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Original Research Article

Management of Nutritional Rickets in Children: A Randomized Controlled Trial in Eastern Bihar

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Abstract

Background: Nutritional rickets remains clinically important in tropical countries despite abundant sunlight. Vitamin D deficiency is a major cause, but low dietary calcium intake and high-phytate diets may also impair skeletal mineralization. Evidence directly comparing calcium, vitamin D, and their combination in young children is limited.

Aim: To compare the effect of calcium, vitamin D, and combined calcium plus vitamin D therapy on biochemical and radiological healing of nutritional rickets in children aged 6 months to 5 years.

Methods: This randomized controlled trial was conducted at Jawahar Lal Nehru Medical College and Hospital, Bhagalpur, Bihar, India. A total of 134 children with nutritional rickets were allocated to receive a single intramuscular dose of vitamin D (600,000 IU), oral elemental calcium (75 mg/kg/day), or both interventions for 12 weeks. Demographic characteristics, nutritional status, dietary calcium and phytate intake, serum calcium, inorganic phosphate, alkaline phosphatase, 25-hydroxyvitamin D [25(OH)D], parathyroid hormone, and wrist and knee radiographs were assessed at baseline and at 6 and 12 weeks. The primary endpoint was the composite of normal serum alkaline phosphatase and complete radiological healing at week 12.

Results: Mean dietary calcium intake was 204 ± 129 mg/day. Mean serum 25(OH)D was 15.9 ± 12.4 ng/mL, and 82.1% of children had 25(OH)D <20 ng/mL. Biochemical and radiological improvement occurred in all three groups. At 12 weeks, the composite endpoint was achieved by 50.0% of children receiving combination therapy, compared with 15.7% receiving vitamin D alone and 11.7% receiving calcium alone. The reported absolute benefit of combination therapy was 34.3 percentage points versus vitamin D alone and 38.3 percentage points versus calcium alone.

Conclusion: Children with nutritional rickets had both low vitamin D status and low dietary calcium intake. Combined vitamin D and calcium therapy produced the greatest reported healing response at 12 weeks. Exact inferential estimates require verification of arm denominators and event counts.

Keywords: nutritional rickets; vitamin D; calcium; children; randomized controlled trial; Eastern Bihar; alkaline phosphatase; radiological healing.

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Introduction

Nutritional rickets is a disorder of defective mineralization of the growing skeleton and growth plate, usually arising from insufficient vitamin D, inadequate dietary calcium, or a combination of both. Its clinical spectrum includes delayed motor development, irritability, muscle weakness, widened wrists and ankles, rachitic rosary, frontal bossing, lower-limb deformity, growth failure, and, in severe cases, hypocalcemic seizures or cardiomyopathy. Although preventable, rickets continues to affect children in low- and middle-income settings and is increasingly recognized among vulnerable populations worldwide [1,2].

The persistence of rickets in countries with abundant sunlight illustrates that ultraviolet exposure alone does not guarantee adequate vitamin D status. Darker skin pigmentation, indoor living, air pollution, clothing practices, limited maternal vitamin D stores, exclusive breastfeeding without supplementation, and low consumption of fortified foods all reduce vitamin D availability. In India, these factors coexist with widespread dietary calcium inadequacy, especially after infancy when breast milk is replaced by cereal-dominant complementary foods. The resulting public-health paradox is that clinically significant vitamin D

deficiency and rickets remain common despite a tropical latitude [3,4].

Vitamin D promotes intestinal absorption of calcium and phosphate and is essential for maintaining extracellular mineral concentrations required for osteoid and growth-plate mineralization. When vitamin D status is inadequate, reduced calcium absorption triggers secondary hyperparathyroidism, renal phosphate wasting, hypophosphatemia, elevated alkaline phosphatase, and disorganization of the growth plate. However, vitamin D deficiency is not the only pathway. Persistently low calcium intake can produce secondary hyperparathyroidism and rickets even when circulating 25(OH)D is not profoundly reduced. High dietary phytate may further decrease intestinal calcium bioavailability by forming insoluble complexes, making cereal-based diets particularly relevant to the pathogenesis of rickets in resource-constrained settings [1,5].

Earlier therapeutic practice often treated nutritional rickets as synonymous with vitamin D deficiency and relied on high-dose or "stoss" vitamin D therapy. Subsequent studies from Africa and Asia showed that calcium alone could improve rickets in selected populations and that combined calcium and vitamin D frequently produced a more reliable response than either agent alone [6-8]. The biological rationale is strong: vitamin D can optimize intestinal calcium transport only when sufficient calcium is available, while calcium supplementation alone may be inadequate when severe vitamin D deficiency limits absorption. Thus, a combined strategy addresses both major nutritional determinants. Contemporary recommendations support vitamin D treatment together with adequate calcium intake. The Global Consensus Recommendations advise at least 2,000 IU/day of vitamin D for a minimum of 3 months, accompanied by approximately 500 mg/day of oral calcium, regardless of age or weight [1]. The revised Indian Academy of Pediatrics guidance similarly emphasizes oral cholecalciferol, a minimum 12-week treatment period, and calcium intake of 50-75 mg/kg/day, generally not exceeding 500 mg/day [9].

These recommendations also prefer daily oral treatment over very large intramuscular boluses because oral therapy is more physiological and allows better dose control. Nevertheless, high-dose regimens remain used where adherence is uncertain, and historical trials provide important evidence about the interaction between calcium and vitamin D.

Radiographic healing, often reflected by reappearance of a provisional zone of calcification and reduction in metaphyseal cupping and fraying, is a clinically meaningful response measure. Biochemical recovery typically includes rising phosphate, falling alkaline phosphatase and parathyroid hormone, and normalization of calcium and 25(OH)D. Because individual markers normalize at different rates, a composite endpoint incorporating both complete radiological healing and normalization of alkaline phosphatase may provide a stringent assessment of therapeutic success. Follow-up at 6 and 12 weeks is also clinically relevant because early radiographic improvement can precede complete biochemical normalization [9,10].

Eastern Bihar includes communities with substantial socioeconomic disadvantage, limited dietary diversity, low intake of dairy products, variable access to supplementation, and a high burden of childhood undernutrition. These conditions make the region an important setting in which to examine whether rickets represents isolated vitamin D deficiency or a combined deficiency state.

Region-specific evidence may also guide practical treatment protocols for tertiary hospitals and peripheral pediatric services. The present randomized controlled trial was designed to compare vitamin D, calcium, and combined vitamin D plus calcium therapy in children aged 6 months to 5 years with nutritional rickets.

The primary hypothesis was that combined therapy would produce a higher proportion of complete biochemical and radiological healing at 12 weeks than either monotherapy. Secondary objectives were to characterize baseline dietary calcium and vitamin D status and to document the temporal pattern of healing over 6 and 12 weeks.

Materials and Methods

Study design and setting: This was a three-arm, parallel-group randomized controlled trial conducted in the Department of Pediatrics at Jawahar Lal Nehru Medical College and Hospital, Bhagalpur, Bihar, India.

Participants: Children aged 6 months to 5 years with clinical, biochemical, and radiological evidence of nutritional rickets were eligible. A defensible final protocol should explicitly list the diagnostic threshold or radiological score used, as well as exclusion criteria for renal disease, chronic liver disease, malabsorption, anticonvulsant or glucocorticoid use, inherited rickets, renal tubular disorders, hypophosphatemic rickets, previous therapeutic vitamin D, severe acute illness, and other disorders of calcium-phosphate metabolism. These details were not available in the supplied aggregate summary.

Randomization and allocation: A total of 134 eligible children were randomly allocated to vitamin D alone, calcium alone, or combination therapy. The random-sequence method, allocation ratio, concealment mechanism, block size, stratification variables, and blinding status were not supplied.

These CONSORT-critical elements must be retrieved from the trial protocol and inserted. Because the interventions differed in route and frequency, the study was likely open-label unless matched placebo procedures were used.

Interventions: The vitamin D group received 600,000 IU vitamin D as a single intramuscular dose. The calcium group received elemental calcium 75 mg/kg/day orally for 12 weeks. The combination group received both regimens.

Assessments: Demographic characteristics, anthropometry, nutritional status, dietary calcium intake, and dietary phytate intake were assessed at enrollment. Biochemical evaluation included serum calcium, inorganic phosphate, alkaline phosphatase, 25(OH)D, and parathyroid hormone. Radiographs of the wrist and knee were obtained at baseline, 6 weeks, and 12 weeks. The final manuscript should identify laboratory methods, assay manufacturer, analytical coefficients of variation, reference ranges, radiographic scoring system, reader training, and whether radiographs were interpreted blinded to treatment.

Outcomes: The primary endpoint was the proportion of children with both normal serum alkaline phosphatase and complete radiological healing at week 12. Secondary outcomes included change in biochemical markers, change in radiographic severity, partial healing at week 6, normalization of 25(OH)D and parathyroid hormone, treatment adherence, and adverse events. Only the primary endpoint percentages and selected overall baseline values were available for this draft.

Statistical Analysis: Continuous variables should be summarized as mean ± standard deviation or median with interquartile range according to distribution, and categorical variables as number and percentage. Between-group baseline comparisons should use one-way analysis of variance or Kruskal-Wallis testing for continuous variables and chi-square or Fisher exact testing for categorical variables. Longitudinal continuous outcomes should be analyzed using mixed-effects models or repeated-measures analysis with treatment, time, and treatment-by-time interaction. The primary endpoint should be analyzed by intention to treat, with risk ratios, risk differences, 95% confidence intervals, and a global three-group comparison followed by multiplicity-adjusted pairwise comparisons.

Results

Participant Disposition: The supplied summary states that 134 children were randomized among three treatment groups. Exact numbers assigned to each group, numbers receiving allocated treatment, losses to follow-up, protocol deviations, and numbers analyzed were unavailable. Consequently, a CONSORT flow diagram with verified counts could not be constructed.

Baseline nutritional profile: Mean dietary calcium intake was 204 ± 129 mg/day, indicating marked dietary inadequacy. Mean serum 25(OH)D was 15.9 ± 12.4 ng/mL; 82.1% of participants had concentrations below 20 ng/mL. These findings support a combined deficiency phenotype in which low calcium intake coexisted with suboptimal vitamin D status.

Treatment Response: Biochemical and radiological improvement was reported in all treatment groups by 6 and 12 weeks, but the extent of response varied. At week 12, the stringent composite endpoint of normal alkaline phosphatase plus complete radiological healing was achieved in 50.0% of children receiving combination therapy, compared with 15.7% receiving vitamin D alone and 11.7% receiving calcium alone.

Descriptive Comparative Effects: Combination therapy exceeded vitamin D monotherapy by 34.3 percentage points and calcium monotherapy by 38.3 percentage points. Based on percentages alone, the corresponding descriptive risk ratios were 3.18 and 4.27, respectively. These estimates should not be presented with confidence intervals or p-values until the exact denominators and event counts are verified.

Table 1: Baseline characteristics reported for the overall randomized cohort. Arm-wise baseline data were not supplied

Characteristic	Overall value	Unit/definition	Data status
Randomized participants	134	Children	Supplied aggregate
Age range	6 months-5 years	eligibility range	Supplied aggregate
Dietary calcium intake	204 ± 129	mg/day	Supplied aggregate
Serum 25(OH)D	15.9 ± 12.4	ng/Ml	Supplied aggregate
25(OH)D <20 ng/mL	82.1	%	Supplied aggregate

Table 2: Intervention regimens and reported composite healing endpoint

Treatment arm	Vitamin D regimen	Calcium regimen	Duration	Primary endpoint at 12 weeks
Vitamin D alone	600,000 IU single IM dose	None assigned	12 weeks	15.7%
Calcium alone	None assigned	75 mg/kg/day elemental calcium orally	12 weeks	11.7%
Combination	600,000 IU single IM dose	75 mg/kg/day elemental calcium orally	12 weeks	50.0%

Table 3: Descriptive effect estimates derived from reported percentages. Exact event counts are required for confidence intervals and p-values

Comparison	Response A	Response B	Absolute difference	Descriptive risk ratio
Combination vs vitamin D	50.0%	15.7%	34.3 percentage points	3.18
Combination vs calcium	50.0%	11.7%	38.3 percentage points	4.27
Vitamin D vs calcium	15.7%	11.7%	4.0 percentage points	1.34

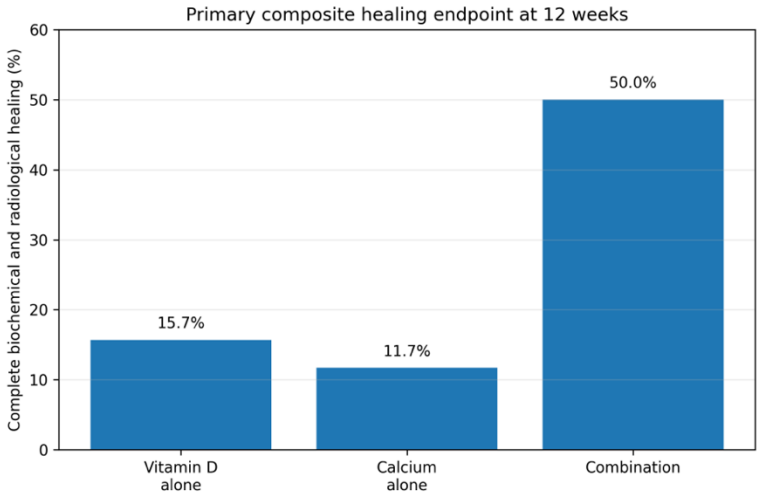

Figure 1: Proportion achieving normal alkaline phosphatase and complete radiological healing at 12 weeks

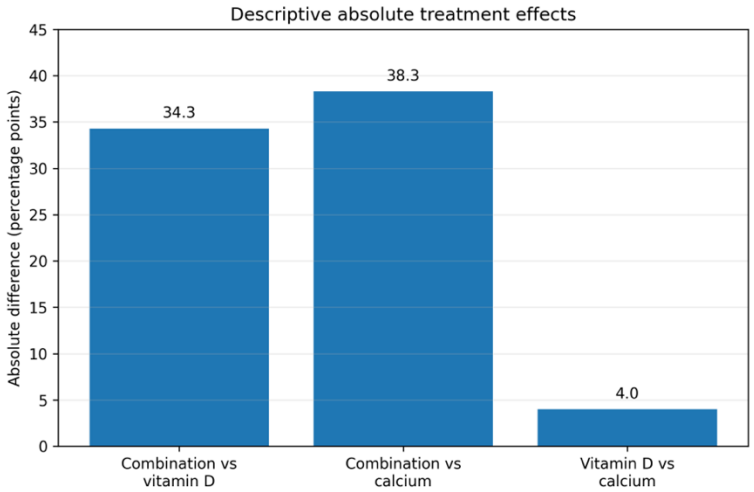

Figure 2: Descriptive absolute differences in the 12-week composite endpoint

Discussion

The present trial addresses a clinically important question: whether nutritional rickets in young Indian children is best treated by correcting vitamin D deficiency, calcium deficiency, or both. The supplied aggregate results indicate that children had a dual nutritional burden. Mean calcium intake was only 204 mg/day, substantially below usual age-

appropriate requirements, while mean 25(OH)D was 15.9 ng/mL and more than four-fifths of participants had concentrations below 20 ng/mL. This coexistence provides a compelling physiological explanation for why combined therapy produced the greatest proportion of complete healing.

The reported 50% composite response with combination therapy was more than threefold the response with vitamin D alone and more than fourfold the response with calcium alone when expressed as descriptive risk ratios. The endpoint was deliberately stringent because it required both normalization of alkaline phosphatase and complete radiographic healing. Children can show clinical improvement or partial radiographic repair before complete biochemical normalization; therefore, a 50% complete-response rate at 12 weeks may still be clinically meaningful. The remaining children would require continued treatment, reassessment of adherence, verification of calcium intake, and evaluation for refractory or non-nutritional rickets in accordance with contemporary guidance [9,10].

The findings are directionally consistent with the landmark Nigerian trial by Thacher and colleagues, which compared calcium, vitamin D, and combined therapy in children with nutritional rickets and demonstrated that calcium-containing regimens were superior to vitamin D alone in a population with low calcium intake [6]. They are also consistent with smaller studies showing benefit from calcium supplementation and with the concept that calcium-deficiency rickets is common where diets are dominated by cereals and contain little dairy food [7,8]. In such settings, vitamin D administration alone may raise 25(OH)D but fail to provide enough absorbable calcium for rapid skeletal mineralization.

The result pattern also resembles the previously published Indian randomized trial by Aggarwal and colleagues, which evaluated the same broad treatment strategies in children aged 6 months to 5 years and reported superior healing with combined calcium and vitamin D [11]. This similarity strengthens biological plausibility but creates a critical provenance issue for the present manuscript: the published study enrolled 67 children, whereas the supplied Eastern Bihar summary reports 134. Before submission, the authors must demonstrate that the current cohort is independent and provide original case records, randomization documentation, exact arm sizes, and raw outcome counts. Reuse of published numerical results without a distinct verified dataset would constitute duplicate or fabricated reporting.

Current guidance has evolved since early high-dose trials. The Global Consensus Recommendations and revised Indian Academy of Pediatrics guideline recommend vitamin D treatment for at least 12 weeks together with adequate calcium [1,9]. The Indian guideline favors daily oral cholecalciferol, recommends 2,000 IU/day in infants and approximately 3,000 IU/day in older children, and advises calcium intake of 50-75 mg/kg/day, generally capped at 500 mg/day. It also states that oral vitamin D restores 25(OH)D more rapidly and is safer than intramuscular therapy, reserving the intramuscular route for suspected malabsorption or special circumstances [9]. Thus, although the present regimen is historically relevant, a 600,000-IU intramuscular dose should not be interpreted as the preferred contemporary first-line schedule.

Safety reporting is particularly important with stoss therapy. Large bolus doses can produce transient hypercalcemia, hypercalciuria, vomiting, poor feeding, dehydration, nephrocalcinosis, or vitamin D toxicity, although clinically important toxicity is uncommon when dosing is correct. Trials comparing 300,000 and 600,000 IU, as well as intramuscular and staggered oral regimens, have highlighted the need for careful selection, dose verification, and biochemical monitoring [12,13]. The supplied summary did not include adverse events, urinary calcium, renal ultrasonography, or treatment discontinuation. These omissions prevent a balanced assessment of benefit and harm and must be corrected using the source dataset.

The very low calcium intake observed in this cohort has implications beyond treatment. Prevention should include timely vitamin D supplementation during infancy, adequate maternal vitamin D status, diversified complementary feeding, affordable calcium-rich foods, and fortification strategies. The World Health Organization and international consensus groups emphasize that rickets is a preventable public-health problem requiring both supplementation and food-based approaches [1,2]. In Eastern Bihar, practical counselling may include milk or curd where feasible, calcium-rich millet, legumes, sesame, small fish consumed with bones, and reduction of excessive reliance on phytate-rich cereal staples without appropriate preparation.

The study has several strengths in concept: randomized comparison of three mechanistically distinct regimens, inclusion of both biochemical and radiological outcomes, and repeated assessment over 12 weeks. However, the current aggregate summary has major reporting limitations. Arm-wise baseline characteristics are absent, preventing assessment of randomization balance. Exact numbers randomized and analyzed by group, attrition, adherence, and missing data are unknown. The randomization and concealment methods are unspecified. No trial registration, ethics approval, adverse-event data, assay details, or blinded radiographic assessment is provided. Most importantly, exact event counts are unavailable, so confidence intervals and p-values cannot be calculated reliably. A publication-ready analysis

should follow CONSORT guidance. The primary analysis should be intention to treat, with exact responders and denominators for each arm. A global test should be followed by adjusted pairwise comparisons, and effect sizes should include risk differences and risk ratios with 95% confidence intervals. Continuous biochemical and radiographic outcomes should be reported by group and time point, ideally using mixed-effects models. Sensitivity analyses should address missing outcomes and per-protocol adherence. Subgroup analyses by baseline 25(OH)D, calcium intake, age, nutritional status, and radiographic severity may be clinically informative but should be prespecified and interpreted cautiously. In conclusion, the supplied results support the modern understanding that nutritional rickets frequently reflects combined vitamin D and calcium inadequacy rather than an isolated vitamin deficiency. Combination therapy appears to offer the most complete healing at 12 weeks. Nevertheless, the manuscript should not be submitted until the Eastern Bihar cohort, sample size, event counts, ethics documentation, registration, safety outcomes, and all longitudinal biochemical and radiographic data are independently verified.

Conclusion

Young children with nutritional rickets in this Eastern Bihar cohort had low dietary calcium intake and low vitamin D status. Combined vitamin D and calcium therapy produced the highest reported rate of complete biochemical and radiological healing at 12 weeks and was descriptively superior to either monotherapy.

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