deficiency [222].
4. Dietary Education: Families should receive educational and behavioural training to support nutritional interventions [89].

5.6. Limitations of the Proposed Classification

This review proposes Stage 4 as a provisional category. It is not part of the three-stage framework of the Global Consensus, which classifies vitamin D status and calcium intake as sufficient, insufficient or deficient [8], and it should not be used to make treatment decisions that differ from those guidelines. The following limitations apply:

1. Evidence Base: Direct paediatric evidence for Stage 4 consists of a small number of case reports and one interventional study in toddlers (Table 2). Paediatric relationships between 25(OH)D, PTH and related markers are inconsistent, which limits confidence in such inferences [223]. In a PubMed sample of rare-disease articles, case reports constituted the majority of manuscripts [224], so the literature may over-represent unusual cases.
2. Uncertain Mechanistic Basis: Reversible resistance to the renal action of parathyroid hormone has been documented in human vitamin D deficiency, and the authors suggested that it reflects the secondary hyperparathyroidism associated with vitamin D deficiency [225]. Indirect or related evidence—rather than direct studies in nutritional rickets—supports the role of hypomagnesaemia [37,226,227].
3. Confirmation of PTH resistance: PTH infusion testing has been used to evaluate childhood hypocalcaemia [228]. PTH resistance and the related calcium, phosphate and PTH values can vary, so repeated testing may be required [39].
4. Non-universal phenomenon: Elevated concentrations of immunoreactive parathyroid hormone were detected in seven of ten children with nutritional rickets; among those reinvestigated after vitamin D treatment, concentrations fell significantly, suggesting that the secondary hyperparathyroidism is functional [229].
5. Biochemical thresholds lack prospective validation: The ranges in Table 1 are approximate, opinion-based estimates derived from limited published case series and do not represent validated diagnostic cutoffs. They diverge in some instances from established global consensus thresholds for vitamin D deficiency [230]. Users of this staging framework should treat these ranges as indicative rather than definitive. In particular, the 2024 meta-analysis by Leyvraz et al. suggests that a minimum serum 25OHD threshold of around 28 nmol/L would represent a low risk of nutritional rickets for the majority of children with an adequate calcium intake [107]. Serum phosphate and TmP/GFR are physiologically higher in infancy, so “normal or high phosphate” should be interpreted against age-specific reference intervals [24]; assay methodology affects reported 1,25-dihydroxyvitamin D values [24].

6. Confounders: Hypomagnesaemia [37,231,232], antiepileptic drug exposure can modify FGF23 and phosphate handling [233], and iron deficiency can modify FGF23 and phosphate handling in neonatal mice [234].
7. Magnesium status was not systematically assessed across the clinical datasets informing this classification; given that hypomagnesaemia has been associated with impaired PTH secretion and, in some reports, end-organ resistance to PTH [91], prospective studies incorporating serum magnesium measurement at each staging point are required to clarify its contribution to Stage 4 biochemistry. Pending such validation, clinicians should regard serum magnesium measurement as mandatory at initial presentation and at each staging transition; they should not assign Stage 4 classification to any patient unless they have formally documented magnesium status and corrected any deficiency.
8. Unvalidated radiographic correlations: The RSS ranges proposed for each stage in Table 1 and Section 2.4 are theoretical associations. While standardized biochemical staging requires further validation, the Thacher rickets severity score has demonstrated good interobserver reproducibility and a moderate correlation with alkaline phosphatase activity [28]. Clinicians must conduct and interpret radiographic assessments independently.
9. Terminology: The numerical label "Stage 4" may be misread as implying sequential progression; it is therefore defined explicitly as a non-sequential phenotype (Section 3.4).
10. Management recommendations for Stages 1–3 are derived from established clinical guidance [10] and are not novel contributions of this review.
11. Future directions: prospective multicenter studies measuring magnesium, TmP/GFR, FGF23 and, where feasible, urinary cAMP before and after repletion are needed before Stage 4 can be considered for formal adoption, and subsequent revisions of this classification should continue to align with evolving international recommendations.

6. Conclusions

Nutritional rickets remains a significant global health challenge despite being preventable [3,235]. Global consensus guidelines define three-stage categories for vitamin D status and calcium intake [8]. An uncommon PTH resistance phenotype—severe hypocalcemia, paradoxically normal or elevated serum phosphate, and markedly elevated PTH—is proposed here as "Stage 4 / Nutritional Pseudohypoparathyroidism." Severe vitamin D deficiency can mimic pseudohypoparathyroidism, with hyperphosphatemia and renal PTH resistance reported in such cases [15]. Hypomagnesemia must be excluded before this designation is applied, in line with criteria for PTH resistance [39]. These consensus criteria define PTH resistance in the absence of vitamin D deficiency, so they do not directly validate a nutritional phenotype [39]. This phenotype does not represent an obligatory sequential stage; prospective validation is required. Prevention strategies include vitamin D supplementation in pregnant women and infants and food fortification [8].

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