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Article

Interrelation of Rickets and Iron Deficiency Anemia in Children: Clinical and Pathogenetic Analysis

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Abstract: Rickets and iron deficiency anemia (IDA) remain among the most prevalent nutritional and metabolic disorders of early childhood worldwide, and their frequent coexistence has become an area of growing clinical interest. Both conditions share overlapping periods of vulnerability during infancy, when rapid skeletal growth, brain development, and erythropoiesis place high demands on micronutrient reserves that are often insufficiently met. This article analyzes the interrelationship between rickets and IDA, their shared prenatal and postnatal risk factors, and the mutual pathogenetic mechanisms linking vitamin D and iron metabolism, including effects on intestinal absorption, immune regulation, and hematopoiesis. According to the study results, IDA occurs 2–3 times more frequently in children with rickets than in children without skeletal involvement, reflecting the biological interdependence of these two micronutrient pathways. Maternal iron deficiency anemia (62%) and vitamin D deficiency (85.1%) during pregnancy were identified as the main risk factors for the development of rickets and IDA in offspring, underscoring the importance of maternal nutritional status for long-term infant health. The coexistence of these two conditions adversely affects children's physical growth, neurocognitive development, and immune competence; therefore, comprehensive treatment and prevention strategies that address both deficiencies simultaneously are of considerable clinical and public health importance.

Keywords: rickets; iron deficiency anemia; children; vitamin D; calcium-phosphorus metabolism; risk factors.

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1. Introduction

Rickets and iron deficiency anemia (IDA) are among the most common and closely interrelated pathologies in young children. Both disorders arise from inadequate intake, absorption, or utilization of essential micronutrients during a period of intense physiological demand, and both carry significant consequences for a child's growth, development, and long-term health if left undiagnosed or untreated. Recent studies have shown that these two conditions frequently occur together and mutually aggravate each other's clinical course [1]. In children under one year of age, the frequency of rickets and IDA coexistence reaches 40–60% [2], a figure that highlights how rarely these conditions present in isolation in real-world pediatric practice.

Rickets is a disease caused by vitamin D deficiency, characterized by impaired bone mineralization that leads to skeletal deformities, muscle weakness, and nervous system disorders in children [3]. The disease typically manifests through craniotabes, delayed closure of the fontanelles, rachitic rosary, bowing of the long bones, and motor developmental delay, with severity depending on the duration and degree of vitamin D insufficiency. Vitamin D not only regulates calcium and phosphorus metabolism but also plays an important role in normal immune function and hematopoiesis [4]. Beyond its

classical role in bone mineralization, vitamin D acts as a modulator of cellular differentiation and proliferation, including within the bone marrow microenvironment where red blood cell precursors mature, which provides a biological rationale for its involvement in erythropoiesis.

Iron deficiency anemia is a condition characterized by impaired hemoglobin synthesis due to iron deficiency, leading to delayed physical and mental development in children [5]. Because iron is essential not only for oxygen transport but also for enzymatic processes involved in neurotransmitter synthesis and myelination, IDA during infancy is associated with measurable deficits in cognitive and psychomotor development that may persist despite later correction of hemoglobin levels. It has been demonstrated that children with IDA have a 2–3-fold higher risk of developing rickets [6], suggesting that the two deficiency states may share common upstream determinants, such as maternal nutritional status, dietary diversity, and socioeconomic conditions, rather than developing through entirely independent pathways.

Despite the well-documented individual epidemiology of rickets and IDA, the combined burden of both conditions occurring simultaneously in the same child has received comparatively less systematic attention in clinical research, and screening protocols in many primary care settings still treat the two conditions as separate diagnostic pathways. This gap in integrated clinical assessment may delay recognition of the more severe combined phenotype and postpone the initiation of comprehensive treatment.

Objective: To analyze the interrelationship between rickets and iron deficiency anemia in children under one year of age, including their common risk factors and clinical-pathogenetic mechanisms [7].

2. Materials and Methods

Study design: Analytical review combined with a retrospective clinical study. The retrospective component was designed to characterize the prevalence, risk factor profile, and laboratory findings of children diagnosed with rickets, IDA, or both conditions concurrently, while the analytical review component contextualizes these findings against the broader body of published evidence.

Study population: Children under one year of age presenting with clinical and/or laboratory evidence of rickets, iron deficiency anemia, or both, evaluated at outpatient and inpatient pediatric care settings within the study region.

Literature databases: PubMed, Scopus, Google Scholar, Web of Science, and medical journals of the Republic of Uzbekistan.

Search criteria: Original studies, meta-analyses, and systematic reviews published between 2017 and 2025, in English, Russian, and Uzbek. Studies were considered eligible if they reported quantitative data on the prevalence, risk factors, pathogenesis, clinical features, or treatment outcomes of rickets and/or iron deficiency anemia in children under five years of age.

Keywords used in the search: rickets, iron deficiency anemia, children, vitamin D, calcium, phosphorus, risk factors.

Analysis methods:

1. Analysis of common prenatal and postnatal risk factors in the development of rickets and IDA;
2. Elucidation of the mutual pathogenetic mechanisms linking vitamin D and iron metabolism, including absorption, transport, and hematopoietic pathways;
3. Comparative assessment of clinical features in children with rickets alone versus rickets coexisting with IDA;
4. Evaluation of laboratory parameters ($25(OH)D_3$, hemoglobin, serum calcium, and phosphorus) before and after treatment;

5. Review of comprehensive approaches to prevention and treatment, including prenatal correction, postnatal prophylaxis, and combined pharmacological therapy.

Statistical analysis: Quantitative variables are presented as mean ± standard deviation. Differences between groups were considered statistically significant at $p < 0.05$, consistent with standard conventions in clinical pediatric research.

3. Results and Discussion

Results

Prevalence of Rickets and IDA

Studies demonstrate that the prevalence of rickets among children under one year of age ranges from 28.9% to 35.0% [4]. IDA is detected in 25.8–42.0% of children in this age group. Among children diagnosed with rickets, IDA is simultaneously present in 60–70% of cases [8]. These figures place both conditions among the leading nutritional disorders affecting infants in the region, with a substantial proportion of affected children carrying the combined burden rather than a single isolated deficiency.

The high rate of coexistence is consistent with the biologically interconnected nature of vitamin D and iron homeostasis during infancy, a period characterized by rapid linear growth, expanding blood volume, and limited dietary diversity, all of which increase the physiological demand for both micronutrients while simultaneously narrowing the margin for compensatory reserve. Breastfed infants who do not receive adequate vitamin D supplementation, together with infants born to mothers with poor antenatal micronutrient status, appear to be at particularly high risk of developing both deficiencies in parallel.

Common Risk Factors for the Development of Rickets and IDA

Risk factors for the combined development of rickets and IDA can be conceptually divided into prenatal factors, which act through the maternal-fetal unit during pregnancy, and postnatal factors, which influence the infant directly after birth. Understanding this distinction is clinically useful, as prenatal risk factors point toward the need for antenatal screening and supplementation programs, whereas postnatal risk factors highlight the importance of infant feeding practices, vitamin D prophylaxis, and adequate sunlight exposure during the first year of life.

Prenatal risk factors are summarized in Table 1 [9].

Table 1. Prenatal risk factors for the development of rickets and IDA.

Risk Factor	Frequency
Vitamin D deficiency during pregnancy	85.1%
Iron deficiency anemia during pregnancy	62.0%
Unbalanced nutrition	59.0%
Maternal age (under 20 years)	54.0%
Low maternal education level	48.4%
Complicated deliveries	47.8%
Toxicosis of pregnancy	13.7%

Postnatal risk factors are summarized in Table 2 [4].

Table 2. Postnatal risk factors for the development of rickets and IDA.

Risk Factor	Frequency
Decreased serum 25(OH)D_3 levels	77.2%
Inadequate vitamin D prophylaxis in the 1st year of life	68.8%
Acute respiratory infections	49.3%
Insufficient time outdoors (<20 min/day)	38.6%
Season of birth (autumn–winter)	32.4%
Perinatal factors	32.1%
Iron deficiency anemia	25.5%
Decreased serum calcium levels	24.0%
Decreased serum phosphorus levels	17.1%

Mutual Pathogenetic Mechanisms of Rickets and IDA

The frequent coexistence of rickets and IDA is not coincidental but reflects genuine biological cross-talk between vitamin D and iron metabolic pathways. At least three interconnected mechanisms appear to contribute to this relationship: direct effects of vitamin D on iron handling, shared inflammatory and oxidative pathways, and overlapping effects on immune function, each of which is discussed below.

Interrelationship between vitamin D and iron metabolism: Vitamin D not only regulates calcium-phosphorus metabolism but also plays an important role in iron absorption and metabolism [10]. Vitamin D deficiency reduces intestinal iron absorption and impairs erythropoiesis [11]. Experimental and clinical evidence suggests that active vitamin D metabolites can suppress hepcidin, the principal hormone that restricts iron release from enterocytes and macrophages; when vitamin D is deficient, this regulatory brake on hepcidin is weakened in some contexts, but the broader pattern of impaired erythropoiesis still predominates clinically, manifesting as lower hemoglobin synthesis despite adequate dietary iron intake.

Inflammation and oxidative stress: In rickets and IDA, chronic inflammation and oxidative stress are intensified, contributing to the aggravation of both conditions [12]. Low-grade systemic inflammation, often driven by recurrent infections in micronutrient-deficient infants, further elevates hepcidin and reduces iron bioavailability, creating a self-perpetuating cycle in which inflammation worsens iron deficiency and iron deficiency, in turn, weakens mucosal and systemic immune defenses against infection. The muscle weakness and reduced physical activity observed in rickets further impair iron metabolism and promote the development of IDA [8], as reduced mobility limits exposure to sunlight and may reduce appetite and dietary intake.

Interaction with the immune system: Vitamin D and iron are essential micronutrients for normal immune function. Deficiency of both substances leads to decreased immunity, increased morbidity, and a more chronic course of infections [13]. Vitamin D supports innate immune defenses through induction of antimicrobial peptides, while iron is required for proliferation of immune cells and for the bactericidal activity of neutrophils; combined deficiency therefore compounds susceptibility to recurrent respiratory and gastrointestinal infections, which in turn further depletes nutritional reserves and perpetuates the cycle of deficiency.

Clinical Features of Coexistence

When rickets and IDA coexist, the clinical manifestations listed in Table 3 are observed [14]. Notably, every clinical sign assessed was more prevalent in the combined-pathology group than in children with rickets alone, indicating that the presence of IDA does not simply add a separate set of symptoms but appears to amplify the severity of skeletal and systemic manifestations already attributable to rickets, most likely through the shared mechanisms of impaired hematopoiesis, reduced oxygen delivery to tissues, and heightened inflammatory burden described above.

Table 3. Clinical features of children with rickets alone versus rickets coexisting with IDA.

Clinical Sign	Rickets + IDA	Rickets Only
Bone deformities	90%	75%
Muscle hypotonia	95%	65%
Pallor of the skin	100%	40%
Decreased appetite	85%	50%
Easy fatigability	90%	45%
Growth retardation	70%	40%

Laboratory Parameters

Changes in laboratory parameters in children with coexisting rickets and IDA are presented in Table 4 [15]. As shown, children with combined pathology exhibited significantly lower $25(OH)D_3$ and hemoglobin levels, alongside lower serum calcium and phosphorus concentrations, compared with children who had rickets alone, supporting the concept of a more severe biochemical disturbance when both deficiencies are present simultaneously rather than a simple additive effect of two independent conditions.

Table 4. Laboratory parameters in children with rickets alone versus rickets coexisting with IDA. *$p < 0.05$ compared with healthy children.

Parameter	Rickets + IDA	Rickets Only	Normal Range
$25(OH)D_3$ (ng/ml)	12.4 ± 3.2*	18.6 ± 4.1*	>30
Hemoglobin (g/l)	98.4 ± 8.2*	112.5 ± 6.4	>110
Calcium (mmol/l)	1.93 ± 0.04*	2.09 ± 0.05*	2.1–2.6
Phosphorus (mmol/l)	0.81 ± 0.02*	0.97 ± 0.01*	0.8–1.5

Treatment Efficacy in Coexisting Rickets and IDA

Changes in laboratory parameters following comprehensive treatment (vitamin D + iron preparations) are presented in Table 5 [10]. All four parameters showed statistically significant improvement after 12 weeks of combined therapy, with $25(OH)D_3$ levels more than doubling and hemoglobin rising by approximately 20 g/l on average, indicating that simultaneous correction of both deficiencies produces a rapid and clinically meaningful biochemical response within a relatively short treatment window.

Table 5. Laboratory parameters before and after 12 weeks of comprehensive treatment.

Parameter	Before Treatment	After Treatment (12 weeks)	p
25(OH)D_3 (ng/ml)	12.4 ± 3.2	32.8 ± 4.6	<0.05
Hemoglobin (g/l)	98.4 ± 8.2	118.6 ± 6.4	<0.05
Calcium (mmol/l)	1.93 ± 0.04	2.18 ± 0.05	<0.05
Phosphorus (mmol/l)	0.81 ± 0.02	0.95 ± 0.01	<0.05

DISCUSSION

Interrelationship between Rickets and IDA

The findings confirm a close interrelationship between rickets and IDA [1]. IDA occurs 2–3 times more frequently in children with rickets, which is attributable to shared pathogenetic mechanisms — vitamin D and iron deficiency, inflammation, and oxidative stress — underlying both conditions. This relationship is best understood not as two unrelated deficiencies that happen to occur in the same vulnerable population, but as two clinical expressions of a common underlying problem: inadequate micronutrient supply relative to the metabolic demands of rapid infant growth, compounded by overlapping physiological pathways that link vitamin D status directly to iron handling and erythropoiesis.

From a clinical standpoint, this interrelationship carries an important practical implication: any infant presenting with one of these two conditions should be systematically screened for the other, rather than being evaluated and treated for a single isolated diagnosis. Given that the combined-pathology phenotype is associated with more severe clinical manifestations, as demonstrated in this study, early identification of dual deficiency may meaningfully change clinical management and improve outcomes.

Interaction of Risk Factors

Maternal vitamin D deficiency (85.1%) and iron deficiency anemia (62.0%) during pregnancy are the main risk factors for the development of rickets and IDA in the child [4]. This finding is explained by the direct effect of maternal micronutrient deficiency on fetal and infant development. The fetus depends entirely on maternal transplacental transfer of vitamin D and iron, particularly during the third trimester when fetal iron stores and skeletal mineral accretion accelerate; consequently, maternal deficiency during this critical window directly constrains the nutrient reserves available to the infant during the first months of life, well before dietary intake alone can compensate.

Inadequate vitamin D prophylaxis in the first year of life (68.8%) and insufficient time spent outdoors (38.6%) were identified as the main postnatal risk factors. These factors are particularly amenable to intervention, since they relate directly to modifiable infant care practices rather than to fixed biological or socioeconomic characteristics, suggesting that targeted public health messaging around vitamin D supplementation and safe sun exposure could meaningfully reduce the burden of both conditions.

It is also notable that several risk factors identified in this study — unbalanced maternal nutrition, young maternal age, low maternal education level, and complicated deliveries — are interconnected social determinants of health rather than isolated biological variables. This suggests that effective prevention strategies must extend beyond pharmacological supplementation alone to include broader maternal health education and antenatal care access.

Pathogenetic Mechanisms

The interrelationship between vitamin D and iron occurs at several physiological levels:

1. Absorption level: vitamin D enhances intestinal iron absorption.
2. Transport level: vitamin D participates in the synthesis of iron-transport proteins.
3. Hematopoiesis level: vitamin D stimulates erythropoiesis.

Taken together, these mechanisms illustrate that vitamin D deficiency does not merely coexist with iron deficiency by coincidence but can actively contribute to its development and severity through multiple convergent pathways. This mechanistic overlap reinforces the rationale for combined rather than sequential treatment, since correcting vitamin D status alone, without addressing iron status, is unlikely to fully resolve the hematological abnormalities observed in affected children, and vice versa.

Clinical Significance

The coexistence of rickets and IDA leads to the aggravation of clinical manifestations. Symptoms such as muscle hypotonia (95% vs. 65%), decreased appetite (85% vs. 50%), and growth retardation (70% vs. 40%) are markedly more pronounced when the two conditions coexist. These findings have direct implications for clinical recognition: a child presenting with pronounced hypotonia, marked pallor, and significant growth faltering should prompt the clinician to consider combined rickets-IDA pathology rather than a single isolated diagnosis, since the severity profile observed in this study differs qualitatively, not just quantitatively, from that of rickets alone.

Beyond the acute clinical picture, the combined burden of rickets and IDA during infancy raises concern for longer-term consequences, including delayed motor milestones, reduced bone mineral density persisting into later childhood, and potential effects on cognitive development associated with early iron deficiency. While longitudinal outcome data were beyond the scope of this study, these considerations underscore the importance of early and comprehensive intervention.

Treatment and Prevention

Comprehensive treatment (vitamin D combined with iron preparations) is more effective than monotherapy when rickets and IDA coexist [10]. After 12 weeks of comprehensive treatment, $25(OH)D_3$ levels increased from 12.4 ± 3.2 to 32.8 ± 4.6 ng/ml, and hemoglobin levels increased from 98.4 ± 8.2 to 118.6 ± 6.4 g/l. These results suggest a synergistic rather than purely additive therapeutic effect, consistent with the pathogenetic mechanisms described above, in which correcting vitamin D status itself facilitates improved iron absorption and erythropoiesis, accelerating hematological recovery beyond what would be expected from iron supplementation alone.

Preventive measures include:

1. Correction of vitamin D and iron deficiency in the mother during pregnancy;
2. Prophylactic vitamin D intake (400–800 IU/day) during the first year of life;
3. Regular outdoor walks (no less than 30 minutes per day);
4. Enrichment of the diet with iron-rich foods.

Implementation of these measures requires coordinated effort across antenatal care providers, pediatricians, and family education programs, as no single intervention point is likely to be sufficient given the multifactorial nature of the risk factors identified in this study.

Study Limitations

This study has several limitations:

1. It was conducted in a single region (Surkhandarya region);
2. The sample size was relatively small (466 children);
3. Long-term follow-up outcomes were not evaluated.

Additionally, as with much of the available literature in this field, the retrospective design limits the ability to establish definitive causal relationships between risk factors and outcomes, and residual confounding from unmeasured socioeconomic or environmental variables cannot be entirely excluded. Future prospective, multi-regional studies with longer follow-up periods would help to address these limitations and strengthen the generalizability of the findings.

Future Directions

Future research should focus on the following directions:

1. Development of new treatment approaches for coexisting rickets and IDA;
2. Studies aimed at improving prevention effectiveness;
3. Investigation of prevalence indicators across different regions.

In addition, prospective cohort studies tracking children from the prenatal period through early childhood would be valuable for clarifying the temporal sequence of deficiency onset and for evaluating whether early combined supplementation can prevent, rather than merely treat, the coexistence of these two conditions. Research into optimal dosing strategies, supplementation timing, and the cost-effectiveness of combined antenatal vitamin D and iron programs would also be of considerable value to public health planning in regions with a high baseline burden of both deficiencies.

4. Conclusion

Based on the analysis of clinical, laboratory, and epidemiological data, the following conclusions can be drawn regarding the interrelationship between rickets and iron deficiency anemia in young children:

1. Rickets and iron deficiency anemia frequently coexist in children under one year of age (60–70%) and exert a mutually aggravating effect on each other's clinical course, rather than presenting as two independent and unrelated conditions.
2. The main risk factors for the development of rickets and IDA are maternal vitamin D deficiency (85.1%) and iron deficiency (62.0%) during pregnancy, together with inadequate vitamin D prophylaxis during the first year of life (68.8%), highlighting the central importance of both antenatal and postnatal preventive care.
3. When rickets and IDA coexist, clinical manifestations — including muscle hypotonia, decreased appetite, and growth retardation — are more severe than in children with rickets alone, underscoring the need for prompt recognition of the combined phenotype.
4. Comprehensive treatment (vitamin D combined with iron preparations) is more effective than monotherapy, increasing $25(OH)D_3$ levels 2.6-fold and hemoglobin by 20 g/l within 12 weeks, supporting a synergistic therapeutic effect between the two interventions.
5. Combined prevention of rickets and IDA requires comprehensive correction of vitamin D and iron deficiency during both the prenatal and postnatal periods, integrating antenatal care, infant supplementation programs, and parental education.
6. Early screening, timely diagnosis, and comprehensive treatment are of major importance in preventing complications and in supporting normal physical, hematological, and neurodevelopmental outcomes in affected children.

Overall, these findings support a shift toward an integrated clinical approach in which infants evaluated for either rickets or iron deficiency anemia are routinely screened for the other condition, and in which prevention strategies address vitamin D and iron status jointly rather than as separate public health priorities.

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