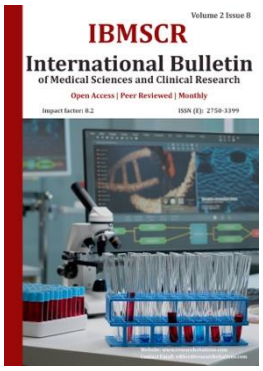

CALCIUM-PHOSPHATE HOMEOSTASIS DISTURBANCES IN PEDIATRIC PATIENTS WITH CHRONIC GASTROINTESTINAL DISORDERS: CLINICAL MANIFESTATIONS AND PATHOGENETIC MECHANISMS

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Abstract. Disturbances of calcium-phosphate metabolism represent a clinically significant and frequently underrecognized complication of chronic gastrointestinal (GI) diseases in children; however, the pathogenetic mechanisms underlying these disturbances across different nosological entities remain incompletely characterized. The present prospective comparative study examined clinical manifestations and laboratory markers of calcium-phosphate homeostasis in 72 children with chronic GI diseases admitted to the National Children's Medical Center (NCMC, Tashkent, Uzbekistan). Patients were stratified into three groups according to their primary diagnosis: chronic gastroduodenitis (CGD), inflammatory bowel disease (IBD), and malabsorption syndrome (MAS). The severity of calcium-phosphate homeostasis disturbances was found to increase progressively in the sequence CGD → IBD → MAS and was determined both by the degree of mucosal inflammatory involvement and by the depth of nutrient absorption impairment. Vitamin D deficiency was documented in 17.9%, 54.2%, and 80.0% of patients in the CGD, IBD, and MAS groups, respectively. Secondary hyperparathyroidism was identified in 7.1%, 41.7%, and 65.0% of patients, while reduced bone mineral density (BMD) was detected in 10.7%, 37.5%, and 70.0% of cases. The strongest predictors of BMD reduction were serum 25(OH)D ($r = 0.72$), parathyroid hormone ($r = -0.68$), and ionized calcium ($r = 0.64$). The identified clinicopathogenetic patterns provide a scientific basis for developing differentiated approaches to the diagnosis and correction of mineral metabolism disturbances in this patient population.

Keywords: calcium-phosphate metabolism, chronic gastrointestinal diseases, children, malabsorption, inflammatory bowel disease, chronic gastroduodenitis, vitamin D, parathyroid hormone, osteopenia, pediatric gastroenterology, bone mineral density.

Introduction

Chronic gastrointestinal diseases occupy a prominent position in the structure of somatic morbidity in childhood and are characterized by a steadily increasing prevalence across most regions of the world. According to World Health Organization estimates, chronic gastroenterological conditions are diagnosed in 15–25% of school-age children, with a particularly pronounced rise in the incidence of inflammatory bowel disease — Crohn's disease and ulcerative colitis — observed over the past two decades [Benchimol et al., 2011]. Chronic inflammatory involvement of the gastrointestinal mucosa inevitably disrupts the digestion and absorption of nutrients, including macro- and microelements, thereby creating the prerequisites for the development of diverse metabolic disorders. Among these, disturbances of calcium-phosphate metabolism occupy a special place, given that childhood and adolescence represent the critical period of peak bone mass accrual, which determines skeletal mineral density throughout the remainder of an individual's life.

Calcium-phosphate homeostasis constitutes a complex, multilevel regulatory system in which parathyroid hormone (PTH), calcitriol — the biologically active form of vitamin D, $1,25(OH)_2D_3$ — fibroblast growth factor 23 (FGF-23), and calcitonin play pivotal roles. The normal functioning of this system depends substantially on the integrity of intestinal calcium and phosphorus absorption, which is in turn determined by the structural integrity of the small intestinal mucosa, the adequacy of gastric acid secretion, and sufficient vitamin D availability [Christakos et al., 2016]. In chronic GI diseases, all of these mechanisms may be compromised to varying degrees and through different pathways: inflammatory infiltration of the mucosa reduces the expression of calcium transport proteins (TRPV6, calbindin-D9k); villous atrophy diminishes the absorptive surface area; and impaired bile secretion interferes with the assimilation of fat-soluble vitamins, including vitamin D. Furthermore, chronic inflammation per se disrupts vitamin D metabolism through pro-inflammatory cytokines — principally interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) — which suppress renal 1α-hydroxylase activity and thereby reduce the conversion of 25(OH)D to its active metabolite [Fabri et al., 2011].

The clinical consequences of calcium-phosphate metabolism disturbances in children with chronic GI diseases are diverse and encompass reduced bone mineral density (osteopenia and osteoporosis), impaired linear growth, neuromuscular hyperexcitability, dental caries and enamel hypoplasia, and, in severe cases, frank rickets and pathological fractures. Sylvester et al. (2007) reported that reduced BMD is detectable in 30–50% of children with Crohn's disease and in 20–35% of those with ulcerative colitis at the time of diagnosis. In celiac disease and other malabsorption syndromes, the prevalence of osteopenia reaches 70–80% [Zanchetta et al., 2016]. By contrast, calcium-phosphate disturbances in chronic gastroduodenitis — the most prevalent gastroenterological condition in children — have been considerably less studied, although available evidence suggests that reduced gastric acid secretion substantially impairs the ionization and absorption of calcium in the proximal small intestine.

Despite the obvious clinical relevance of this issue, comparative studies examining the clinicopathogenetic features of calcium-phosphate metabolism disturbances across different nosological forms of chronic GI disease in children are virtually absent from the literature. The majority of published investigations focus on individual diseases, while comparative analyses capable of revealing nosology-specific metabolic patterns have rarely been conducted. Data pertaining to pediatric populations in the Central Asian region are particularly scarce, where the structure of gastroenterological morbidity, dietary habits, solar irradiance levels, and genetic determinants of vitamin D metabolism differ substantially from those of European and North American populations. The present study, conducted at the NCMC in Tashkent, was designed to address this gap and to establish a scientific foundation for the development of differentiated approaches to the diagnosis and management of calcium-phosphate metabolism disturbances in children with chronic GI diseases.

The aim of the present study was to investigate the clinical manifestations and laboratory-instrumental indicators of calcium-phosphate metabolism in children with various forms of chronic gastrointestinal disease, with a view to establishing the nosology-specific features of pathogenetic mechanisms and developing criteria for the early diagnosis of mineral metabolism disturbances.

Materials and Methods

This prospective comparative study was conducted at the Children's Diagnostic Centre of the Ministry of Health of the Republic of Uzbekistan (Tashkent) between March 2024 and November 2025. The study enrolled 72 children aged 5 to 16 years with verified chronic gastrointestinal (GI) diseases who were admitted for inpatient evaluation and treatment. Diagnoses were established in accordance with current international classification criteria: chronic gastroduodenitis was diagnosed according to the Sydney Classification with mandatory endoscopic and morphological confirmation; inflammatory bowel disease was diagnosed according to the Porto Criteria of ESPGHAN (2014); and malabsorption syndrome was diagnosed on the basis of clinical, laboratory, and morphological data, including small intestinal mucosal biopsy.

Inclusion criteria were as follows: age between 5 and 16 years; a verified diagnosis of a chronic GI disease; disease duration of at least 6 months; absence of acute infectious illness within 4 weeks prior to enrollment; and written informed voluntary consent from parents or legal guardians.

Exclusion criteria were: primary parathyroid gland pathology; chronic kidney disease (eGFR < 60 mL/min/1.73 m^2); diabetes mellitus; use of calcium supplements, vitamin D preparations, glucocorticosteroids, or antacids within 3 months prior to enrollment; malignant neoplasms; and severe concomitant hepatic disease.

All 72 patients were allocated to three clinical groups:

- Group 1 — Chronic Gastroduodenitis (CGD): n = 28; median age 10.8 [8.4; 13.2] years; male/female ratio 15/13. This group comprised children with endoscopically and morphologically confirmed chronic gastroduodenitis, including *Helicobacter pylori*-associated disease (57.1% of cases).

- Group 2 — Inflammatory Bowel Disease (IBD): n = 24; median age 12.1 [9.6; 14.8] years; male/female ratio 14/10. This group included children with Crohn's disease (n = 10) and ulcerative colitis (n = 14), verified endoscopically, histologically, and by imaging studies.

- Group 3 — Malabsorption Syndrome (MAS): n = 20; median age 9.4 [6.8; 12.6] years; male/female ratio 11/9. This group comprised children with celiac disease (n = 12), confirmed serologically (anti-tTG IgA, anti-DGP IgG) and morphologically (villous atrophy grade III–IV according to the Marsh classification), and children with other forms of MAS (n = 8).

The control group consisted of 25 apparently healthy children of comparable age and sex who had no chronic diseases and were not receiving calcium or vitamin D supplementation.

Results and Discussion. Analysis of clinical symptoms indicative of calcium-phosphate metabolism disturbances revealed substantial between-group differences. The most pronounced clinical picture was observed in patients with malabsorption syndrome, whereas symptoms were minimal or absent in children with chronic gastroduodenitis. Muscle pain and calf muscle cramps were reported by 10.7% of patients in the CGD group, 33.3% in the IBD group, and 65.0% in the MAS group ($p < 0.001$). Growth retardation (height below the 10th percentile for age and sex) was documented in 7.1%, 29.2%, and 55.0% of patients, respectively. Rachitic skeletal changes (chest deformities, genu varum or genu valgum) were identified exclusively in the MAS group, affecting 5 children (25.0%), indicating prolonged and profound mineral metabolism disturbance in this patient category. Chvostek's sign was positive in 3.6% of children with CGD, 16.7% with IBD, and 35.0% with MAS.

The clinical findings are consistent with the concept that the severity of calcium-phosphate metabolism disturbances is determined primarily by the depth of intestinal absorptive dysfunction rather than merely by the presence of an inflammatory process per se. This explains why, in malabsorption syndrome — where villous atrophy drastically reduces the absorptive surface area — clinical manifestations are most pronounced. Similar patterns have been described by Zanchetta et al. (2016), who demonstrated that growth retardation and skeletal deformities occur significantly more frequently in children with untreated celiac disease than in IBD patients with comparable disease duration.

The results of biochemical blood analysis are presented in Table 1. Total calcium levels were significantly reduced in all three patient groups compared with controls, with the most pronounced hypocalcemia observed in the MAS group. Ionized calcium, which more accurately reflects the physiologically active fraction of the element, demonstrated an analogous stepwise decline. Serum phosphorus was reduced only in the MAS group, while in the CGD and IBD groups it remained within the age-specific reference range, though it was significantly lower than in controls ($p < 0.05$). Magnesium levels declined in parallel with calcium, which is explained by the shared mechanisms governing their intestinal absorption.

Table 1. Biochemical indicators of calcium-phosphate metabolism in children with chronic GI diseases according to nosological group (M ± SD)

Parameter	Control (n=25)	CGD (n=28)	IBD (n=24)	MAS (n=20)	p
Total calcium, mmol/L	2.41 ± 0.12	2.28 ± 0.14*	2.19 ± 0.16	2.04 ± 0.18	<0.001
Ionized calcium, mmol/L	1.24 ± 0.07	1.18 ± 0.08*	1.11 ± 0.09	1.02 ± 0.10	<0.001
Phosphorus, mmol/L	1.58 ± 0.18	1.44 ± 0.17*	1.38 ± 0.19*	1.21 ± 0.21**	<0.001
Magnesium, mmol/L	0.89 ± 0.09	0.82 ± 0.10*	0.76 ± 0.11	0.68 ± 0.12	<0.001
Alkaline phosphatase, U/L	186 ± 42	214 ± 51*	268 ± 64	342 ± 78	<0.001
Albumin, g/L	44.2 ± 3.1	41.8 ± 3.4*	38.4 ± 4.2	33.6 ± 5.1	<0.001
CRP, mg/L	2.1 [1.4; 3.2]	4.8 [3.6; 6.4]*	12.4 [9.8; 16.2]	8.6 [6.4; 11.8]	<0.001
Urinary calcium, mmol/day	4.8 ± 1.2	3.9 ± 1.1*	3.2 ± 1.0	2.4 ± 0.9	<0.001

$p < 0.05$ vs. control group; **$p < 0.01$ vs. control group and $p < 0.05$ vs. CGD group.

The progressive elevation of ALP activity across all patient groups — increasing in the sequence CGD → IBD → MAS — reflects osteoblast activation in response to calcium deficiency and constitutes an indirect marker of impaired bone remodeling. The reduction in serum albumin, most pronounced in the MAS group, is attributable both to impaired amino acid absorption and to protein-losing enteropathy in IBD, and carries independent pathogenetic significance, since albumin is the principal transport protein for calcium in the bloodstream. The reduction in urinary calcium excretion across all patient groups indicates activation of renal tubular calcium reabsorption as a compensatory mechanism in response to calcium deficiency.

It is noteworthy that CRP levels were higher in the IBD group than in the MAS group, reflecting the more pronounced systemic inflammatory response characteristic of IBD. Chronic inflammation itself, independently of malabsorption, constitutes a distinct pathogenetic factor in the disruption of calcium-phosphate homeostasis in IBD: pro-inflammatory cytokines (TNF-α, IL-6) activate osteoclasts through the RANK/RANKL signaling pathway, thereby promoting enhanced bone resorption [Sylvester et al., 2007].

Analysis of 25(OH)D and PTH levels revealed patterns of fundamental importance for understanding the pathogenesis of calcium-phosphate metabolism disturbances across the different GI diseases studied (Table 2). Vitamin D deficiency [25(OH)D < 20 ng/mL] was documented in 17.9% of patients with CGD, 54.2% with IBD, and 80.0% with MAS — significantly exceeding the prevalence in the control group (8.0%; $p < 0.001$ for all comparisons). Vitamin D insufficiency [25(OH)D 20–29 ng/mL] was additionally identified in 32.1%, 33.3%, and 15.0% of patients, respectively. Consequently, a normal vitamin D status (≥ 30 ng/mL) was preserved in only 50.0% of children with CGD, 12.5% with IBD, and 5.0% with MAS.

Table 2. Vitamin D status and parathyroid hormone levels in children with chronic GI diseases (Me [Q1; Q3])

Parameter	Control (n=25)	CGD (n=28)	IBD (n=24)	MAS (n=20)	p
25(OH)D, ng/mL	34.8 [29.6; 41.2]	26.4 [21.8; 32.6]*	18.2 [13.4; 23.8]	12.6 [9.1; 17.4]	<0.001
PTH, pg/mL	32.4 [26.8; 38.9]	44.8 [38.2; 52.6]*	62.4 [54.8; 71.6]	84.6 [72.4; 96.8]	<0.001
Vitamin D deficiency (<20 ng/mL), %	8.0%	17.9%*	54.2%	80.0%	<0.001
Vitamin D insufficiency (20–29 ng/mL), %	20.0%	32.1%	33.3%*	15.0%	0.042
Secondary hyperparathyroidism (PTH >65 pg/mL), %	0%	7.1%	41.7%	65.0%	<0.001

$p < 0.05$ vs. control group; **$p < 0.01$ vs. control group and $p < 0.05$ vs. CGD group.

PTH levels increased progressively from the control group to the MAS group, reflecting augmented compensatory parathyroid hormone secretion in response to hypocalcemia and vitamin D deficiency. Secondary hyperparathyroidism (PTH > 65 pg/mL) was diagnosed in 41.7% of IBD patients and 65.0% of MAS patients, while in the CGD group its prevalence was only 7.1% and did not reach statistical significance compared with controls ($p = 0.18$). Chronically elevated PTH represents one of the key pathogenetic mechanisms underlying BMD reduction, since PTH stimulates osteoclastic bone resorption, mobilizing calcium from the skeletal reservoir to maintain normocalcemia [Christakos et al., 2016].

The mechanisms of vitamin D deficiency differ across the various GI diseases studied. In MAS, the predominant mechanism is impaired absorption of fat-soluble vitamin D in the small intestine as a consequence of villous atrophy and steatorrhea. In IBD, in addition to absorptive impairment, a substantial contribution is made by the suppression of renal 1α-hydroxylase activity by pro-inflammatory cytokines, as well as by reduced cutaneous vitamin D synthesis resulting from limited sun exposure due to the severity of the underlying disease. In CGD, impairment of vitamin D absorption is less pronounced; however, reduced gastric acid secretion interferes with the liberation of calcium from dietary complexes, which indirectly diminishes the stimulus for $1,25(OH)_2D_3$ synthesis [Fabri et al., 2011].

The results of densitometric evaluation (Table 3) corroborated the clinical and biochemical picture of progressively worsening mineral metabolism disturbances in the sequence CGD → IBD → MAS. Reduced lumbar spine BMD (Z-score ≤ −2.0) was identified in 10.7% of children with CGD, 37.5% with IBD, and 70.0% with MAS. The mean lumbar spine Z-score was −0.8 ± 0.6, −1.6 ± 0.8, and −2.4 ± 0.9, respectively — all significantly different from the control group (−0.2 ± 0.5; $p < 0.001$ for all comparisons). Analogous patterns were observed for proximal femur BMD.

Table 3. Bone mineral density by DXA in children with chronic GI diseases (M ± SD)

Parameter	Control (n=25)	CGD (n=28)	IBD (n=24)	MAS (n=20)	p
Z-score L1–L4	−0.2 ± 0.5	−0.8 ± 0.6*	−1.6 ± 0.8	−2.4 ± 0.9	<0.001
Z-score proximal femur	−0.1 ± 0.4	−0.6 ± 0.5*	−1.3 ± 0.7	−2.1 ± 0.8	<0.001
BMD L1–L4, g/cm²	0.842 ± 0.071	0.798 ± 0.068*	0.741 ± 0.074	0.682 ± 0.081	<0.001
Z-score ≤ −2.0 (spine), %	0%	10.7%*	37.5%	70.0%	<0.001
Z-score ≤ −2.0 (femur), %	0%	7.1%	29.2%	60.0%	<0.001

p < 0.05 vs. control group; **p < 0.01 vs. control group and p < 0.05 vs. CGD group.

These findings are consistent with the results of the large systematic review by Benchimol et al. (2011), which demonstrated that reduced BMD is a universal complication of chronic inflammatory bowel disease in children, detectable in 30–50% of patients at the time of diagnosis. The high prevalence of reduced BMD in the MAS group (70.0%) in our study corresponds closely to the data reported by Zanchetta et al. (2016), who identified osteopenia in 67.4% of children with untreated celiac disease. It is important to emphasize that the BMD reduction observed in the CGD group, although less pronounced, was nonetheless statistically significant, indicating that even relatively mild GI pathology exerts a measurable negative impact on bone metabolism in children during the period of active growth.

To identify relationships between biochemical markers of calcium-phosphate metabolism and indicators of disease activity, Spearman's rank correlation analysis was performed (Table 4). The strongest correlations with lumbar spine BMD Z-score were identified for serum 25(OH)D ($r = 0.72$; $p < 0.001$), PTH ($r = -0.68$; $p < 0.001$), and ionized calcium ($r = 0.64$; $p < 0.001$). CRP levels correlated significantly with PTH ($r = 0.58$; $p < 0.001$) and inversely with 25(OH)D ($r = -0.54$; $p < 0.001$), confirming the role of systemic inflammation in disrupting vitamin D metabolism. Serum albumin was positively correlated with both BMD ($r = 0.61$; $p < 0.001$) and 25(OH)D ($r = 0.56$; $p < 0.001$), reflecting the close relationship between nutritional status and bone metabolic health.

Table 4. Correlation matrix of calcium-phosphate metabolism indicators and clinico-laboratory parameters (Spearman's r, entire sample n = 72)

Parameter	25(OH)D	PTH	Ionized Ca^{2+}	BMD Z-score	ALP
CRP	r = −0.54	r = 0.58	r = −0.46	r = −0.51	r = 0.49**
Albumin	r = 0.56	r = −0.48	r = 0.52	r = 0.61	r = −0.44**
Disease duration, months	r = −0.48	r = 0.52	r = −0.43	r = −0.58	r = 0.46**
PTH	r = −0.64	—	r = −0.61	r = −0.68	r = 0.55
25(OH)D	—	r = −0.64	r = 0.59	r = 0.72	r = −0.52
Phosphorus	r = 0.41	r = −0.38	r = 0.46	r = 0.44	r = −0.36**

$p < 0.05$; **$p < 0.01$.

The negative correlation between disease duration and BMD ($r = -0.58$; $p < 0.001$) indicates that bone metabolic disturbances progress as the duration of chronic GI disease increases. This underscores the necessity of early monitoring of calcium-phosphate metabolism indicators in children with chronic GI diseases, without waiting for the development of clinically manifest osteopenia. The correlation between PTH and CRP ($r = 0.58$; $p < 0.001$) further corroborates the concept that chronic inflammation constitutes an independent pathogenetic factor in the disruption of calcium-phosphate homeostasis — one that operates through the suppression of active vitamin D metabolite synthesis and the activation of osteoclastogenesis, independently of malabsorption [Fabri et al., 2011; Sylvester et al., 2007].

Conclusions: The present study established that chronic gastrointestinal diseases in children are consistently associated with disturbances of calcium-phosphate metabolism, the severity of which is determined by the nosological form of the disease and increases progressively in the sequence chronic gastroduodenitis → inflammatory bowel disease → malabsorption syndrome.

In chronic gastroduodenitis, disturbances are predominantly subclinical in nature and manifest as moderate reductions in total and ionized calcium, vitamin D insufficiency or deficiency in every second patient, and incipient BMD reduction in approximately one in ten children — attributable primarily to impaired acid-dependent calcium absorption in the proximal small intestine.

In inflammatory bowel disease, the pathogenesis of mineral metabolism disturbances is dual in character: alongside absorptive impairment, chronic systemic inflammation plays a substantial independent role by suppressing the synthesis of active vitamin D metabolites and activating osteoclastogenesis through the RANK/RANKL pathway. Vitamin D deficiency was identified in 54.2% of IBD patients, secondary hyperparathyroidism in 41.7%, and reduced BMD in 37.5%.

In malabsorption syndrome, calcium-phosphate metabolism disturbances are most profound and clinically manifest: vitamin D deficiency was documented in 80.0% of patients, secondary hyperparathyroidism in 65.0%, and BMD below the expected range for age in 70.0% of cases.

The most informative laboratory predictors of BMD reduction were serum 25(OH)D ($r = 0.72$), PTH ($r = -0.68$), and ionized calcium ($r = 0.64$). The negative correlation between disease duration and BMD ($r = -0.58$) highlights the importance of early intervention.

The findings substantiate the necessity of mandatory monitoring of calcium-phosphate metabolism indicators — including 25(OH)D, PTH, ionized calcium, and alkaline phosphatase — as well as densitometric assessment in all children with chronic GI diseases from the time of diagnosis verification. They also provide a rationale for developing differentiated protocols for the correction of identified disturbances, taking into account the predominant pathogenetic mechanism specific to each nosological entity.

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