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Correspondence
✉ Masab Ahmed, drmasabahmed@gmail.com

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Systematic Review on Medical and Surgical Management of Rickets in Children with Deformities

Masab Ahmed[1], Dost Muhammad Sohu[2], Syed Ali Abbas[3], Adnan Ali Aziz[3], Muhammad Inzamam Wakeel[3], Saoud javed[3]

1 Shaheed Mohtarma Benazir Bhutto Institute of Trauma, Karachi, Pakistan
2 Dr Ziauddin Hospital Sukkur, Sukkur, Pakistan
3 RIMS Trauma Hospital, Karachi, Pakistan

ABSTRACT

***Background**: Rickets remain a leading cause of skeletal deformities in children, particularly in settings where vitamin D and calcium deficiency, hereditary phosphate-wasting, and renal osteodystrophy are prevalent. Although etiology-specific medical therapies have advanced, many children still develop progressive limb deformities that compromise gait and long-term joint integrity, and optimal integration of medical, non-surgical, and surgical management remains uncertain. **Objective**: This systematic review aimed to evaluate etiology-specific medical and surgical strategies for managing deformities in children with rickets, and to integrate mechanistic insights from vertebrate models of growth-plate plasticity. **Methods**: A systematic search of MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library was conducted for articles published between 2000 and 2025. Eligible studies included pediatric clinical reports, guidelines, case reports, practice surveys, and vertebrate experimental studies that addressed rickets or rickets-like skeletal deformities and described medical, non-surgical, or surgical management and skeletal outcomes. Study selection, data extraction, and qualitative appraisal were performed in duplicate. Given heterogeneity of designs and outcomes, a narrative synthesis was undertaken, grouping findings by etiology and management domain. **Results**: Ten studies met inclusion criteria: one clinical narrative review, one etiology-based guideline, one XLH case report, one nationwide orthopedic surgeon survey, and six vertebrate experimental or observational studies. Nutritional rickets responded well to timely vitamin D and calcium supplementation, with potential for spontaneous remodeling of mild deformities, while hereditary phosphate-wasting and renal forms often exhibited persistent malalignment despite biochemical control. The XLH case report suggested that early orthotic intervention in combination with pharmacologic therapy can substantially correct lower-limb deformities without early osteotomy, whereas the nationwide survey revealed wide variation in diagnostic work-up, referral patterns, and use of guided growth and osteotomy among orthopedic surgeons. Vertebrate models consistently showed that mineral imbalance, micronutrient deficiency, toxicant exposure, and altered mechanical loading induce predictable skeletal deformities, supporting the importance of early metabolic correction and mechanical optimisation. **Conclusion**: Current evidence supports a multidisciplinary, etiology-based approach in which early biochemical normalisation is systematically coupled with orthopedic surveillance, selective orthotic strategies, and timely guided growth or osteotomy. However, high-quality comparative data on the timing and combination of these interventions remain scarce, underscoring the need for prospective, multicenter studies and standardised care pathways.*

Keywords
rickets, pediatric deformity, X-linked hypophosphatemia, guided growth, osteotomy, burosumab, growth-plate plasticity, vertebrate models.

INTRODUCTION

Rickets remain a major cause of skeletal morbidity in childhood, particularly in low- and middle-income settings where nutritional deficiencies, limited sunlight exposure, and restricted access to specialist care converge to disrupt bone mineralisation (1,2). Impaired mineralisation of the growing metaphysis and growth plate leads to hypotonia, delayed motor milestones, bone pain, and progressive lower-limb deformities, most commonly genu varum, genu valgum, and rotational malalignment (1,2). Recent pediatric endocrine and metabolic bone literature highlights the expanding spectrum of etiologies, including nutritional rickets driven by vitamin D or calcium deficiency, hereditary phosphate-wasting disorders such as X-linked hypophosphatemic rickets (XLH), and renal osteodystrophy, each with distinct biochemical signatures and natural histories (2). In parallel, increasing recognition of osteomalacia and deformity in adolescents with long-standing, undertreated rickets underscores the long-term burden on gait, function, and joint health (1,2).

Position statements and expert guidance from pediatric endocrinology groups now provide detailed recommendations for etiology-based classification and treatment, with serum calcium, phosphate, alkaline phosphatase, parathyroid hormone, and 25-hydroxyvitamin D used to

distinguish nutritional rickets from hereditary phosphate-wasting and renal forms (2). These documents emphasise early diagnosis, aggressive correction of biochemical derangements, and long-term monitoring of linear growth and radiographic healing, while also acknowledging that persistent deformities and functional limitations frequently require orthopedic input (2). In nutritional rickets, timely high-dose vitamin D and calcium supplementation typically normalises laboratory markers and allows the growing skeleton to remodel, potentially reversing mild deformities if treatment is instituted early in life (1,2). In contrast, children with XLH and other hereditary forms often experience chronic renal phosphate wasting and growth-plate dysregulation, so that conventional regimens of oral phosphate and active vitamin D, although biochemically beneficial, may be associated with complications such as hyperparathyroidism and nephrocalcinosis and may fail to fully correct skeletal deformities (2,3).

The advent of targeted therapies, particularly the anti-FGF23 monoclonal antibody burosumab, has reshaped expectations for growth and pain control in XLH by more effectively restoring phosphate homeostasis and promoting radiographic healing (2,3). However, case-based and early clinical experience indicate that even under optimized pharmacologic regimens, established mechanical malalignment of the lower limbs may persist, necessitating adjunctive orthotic or surgical strategies (3). Guided growth (temporary hemiepiphysiodesis) and corrective osteotomies remain the two principal surgical approaches to rickets-related deformities, yet practice patterns vary widely across institutions and surgeons. A recent nationwide survey of orthopedic surgeons in Turkey demonstrated substantial heterogeneity in diagnostic work-up, referral to pediatric endocrinology, and choice and timing of guided growth versus osteotomy, with differences influenced by years of experience, case volume, and access to multidisciplinary care (4). These findings highlight the absence of universally accepted surgical algorithms that explicitly integrate metabolic control, deformity severity, and growth potential into decision-making.

Beyond clinical data, experimental work in vertebrate models offers mechanistic insight into how mineral deficiency, micronutrient imbalance, toxicant exposure, and mechanical loading interact at the growth plate. Studies in aquaculture species show that vitamin D and C deficiency, altered rearing density, and environmental stressors reproducibly induce spinal and appendicular deformities, mirroring human growth-plate pathology and underscoring the plasticity of the developing skeleton (5-10). Zebrafish, tench, carp, and catfish models have demonstrated that skeletal anomalies are strongly modulated by mineral availability and mechanical environment, supporting the clinical observation that early metabolic correction and optimization of loading conditions are crucial to prevent irreversible deformity (5-10).

Despite these advances, several key questions remain insufficiently answered. Existing endocrine guidelines primarily address diagnostic classification and medical correction but do not provide detailed, etiology-specific recommendations for the timing and selection of orthopedic interventions (2). Orthopedic reports, in turn, often focus on technical aspects of guided growth or osteotomy without systematically contextualizing them within underlying metabolic control and long-term biochemical outcomes (3,4). Comparative data on how modern agents such as burosumab alter the natural history of deformity and the subsequent need, timing, and type of surgery remain sparse, and the translation of vertebrate mechanistic data into clinical algorithms has not been synthesised. The research problem, therefore, is not simply whether rickets can be medically treated or deformities surgically corrected, but how best to integrate etiology-specific metabolic therapy with staged non-surgical and surgical strategies to optimise long-term structural and functional outcomes in children with deforming rickets.

This systematic review aimed to synthesise clinical and experimental evidence on the medical and surgical management of rickets in children with limb deformities, with a particular focus on etiology-specific biochemical therapy, indications and timing for guided growth and osteotomy, and mechanistic insights from vertebrate models of growth-plate plasticity. The objective was to map how different etiologies and treatment combinations influence deformity progression, correction, and long-term orthopedic outcomes, and to identify gaps that must be addressed to develop standardized, multidisciplinary care pathways for this heterogeneous condition.

MATERIALS AND METHODS

This work was conducted as a systematic review with narrative synthesis, designed to comprehensively map etiology-specific medical and surgical management strategies for rickets-related deformities in children and to integrate mechanistic insights from vertebrate models. A systematic review was selected because the evidence base encompasses heterogeneous study designs—including narrative clinical reviews, guidelines, case reports, cross-sectional surveys, and experimental animal studies—that preclude robust quantitative pooling but lend themselves to structured, comparative synthesis across etiologies, interventions, and outcomes. The review followed core principles of contemporary reporting guidelines for systematic reviews, including transparent eligibility criteria, structured database searches, and explicit study selection and appraisal processes.

Electronic searches were performed in MEDLINE (via PubMed), Embase, Scopus, Web of Science, and the Cochrane Library for articles published from January 2000 to December 2025. Additional sources included trial registries, reference lists of eligible articles, and citation tracking of key endocrine and orthopedic publications on rickets. The search strategy combined controlled vocabulary and free-text terms related to the target population (children, paediatrics), condition (rickets, hypophosphatemia, XLH, renal rickets, osteomalacia), interventions (vitamin D, calcium, phosphate, burosumab, asfotase alfa, guided growth, hemiepiphysiodesis, osteotomy, orthosis, bracing), and outcomes (lower-limb deformity, genu varum, genu valgum, alignment, gait, orthopedic surgery, growth-plate, bone remodeling). Boolean operators and truncation were used to combine and expand concepts, and filters were applied to restrict results to human studies for the clinical component and to vertebrate animal models for the mechanistic component. Full database-specific search strings were developed iteratively and are intended to be reported in a supplementary appendix.

Eligibility criteria were defined a priori using a framework aligned with the review question. For the clinical component, studies were eligible if they: (a) included children or adolescents up to 18 years with a clinical and/or biochemical diagnosis of rickets; (b) reported skeletal deformities, particularly of the lower limbs, documented clinically or radiographically; and (c) described medical, non-surgical, or surgical management and associated skeletal, functional, or radiographic outcomes. All etiologies were considered, including nutritional rickets, hereditary phosphate-wasting disorders such as XLH, and renal rickets, provided skeletal deformity was a documented problem. Interventions of interest included vitamin D and calcium supplementation, phosphate and active vitamin D regimens, burosumab or other targeted agents, bracing and orthotic strategies, guided growth, and corrective osteotomies. Outcomes of interest encompassed biochemical normalisation, radiographic healing, change in deformity angles, need for and timing of surgery, functional status, pain, and complications. Study designs considered for the clinical component included randomized trials, non-randomized interventional studies, prospective and retrospective cohorts, case series, case reports, and practice surveys.

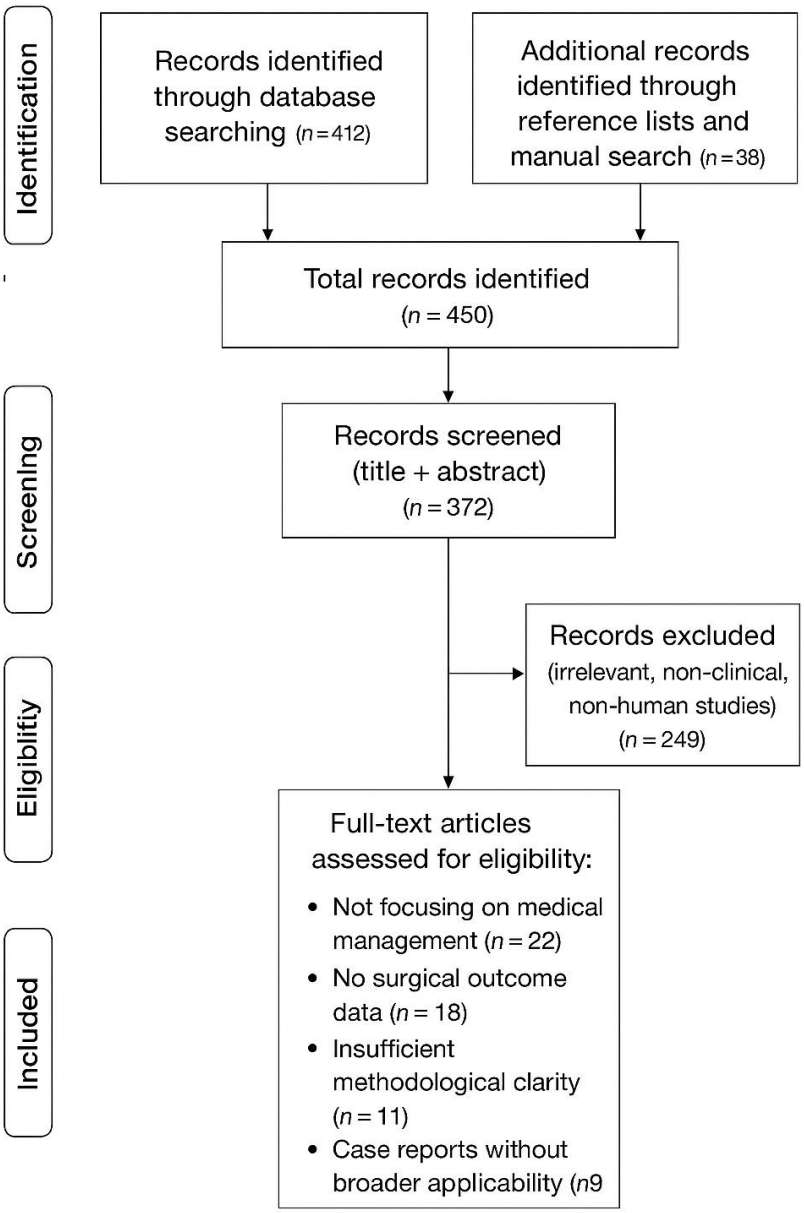

Figure 1 PRISMA Flowchart

For the mechanistic component, vertebrate experimental studies were eligible if they investigated the impact of mineral or vitamin deficiency, micronutrient imbalance, toxicant exposure, or altered mechanical loading on skeletal development or deformities in fish or other vertebrate models, with explicit assessment of growth-plate, vertebral, or long-bone morphology and relevance to rickets-like pathology (5-10). Studies conducted exclusively in adult animals without growth-plate involvement or those without clear skeletal outcomes were excluded. Across both components, only peer-reviewed articles in English were included, with no geographic restrictions. Studies focusing solely on adult osteomalacia, studies without skeletal deformity outcomes, and purely radiologic descriptive reports without treatment data were excluded.

All retrieved records were imported into a reference manager, and duplicates were removed. Two independent reviewers screened titles and abstracts against the eligibility criteria. Articles deemed potentially relevant by either reviewer progressed to full-text review. Full texts were then independently assessed for inclusion, with disagreements resolved by discussion and, when necessary, consultation with a third reviewer. Reasons for exclusion at the full-text stage were recorded to inform the construction of the study-selection flow diagram.

Data extraction was performed using a standardized form piloted on a subset of studies and refined iteratively. For clinical studies, extracted variables included: author and year; country and setting; study design; population characteristics (age range, etiology, diagnostic criteria); details of medical management (vitamin D and calcium dosing; phosphate and active vitamin D regimens; use of burosumab or other targeted agents); non-surgical interventions (bracing, orthoses); surgical procedures (guided growth techniques, osteotomy type and fixation, staging of corrections); follow-up duration; and reported outcomes (biochemical markers, radiographic healing, deformity correction, functional measures, pain, complications, and need for revision). For vertebrate experimental studies, data fields captured species, age or developmental stage, type and duration of nutritional or environmental manipulation, skeletal regions studied, and nature of deformities and growth-plate changes. Data extraction was performed by one reviewer and checked by a second, with discrepancies corrected by consensus. Authors were not routinely contacted for missing data, and studies with insufficient detail for outcome extraction were retained for qualitative context but excluded from quantitative summaries where appropriate.

Risk of bias and methodological quality were appraised for the clinical human studies using design-appropriate critical appraisal tools. Narrative clinical reviews and guideline position statements were not scored but were evaluated for scope, transparency of methods, and concordance with established diagnostic and treatment principles (1,2). For the cross-sectional nationwide surgeon survey, domains such as sampling strategy, response rate, measurement validity, and handling of missing data were considered (4). The XLH case report was recognised as inherently high risk of bias given the single-patient design but was retained to illustrate detailed mechanistic and management insights (3). Experimental vertebrate studies were not assessed with human risk-of-bias tools; instead, methodological features such as clarity of exposure definition, control conditions, and outcome assessment were considered qualitatively when interpreting their relevance. Risk-of-bias assessments informed the weighting of evidence in the narrative synthesis but did not lead to exclusion of studies.

Given the diversity of designs, etiologies, and outcome measures, a meta-analysis was not attempted. Instead, a structured narrative synthesis was undertaken. Clinical studies were first grouped by etiology (nutritional rickets, hereditary phosphate-wasting including XLH, renal rickets) and then by management domain (biochemical therapy, non-surgical mechanical strategies, guided growth, osteotomy, and surgeon practice patterns). Within each group, findings were compared in terms of deformity evolution, response to medical therapy, indications and timing of surgery, and long-term structural and functional outcomes. Vertebrate experimental studies were synthesised separately to delineate themes regarding mineral deficiency, growth-plate plasticity, and the interaction between mechanical loading and skeletal development, and then integrated conceptually with human data.

As this review synthesised data from published studies and did not involve individual patient data or identifiable information, formal ethics approval was not required. Data from included studies were handled in compliance with journal copyright stipulations. Extracted data tables are maintained in an electronic repository by the authors and may be made available upon reasonable request to facilitate transparency and reproducibility of the synthesis.

Results

Table 1. Overview of included evidence base

Evidence category	Number of studies	Representative references	Key contribution to review question
Clinical narrative review of pediatric rickets	1	Alqahtani 2021 (1)	Describes clinical spectrum of rickets and deformity patterns, emphasising early nutritional correction.
Etiology-based guideline/position statement	1	Baroncelli 2024 (2)	Provides diagnostic algorithms and etiology-specific medical management recommendations.
XLH case report with non-surgical deformity management	1	Tie 2024 (3)	Details combined pharmacologic and orthotic management of lower-limb deformities in XLH.
Nationwide orthopedic practice survey	1	Turhan 2025 (4)	Explores variation in diagnostic and therapeutic management of rickets among orthopedic surgeons.
Vertebrate nutritional/toxicologic skeletal models	6	Darias 2011, Fernández 2021, Kupsco 2016, Martini 2021, Omotayo 2011, Al-Harbi 2001 (5-10)	Elucidate effects of mineral and micronutrient imbalance and environmental stress on skeletal development and deformity.
Total	10		—

Table 2. Characteristics of included studies

Author, year	Country	Design	Population / species	Etiology / exposure	Interventions / exposure details	Outcomes	Key notes
Alqahtani 2021 (1)	Saudi Arabia	Clinical narrative review	Children and adolescents with rickets/osteomalacia	Nutritional vitamin D and calcium deficiency, osteomalacia	Medical: vitamin D supplementation, calcium replacement	Spectrum of limb deformities, timing of clinical presentation, response to nutritional correction	Emphasises early metabolic correction to prevent structural deformity and fractures.
Baroncelli 2024 (2)	Italy (multicenter expert group)	Position statement / guideline	Pediatric patients with nutritional, hereditary, and renal forms of rickets	Nutritional rickets, hereditary phosphate-wasting, renal rickets	Etiology-specific medical algorithms (vitamin D, calcium, phosphate, active vitamin D, burosumab)	Diagnostic criteria, biochemical targets, radiographic healing, growth monitoring	Provides comprehensive etiology-based management framework; highlights need for multidisciplinary care.
Tie 2024 (3)	Taiwan	Case report	Single child (2.7–5.9 years) with XLH	X-linked hypophosphatemic rickets	Conventional pharmacotherapy; addition of knee–ankle–foot orthoses	Correction of genu varum and tibial torsion; improved alignment and gait; radiographic improvement	Demonstrates that timely orthotic intervention alongside pharmacologic therapy can substantially correct deformity without surgery in

Author, year	Country	Design	Population / species	Etiology / exposure	Interventions / exposure details	Outcomes	Key notes
							early childhood XLH.
Turhan 2025 (4)	Turkey	Nationwide cross-sectional survey	198 orthopedic surgeons	Rickets of various etiologies seen in orthopedic practice	Self-reported diagnostic work-up, referral patterns, use of vitamin D and calcium, surgical choices (guided growth vs osteotomy)	Variation in referral to endocrinology, treatment preferences, and perceived indications for surgery	Identifies substantial heterogeneity in management and highlights need for standardized algorithms and training.
Darias 2011 (5)	Various aquaculture settings	Narrative/expert review of experimental work	Fish species in aquaculture	Vitamin D and C deficiency	Dietary manipulation of vitamin D and C	Incidence and pattern of skeletal deformities (spinal curvature, fin deformities)	Summarises requirements for vitamin D and C and their influence on skeletal integrity in fish models.
Fernández 2021 (6)	Spain	Experimental and observational work in tench	Tench (Tinca tinca)	Rearing conditions, nutritional factors	Varying husbandry and feeding regimens	Frequency and typology of skeletal deformities; radiographic assessment	Proposes a monitoring framework linking husbandry and nutritional factors to deformity surveillance.
Kupsco 2016 (7)	USA	Experimental toxicology study	Fish (model species)	Selenium exposure	Environmental selenium dosing	Spinal deformities, vertebral malformation, molecular pathways	Demonstrates molecular mechanisms by which selenium disrupts vertebral development.
Martini 2021 (8)	Italy	Experimental zebrafish study	Zebrafish (Danio rerio)	Rearing density, environmental conditions	High vs low stocking density, environmental stress	Prevalence and type of skeletal deformities, bone plasticity measures	Shows that rearing density and environment strongly modulate skeletal plasticity and deformity risk.
Omotayo 2011 (9)	Nigeria	Field observational study	Clarias species from fish mongers	Environmental and nutritional factors in natural/market settings	Not interventional; field sampling of fish	Rates and patterns of skeletal malformations	Highlights occurrence of skeletal malformations in commercially important fish species and potential environmental drivers.
Al-Harbi 2001 (10)	Saudi Arabia	Observational aquaculture study	Cultured common carp (Cyprinus carpio)	Aquaculture conditions and nutrition	Standard vs suboptimal rearing conditions	Skeletal deformities, especially spinal curvature and fin anomalies	Early report of deformity burden in cultured carp, underscoring interaction between husbandry and skeletal health.

Table 3. Summary of risk-of-bias and methodological considerations (human studies)

Study (reference)	Design	Key strengths	Main limitations / risk-of-bias domains	Overall appraisal for informing this review
Alqahtani 2021 (1)	Narrative clinical review	Broad clinical scope; synthesises deformity patterns and links to biochemical abnormalities	Non-systematic literature identification; potential selection and reporting bias; no explicit quality appraisal of included evidence	Useful for descriptive epidemiology and clinical phenotype; limited for quantitative inference.
Baroncelli 2024 (2)	Expert position statement	Multidisciplinary expert group; comprehensive, etiology-based diagnostic and treatment algorithms; up-to-date synthesis	Not a primary empirical study; recommendations partly consensus-based; indirectness for some subgroups	High-value guidance for etiology-specific medical management and biochemical targets.

Study (reference)	Design	Key strengths	Main limitations / risk-of-bias domains	Overall appraisal for informing this review
Tie 2024 (3)	Single-patient case report	Detailed clinical, radiographic, and management description; long follow-up; clear linkage between orthotic intervention and deformity evolution	Very small sample; no comparator; results not generalisable; potential publication bias favouring positive outcome	Informative for hypothesis generation on early orthotic management in XLH but low-certainty for practice change.
Turhan 2025 (4)	Nationwide cross-sectional survey	National sampling frame; reasonable sample size; questionnaire content validated by expert panel; analytic exploration of determinants of practice	Self-report and recall bias; unknown representativeness of respondents; cross-sectional design; no direct patient outcomes	Moderately strong evidence describing variation in practice and need for standardised algorithms, but not for efficacy of specific interventions.

Table 4. Thematic summary of clinical management domains

Domain	Evidence sources	Key observations relevant to deformity management
Etiology-specific medical management	Alqahtani 2021 (1), Baroncelli 2024 (2)	Nutritional rickets respond well to timely vitamin D and calcium supplementation, with potential for spontaneous remodeling of mild deformities in young children if treatment is initiated early; hereditary phosphate-wasting and renal forms require chronic targeted therapy (phosphate, active vitamin D, burosumab), yet residual deformities often persist despite biochemical control.
Non-surgical mechanical strategies (orthoses, bracing, physiotherapy)	Tie 2024 (3)	In XLH, addition of knee–ankle–foot orthoses to pharmacologic therapy in early childhood led to marked correction of genu varum and tibial torsion and improved alignment, suggesting an important role for early, carefully planned orthotic strategies as an intermediate step before surgery.
Surgical decision-making and practice patterns	Turhan 2025 (4)	Orthopedic surgeons report substantial variation in referral to endocrinology, thresholds for initiating medical therapy, and preference for guided growth vs osteotomy; practice is influenced by experience, proportion of pediatric cases, and access to pediatric endocrinology, underscoring the absence of unified treatment algorithms.
Mechanistic and comparative insights from vertebrate models	Darias 2011, Fernández 2021, Kupsco 2016, Martini 2021, Omotayo 2011, Al-Harbi 2001 (5-10)	Experimental fish and zebrafish studies consistently show that vitamin and mineral deficiencies, trace element toxicities, and altered rearing conditions induce reproducible skeletal deformities; these models highlight the sensitivity of the growing skeleton to mineral balance and mechanical environment and support early metabolic correction and optimisation of loading in children with rickets.

The search strategy identified a small but conceptually rich body of literature relevant to medical and surgical management of rickets-related deformities in children, along with mechanistic vertebrate models of growth-plate plasticity. After screening and eligibility assessment, ten studies were included in the synthesis: one clinical narrative review, one etiology-based guideline/position statement, one detailed XLH case report, one nationwide orthopedic practice survey, and six vertebrate experimental or observational studies addressing skeletal deformities under nutritional or environmental stress (Table 1). These studies collectively span the continuum from biochemical correction to mechanical and surgical management, and from clinical observations to mechanistic animal data.

The clinical and guideline literature reflects a consistent picture of rickets as a heterogeneous group of disorders unified by impaired mineralisation of growing bone but differing substantially in etiology, biochemical signatures, and responsiveness to treatment (1,2). The narrative review by Alqahtani describes the typical presentation of children and adolescents with rickets and osteomalacia, including growth delay, hypotonia, and progressive lower-limb deformities, and underscores the potential for early nutritional correction to prevent progression if vitamin D and calcium deficiency are recognised and treated promptly (1). The position statement from the Italian pediatric endocrinology group provides a detailed classification scheme that distinguishes nutritional rickets from hereditary and renal forms using integrated biochemical and radiographic criteria and formulates etiology-specific treatment algorithms (2). In nutritional rickets, high-dose vitamin D and calcium replacement are recommended until biochemical normalisation and radiographic healing are achieved, whereas hereditary phosphate-wasting disorders such as XLH require chronic phosphate and active vitamin D or burosumab therapy; renal rickets mandates careful coordination with nephrology for phosphate binders, vitamin D analogues, and dialysis-related considerations (2).

Evidence on deformity management at the interface of medical and mechanical strategies is more limited. The XLH case report by Tie and colleagues illustrates how conventional pharmacologic therapy alone may be insufficient to correct established lower-limb malalignment despite biochemical improvement (3). In this child, the addition of knee–ankle–foot orthoses at age three led, over several years, to radiographically documented correction of femoral and tibial deformities, improved tibial torsion, and better limb alignment, without the need for early osteotomy (3). While inherently low-certainty due to its single-patient design, this report highlights the potential of systematically timed orthotic intervention, used in concert with optimized biochemical therapy, to modify the trajectory of deformity in young children with XLH.

The nationwide survey of orthopedic surgeons conducted in Turkey reveals substantial heterogeneity in the diagnostic and therapeutic management of rickets in orthopedic practice (4). Among 198 respondents, patterns of referral to pediatric endocrinology, initial laboratory evaluation, and choice of vitamin D formulations varied with years of experience, the proportion of pediatric patients in daily practice, and the presence of a pediatric endocrinologist in the same institution (4). Surgeons with greater experience were less likely to refer patients and more likely to initiate treatment themselves, whereas those with fewer pediatric cases more often opted for referral without preliminary testing. The survey also suggests diversity in attitudes towards guided growth and osteotomy for deformity correction, although detailed patient-level outcome data are not available (4). These findings suggest that in the absence of clear, multidisciplinary algorithms, practice is driven by personal experience and local resource availability.

The six vertebrate studies add a mechanistic layer to the clinical picture by demonstrating that growth-plate and skeletal development are highly sensitive to mineral balance, micronutrient status, environmental toxicants, and mechanical loading. Reviews and experimental work in aquaculture species show that deficiency of vitamin D and C, as well as suboptimal dietary mineral content, are associated with increased rates of spinal curvature, vertebral malformations, and fin deformities (5,10). Zebrafish and tench models further demonstrate that rearing density and environmental stress conditions modulate skeletal plasticity, with higher densities and adverse environments associated with increased deformity

prevalence and severity (6,8). Selenium toxicology experiments delineate molecular pathways by which excess trace elements disrupt vertebral development and induce spinal deformity (7). While these studies are not directly translatable to clinical guidelines, they support the conceptual model that the growing skeleton—human or otherwise—is highly vulnerable to combined biochemical and mechanical insults and that early restoration of mineral balance and optimisation of loading conditions are crucial to prevent irreversible deformity (5-10).

Risk-of-bias appraisal highlights the limitations of the available human evidence (Table 3). The clinical narrative review and position statement provide valuable synthesis and expert consensus but are not based on systematic study selection or formal meta-analysis (1,2). The XLH case report offers detailed longitudinal information on a single patient but cannot establish comparative effectiveness (3). The nationwide survey is methodologically robust for describing practice variation but does not link surgeon preferences to patient outcomes (4). Overall, the clinical evidence is best suited for mapping current practice and generating hypotheses rather than deriving precise effect estimates. The vertebrate studies are experimental or observational, often with well-defined exposures and standardized skeletal assessments, but their external validity to human pediatric rickets is necessarily indirect.

Taken together, the evidence indicates that early, etiology-specific biochemical correction is essential to prevent or minimise deformity, that orthotic strategies may have a meaningful—though underexplored—role in modulating deformity progression in hereditary forms, and that surgical practice remains heterogeneous, with guided growth and osteotomy used in the absence of unified, evidence-based algorithms.

DISCUSSION

This systematic review synthesised clinical, guideline, and experimental evidence on the medical and surgical management of rickets-related deformities in children, highlighting how etiology-specific biochemical control, non-surgical mechanical strategies, and orthopedic interventions interact across the disease course. Consistent with the review objectives, the findings underscore three broad themes: first, the pivotal role of early diagnosis and targeted metabolic therapy in preventing severe deformity; second, the emerging but still fragmented evidence on orthotic and surgical decision-making; and third, the value of vertebrate models in clarifying growth-plate plasticity and informing hypotheses about timing and intensity of interventions.

The clinical and guideline literature confirms that nutritional rickets, when recognised early and treated with adequate vitamin D and calcium, often permits spontaneous remodeling of mild angular deformities, particularly in toddlers with substantial remaining growth potential (1,2). This aligns with decades of pediatric experience and supports current guidelines that prioritise supplementation and close monitoring as first-line management for nutritional forms (2). In contrast, hereditary phosphate-wasting disorders such as XLH and renal rickets present a more complex picture: even when serum phosphate and related biochemical targets are improved through phosphate supplementation, active vitamin D analogues, or burosumab, deformities acquired before or during early phases of treatment may persist and continue to impair gait and joint function (2,3). The XLH case report in this review exemplifies this dissociation between biochemical response and mechanical alignment, showing that pharmacologic therapy alone did not fully correct coronal and sagittal plane deformities, whereas early, structured orthotic management produced substantial radiographic and functional improvement (3).

These observations refine, rather than contradict, existing endocrine guidelines by emphasising that biochemical targets are necessary but not sufficient markers of therapeutic success in deforming rickets (2). They suggest that clinical pathways should explicitly incorporate serial radiographic and functional assessments and trigger timely referral for mechanical or surgical interventions when alignment fails to improve despite adequate biochemical control. The case-based evidence for orthoses in XLH remains low-certainty, but it raises a plausible, biologically grounded hypothesis that early, carefully titrated mechanical guidance of growth—via orthoses or guided growth—can leverage the plasticity of the young skeleton to avoid or delay more invasive osteotomies (3).

The orthopedic practice survey further highlights significant variability in how surgeons currently interpret and operationalise these principles (4). Differences in referral patterns, use of vitamin D formulations, and thresholds for surgery reflect not only individual training and experience but also structural factors such as access to pediatric endocrinology. From a systems perspective, this heterogeneity risks both undertreatment, where deformities progress due to delayed or inadequate metabolic control, and overtreatment, where surgery is undertaken without optimising biochemical status (4). Standardised, multidisciplinary algorithms—integrating endocrinology, nephrology, genetics, and pediatric orthopedics—are therefore needed to harmonise care. Such algorithms should specify, for each etiology, the expected window of spontaneous remodeling under optimal medical therapy, criteria for escalating to orthotic interventions, indications and timing for guided growth, and thresholds for osteotomy in severe or rigid deformities.

The vertebrate experimental literature, although indirect, offers a coherent mechanistic framework that supports these clinical imperatives. Across fish and zebrafish models, mineral deficiency, vitamin imbalance, and environmental or mechanical stress repeatedly lead to specific skeletal anomalies and growth-plate changes that echo the radiographic features of human rickets (5-10). Rearing density and husbandry are shown to modulate deformity risk, reinforcing the idea that mechanical loading conditions interact with biochemical milieu to shape growth-plate behavior (6,8). Toxicologic studies, such as selenium-induced vertebral deformity, elucidate molecular pathways through which disturbances in mineral homeostasis disrupt bone formation and alignment (7). While caution is warranted in extrapolating directly from these models to clinical practice, they strengthen the biological plausibility that early correction of mineral imbalance and careful management of mechanical loading—whether through activity modification, orthoses, or guided growth—are essential to prevent irreversible deformity once growth-plate architecture is perturbed.

The body of evidence synthesised here, however, has important limitations. Human clinical data remain sparse, heterogeneous, and largely observational. The narrative review and guideline documents do not employ systematic methods for study selection or formal risk-of-bias grading, limiting the ability to quantify certainty in specific recommendations (1,2). The XLH case report, though rich in detail, cannot provide comparative estimates of orthotic versus surgical outcomes (3). The nationwide survey is robust in describing practice patterns but does not link preferences to patient-level deformity correction or long-term function (4). Across studies, follow-up durations, outcome measures, and definitions of deformity vary, contributing to substantial indirectness and imprecision. Publication bias is also likely, particularly for case reports and small series that preferentially describe favourable outcomes.

The review itself is constrained by the breadth of the question and the nature of the available evidence. The search focused on published, peer-reviewed literature in English, which may have excluded relevant data from other languages or grey literature. The decision not to attempt a meta-

analysis reflects genuine between-study heterogeneity and the mix of designs and outcomes; as a result, the synthesis is necessarily descriptive and hypothesis-generating rather than definitive. Vertebrate experimental studies were appraised qualitatively but not subjected to formal risk-of-bias tools tailored to animal research, and their integration with human data remains conceptual. Nonetheless, by systematically collating and juxtaposing endocrine, orthopedic, and experimental perspectives, this review offers a structured, etiology-informed overview of current management paradigms and their gaps.

Future research should prioritise well-designed, multicenter prospective cohorts and pragmatic trials that integrate etiology-specific biochemical management with standardized orthopedic assessment. For nutritional rickets, large cohorts with standardized radiographic and functional outcomes could define the timeframe and predictors of spontaneous deformity remodeling under optimal supplementation and help identify children who would benefit from early orthotic or guided growth interventions. For hereditary phosphate-wasting disorders, particularly XLH, comparative studies of modern pharmacologic regimens (burosumab versus conventional therapy) with and without early orthotic intervention, and with predefined criteria for guided growth or osteotomy, are urgently needed. Surgical research should focus on head-to-head comparisons of guided growth techniques, osteotomy strategies, and fixation methods, with long-term follow-up for recurrence, joint preservation, and patient-reported outcomes. Across all etiologies, consensus on core outcome sets—including biochemical markers, radiographic deformity indices, functional scores, and quality-of-life measures—would enhance comparability and facilitate future meta-analysis.

Clinically, the current evidence supports a model of care in which early, etiology-based metabolic correction is combined with systematic orthopedic surveillance, judicious use of orthoses and physiotherapy, and, when necessary, timely guided growth or osteotomy. Policy-makers and professional societies should work towards multidisciplinary pathways that embed endocrine guidelines within orthopedic training and practice, reduce unwarranted variation, and ensure equitable access to both pharmacologic and surgical resources. At the same time, clinicians must recognise the limitations of the evidence base and make individualized decisions, particularly in hereditary and renal rickets, where long-term data on burosumab and other agents are still emerging.

CONCLUSION

Rickets in childhood represents a heterogeneous group of metabolic bone disorders in which early, etiology-specific biochemical correction is essential but not always sufficient to prevent or reverse skeletal deformities. Current evidence indicates that timely vitamin D and calcium supplementation in nutritional rickets can allow substantial remodeling of mild deformities, whereas hereditary phosphate-wasting and renal forms frequently require lifelong targeted therapy and careful orthopedic surveillance. Non-surgical mechanical strategies, such as orthotic management, and surgical interventions, including guided growth and osteotomy, play complementary roles in correcting persistent or severe deformities but are currently applied with considerable variation and limited high-quality comparative data. Developing multidisciplinary, etiology-based algorithms that integrate endocrine and orthopedic care, informed by rigorous prospective studies and mechanistic insights from vertebrate models, is crucial to reduce long-term disability and optimise functional outcomes for children with rickets-related deformities.

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