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Celiac Disease as a Model of Intestinal Malnutrition: Mechanisms, Biomarkers, and Nutritional Management

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Posted Date: 27 October 2025

doi: 10.20944/preprints202510.1964.v1

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Celiac Disease as a Model of Intestinal Malnutrition: Mechanisms, Biomarkers, and Nutritional Management

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Abstract

Background: In pediatric celiac disease (CD), intestinal malabsorption and the restrictive nature of a gluten-free diet (GFD) frequently result in persistent macro- and micronutrient imbalances, despite histological remission. The present review evaluates the evidence on nutritional adequacy of the GFD, identifies common deficiencies, and considers biomarker strategies and dietary recommendations to optimize growth and metabolic health. **Methods:** A narrative review of the literature was conducted, focusing on studies of nutrient intake, product composition of gluten-free foods, biomarker assessment, and clinical outcomes in children with CD. Both macronutrient (protein, fat, carbohydrate, fiber) and micronutrient (iron, vitamin D, calcium, B-vitamins, zinc, magnesium) domains were included. **Results:** Children with CD on long-term GFD demonstrate higher intake of lipids (especially saturated fat) and simple carbohydrates, alongside consistently low intake of dietary fiber and key micronutrients. Gluten-free products often exhibit lower protein content, higher glycemic index, and reduced fortification compared to gluten-containing equivalents. Biomarkers including prealbumin, ferritin, 25-hydroxyvitamin D, and inflammatory mediators aid in early detection of malnutrition. Nutritional deficits contribute to impaired linear growth, delayed puberty and increased metabolic risk. **Conclusions:** Nutritional adequacy of the GFD cannot be assumed in children with CD. Routine monitoring using standardized biomarker panels, combined with personalized dietary counselling and improved formulation and fortification of gluten-free products, is essential to mitigate long-term adverse outcomes. Future work should advance precision nutrition approaches and public-health initiatives to optimize dietary quality in this vulnerable population.

Keywords: celiac disease; malnutrition; deficiency; biomarkers; children

1. Introduction

An optimal diet is characterized by variety, balance, and moderation, emphasizing the intake of fruits, vegetables, whole grains, legumes, nuts, and fish, while limiting refined grains, free sugars, salt, and saturated fats [1]. Despite well-established nutritional guidelines, malnutrition persists as a widespread, multifactorial condition closely linked to numerous chronic diseases. Evidence indicates that 20–60% of hospitalized patients experience some degree of malnutrition, underscoring its clinical and public health relevance. The World Health Organization (WHO) identifies malnutrition as the greatest global health threat, calling for integrated strategies that combine dietary optimization, early detection, and targeted interventions to mitigate long-term consequences [2].

Malnutrition encompasses both undernutrition, manifested as wasting, stunting, and underweight, and overnutrition, including overweight and obesity [3]. These forms are not mutually exclusive; the concept of the "double burden of malnutrition" denotes their coexistence at population, household, and individual levels [4]. This duality is particularly relevant in pediatric populations, where early dietary exposures critically shape long-term health outcomes.

Among disorders most strongly associated with pediatric malnutrition is celiac disease (CD), an immune-mediated enteropathy affecting approximately 1% of the global population [4]. CD leads to selective malabsorption of macro- and micronutrients due to intestinal damage. Villous atrophy, malabsorption, and chronic inflammation contribute to deficiencies in iron, folate, vitamin B12, and fat-soluble vitamins [5]. Between 20% and 67% of children with CD present signs of malnutrition at diagnosis, depending on assessment methods. Anthropometric indices such as mid–upper arm circumference (MUAC) and BMI reveal variable degrees of nutritional impairment, with stunting affecting approximately 20% of pediatric patients [6].

Clinical manifestations range from classic gastrointestinal symptoms, diarrhea, abdominal distension, and failure to thrive, to extraintestinal or subclinical presentations such as anemia, delayed puberty, and osteoporosis [7]. Iron deficiency anemia affects up to 82% of untreated pediatric CD patients, impairing cognitive and physical development, while vitamin D deficiency, often persisting despite a gluten-free diet (GFD), contributes to reduced bone mineralization and increased fracture risk [8].

Although GFD restores intestinal integrity and improves absorption, nutritional challenges frequently persist. Many gluten-free products (GFPs) are calorie-dense but nutrient-poor, characterized by high contents of saturated fat and simple sugars and low levels of dietary fiber, high-quality protein, iron, and B vitamins [9]. Children adhering to GFDs often consume excessive amounts of ultra-processed gluten-free foods, predisposing them to weight gain, insulin resistance, and the "double burden" of malnutrition, where undernutrition and overnutrition coexist [10].

Non-adherence to the GFD has been associated with elevated serum zonulin levels, indicating increased intestinal permeability and sustained inflammation. Even with strict compliance, however, nutritional deficiencies may persist due to inadequate dietary intake or low-grade inflammation [11].

Socioeconomic determinants further influence dietary quality [12]. Families with limited financial resources often rely on monotonous, nutrient-poor gluten-free foods [13]. In low-resource settings, where fortified products are scarce, malnutrition prevalence is even higher. Maternal education and household income consistently predict dietary adequacy and growth outcomes in children with CD [14].

A modern approach to clinical nutrition must integrate qualitative assessment of macro- and micronutrient intake alongside total caloric evaluation [15]. This principle is especially critical in pediatrics, where optimal nutrition underpins normal growth and development. Biomarkers have emerged as essential tools for the early detection of malnutrition, offering greater sensitivity than anthropometric or dietary methods. These measurable indicators, encompassing cytokines, interleukins, hormones, and markers of oxidative stress or DNA damage, reflect dynamic physiological and pathological processes.

This review examines the complex interplay between macro- and micronutrient imbalances in pediatric celiac disease. By synthesizing current evidence, it highlights the central role of macronutrient quality in both prevention and management of malnutrition across the weight spectrum and underscores the utility of biomarkers for early detection and targeted intervention.

2. Macro- and Micronutrient Alterations in Celiac Disease in Pediatrics

CD is an immune-mediated enteropathy triggered by gluten ingestion, leading to intestinal inflammation, villous atrophy, and crypt hyperplasia that impair nutrient absorption [16,17]. While most studies have focused on micronutrient deficiencies, macronutrient imbalances also play a pivotal role in energy metabolism, cellular function, and immune regulation.

The GFD, the only effective treatment for CD, requires lifelong exclusion of wheat, rye, and barley [18]. Although it restores mucosal integrity and nutrient absorption, complete histological recovery is achieved only in a subset of patients, particularly adults[18,19]. Furthermore, GFD

doi:10.20944/preprints202510.1964.v1

introduces distinct nutritional challenges: commercially available GFPs are often enriched in carbohydrates and fats but deficient in protein, fiber, B vitamins, iron, and folate.

Evidence from pediatric cohorts demonstrates that children and adolescents with CD adhering to GFDs typically consume excessive amounts of total and saturated fats, protein, and simple carbohydrates, while their intake of fiber and key micronutrients, iron, calcium, zinc, magnesium, vitamin D, and folate, remains inadequate [20,21]. Such imbalances are particularly concerning during growth and pubertal development, when nutritional demands are high.

The effects of GFD on body composition remain controversial. Some studies report beneficial outcomes, reduced body fat, improved lean mass, and catch-up growth, while others note excessive weight gain and obesity [22,23]. This variability reflects differences in GFP composition, which often includes higher carbohydrate and lipid content but less protein, fiber, and B vitamins [24].

Children with CD frequently consume fewer cereals, fruits, and vegetables, relying heavily on meat and processed GFPs [25]. Systematic reviews confirm that excessive fat and insufficient fiber and micronutrient intake are common in pediatric populations, but these deficits are exacerbated in GFD consumers [26]. Many children consume GFPs multiple times daily, increasing exposure to nutrient-poor foods [27,28]. Enhanced caloric intake, combined with restored absorption after mucosal healing, may contribute to overweight and obesity [28,29]. Epidemiological studies reveal that overweight and obesity are more prevalent in pediatric CD than previously recognized, with overweight reported in 8.8–20.8% and obesity in 0–6% at diagnosis, increasing after GFD initiation to 9.4–21% and 0–8.8%, respectively [30]. Findings remain inconsistent, as some analyses indicate no significant increase in obesity risk with GFD adherence [31,32].

In summary, children with CD exhibit both macro- and micronutrient imbalances, stemming from pre-diagnosis malabsorption and long-term dietary inadequacies. The coexistence of insufficient fiber and micronutrient intake with excessive lipid and carbohydrate consumption highlights a dual risk of undernutrition and overweight, underscoring the need for continuous nutritional surveillance and individualized dietary counseling.

2.1. Specific Macronutrient Deficiencies in Pediatric CD

Macronutrients, proteins, carbohydrates, and fats, play a pivotal role in health and disease, not only through their quantitative contribution but also through their qualitative composition and distribution within the diet [33]. Alterations in macronutrient balance can exert profound effects on key physiological systems, influencing hormonal regulation, immune responses, basal metabolic rate, and systemic inflammation. The following sections will explore these components in greater detail.

2.2. Protein Intake

Protein malnutrition in CD results from both impaired intestinal absorption and inadequate dietary intake. Villous atrophy and crypt hyperplasia reduce enzymatic activity and absorptive surface area, limiting amino acid assimilation. Consequently, untreated CD patients often exhibit decreased serum albumin and other protein markers, indicating compromised protein status [34]. Although the GFD promotes mucosal recovery, it may exacerbate protein insufficiency, as GFPs generally contain low-quality proteins and high saturated fat levels [35]. This imbalance contributes to suboptimal protein intake and metabolic dysregulation. Diets dominated by processed meats may intensify inflammation, whereas those emphasizing legumes, fish, and plant-based proteins improve amino acid balance and reduce inflammatory stress [36].

Findings on protein intake in CD remain inconsistent. Mariani et al. reported elevated intake among adolescents [37], while Shepherd and Gibson [38] and Van Hees et al. [39] observed reduced vegetable protein consumption. These discrepancies likely reflect regional differences in diet and GFP composition. Recent data by Ekşi et al. (2025) confirmed lower absolute and relative protein intake in pediatric CD patients compared with controls, frequently below dietary reference values [40].

Overall, evidence indicates that although protein inadequacy is not universal, a significant proportion of pediatric patients remain at risk of insufficient intake, warranting individualized dietary counseling and targeted protein optimization strategies.

2.3. Carbohydrate Intake

Carbohydrate intake in CD is often characterized by low complexity and poor fiber content due to dependence on refined gluten-free starches such as rice and corn flour. These starches have high glycemic indices, leading to rapid digestion and postprandial glucose surges that may promote insulin resistance and metabolic syndrome. Insufficient soluble fiber further reduces gastrointestinal motility and alters gut microbiota composition, compromising intestinal barrier function and inducing low-grade inflammation [22].

Current dietary strategies recommend incorporating naturally gluten-free whole grains and pseudocereals, such as quinoa, amaranth, and buckwheat, which have lower glycemic indices and higher fiber content. These foods improve glycemic control, enhance satiety, and support microbial diversity [36]. Nevertheless, population studies consistently report excessive sugar intake and inadequate fiber consumption among children with CD compared with healthy peers [39].

Gluten exclusion may also alter carbohydrate metabolism. Experimental evidence suggests that gluten inhibits starch hydrolysis; thus, its removal may increase glycemic responses to carbohydrate ingestion [41]. Indeed, many GFPs have higher glycemic indices than gluten-containing equivalents [41], and pediatric studies confirm elevated glycemic values in CD compared with controls [42]. This finding is particularly relevant for patients with concurrent type 1 diabetes, a common comorbidity in CD [43].

Although data remain limited, available evidence consistently indicates heightened glycemic exposure in pediatric CD [44]. Further longitudinal studies are required to clarify long-term metabolic risks and guide evidence-based dietary recommendations.

2.4. Fat Intake

In untreated CD, lipid metabolism is disrupted due to fat malabsorption, resulting in deficiencies of essential omega-3 and omega-6 polyunsaturated fatty acids (PUFAs), crucial for membrane integrity and inflammation control [41]. Conversely, adherence to a GFD often leads to excessive saturated fat intake and insufficient unsaturated fat consumption, producing an atherogenic lipid profile with elevated LDL and reduced HDL cholesterol [45].

Comparative analyses of GFPs and gluten-containing foods show marked nutritional disparities. For example, Spanish data revealed that gluten-free breads contain nearly twice the total fat and three times the saturated fat of standard breads, with similar trends in pasta and bakery items [46]. These modifications, designed to enhance texture and palatability, have significant nutritional implications. While some studies report higher fat intake in children with CD than in controls [47], others found no difference [41,48]. Notably, excessive fat intake surpassing dietary recommendations has been documented in both CD and non-CD pediatric populations [26,49]

Beyond caloric excess, high-fat consumption is associated with greater prevalence of overweight and obesity among adolescents with CD on GFDs [50] and an elevated risk of metabolic syndrome, type 2 diabetes, and cardiovascular disease[51,52]. Although causality remains uncertain, the combination of high-fat GFPs, restored nutrient absorption, and modern processed-food habits likely contributes to this trend. Nutritional interventions emphasizing unsaturated fat sources, such as extra virgin olive oil, nuts, and oily fish, are therefore essential to re-establish lipid balance and reduce long-term cardiometabolic risk [53].

2.5. Fiber Intake

The fiber content of GFPs is generally low due to reliance on refined flours and starches, in which the outer grain layers, rich in fiber, are removed during processing [54]. Studies in adults show that GFDs provide less dietary fiber than gluten-containing diets [55]. In children, however, fiber intake typically falls below recommendations regardless of CD status, suggesting a broader dietary shortfall rather than a condition-specific deficit [55]. Mariani et al. reported significantly lower fiber intake among adolescents with CD compared to healthy peers [41], though most evidence points instead to a Westernized dietary pattern, marked by low intake of fiber-rich plant foods and whole grains in favor of refined, processed products. Consequently, suboptimal fiber intake in pediatric CD likely reflects both the limited nutritional value of GFPs and general population-level trends.

Low fiber intake has important clinical consequences, including impaired satiety, slower gastrointestinal transit, and reduced microbial diversity, which increase the risk of obesity, type 2 diabetes, and cardiovascular disease [41]. Recent GFP innovations incorporating pseudocereals such as quinoa, buckwheat, and amaranth have improved fiber content to levels approaching those of traditional wheat-based products [56], though adoption among pediatric patients remains limited.

Cross-sectional data from Babio et al. showed that both CD and non-CD children consume inadequate fiber and few fruits and vegetables [57]. Seasonal variations further complicate interpretation. While two studies reported lower fiber intake in GFD consumers [58,59], the majority confirm that both groups consistently fail to meet dietary fiber recommendations.

Collectively, these findings indicate that inadequate fiber intake is not exclusive to pediatric CD but is exacerbated by dependence on refined GFPs. Nutritional counseling should therefore promote naturally gluten-free, fiber-rich foods, legumes, fruits, vegetables, and pseudocereals, to improve fiber intake and mitigate long-term metabolic and cardiovascular risk.

Table 1 summarizes macronutrient alterations in pediatric celiac disease, highlighting the dual impact of intestinal malabsorption and suboptimal composition of gluten-free products on overall nutritional balance and metabolic health.

Table 1. Specific macronutrient deficiencies and imbalances in pediatric celiac disease (CD): pathophysiology, prevalence, and clinical implications.

Macronutrient	Mechanism of Alteration	Prevalence / Key Findings	Clinical Consequences	Dietary and Clinical Management
Protein	Villous atrophy and crypt hyperplasia reduce absorptive surface and peptidase activity; gluten-free products (GFPs) low in high-quality protein; imbalance from increased fat and sugar intake.	Protein intake reduced in many CD cohorts; lower vegetable protein in long-term GFD users [PMID: 30650530]; some heterogeneity across studies.	Hypoproteinemia, reduced muscle mass, impaired growth, delayed healing.	Emphasize mixed protein sources (legumes, fish, lean meat); improve amino acid profile via pseudocereals; consider protein-fortified GFPs.
Carbohydrates	Reliance on refined starches (rice, corn) with high glycemic index; loss of gluten-mediated inhibition of starch hydrolysis; low intake of complex carbs and fiber.	Elevated glycemic index in CD children vs. controls [PMID: 32093020]; increased sugar intake and low fiber across cohorts [PMID: 30650530].	Postprandial hyperglycemia, insulin resistance, metabolic syndrome risk; altered gut microbiota.	Promote naturally gluten-free whole grains (quinoa, amaranth, buckwheat); limit refined GFPs; integrate prebiotic fibers.

 doi:10.20944/preprints202510.1964.v1

Fats	Malabsorption of essential fatty acids (omega-3, omega-6) due to villous atrophy; high-fat GFPs to improve palatability; excess saturated fat intake on GFD.	Fat intake above recommendations in most pediatric CD cohorts [PMID: 29446437; 32455838]; GFPs contain ~2× more total fat than gluten-containing analogues.	Dyslipidemia (↑ LDL, ↓ HDL), obesity, metabolic syndrome; low PUFA status linked to inflammation.	Prioritize unsaturated fats (olive oil, nuts, fish); limit processed GFPs; regular lipid profile monitoring.
Fiber	Use of refined flours and starches reduces fiber density; removal of outer grain layers during milling; limited intake of plant-based foods.	Fiber intake consistently below dietary reference values; lower in CD adolescents vs. controls [PMID: 31337023].	Constipation, dysbiosis, increased metabolic and cardiovascular risk.	Encourage legumes, fruits, vegetables, and pseudocereals; reformulate GFPs with higher-fiber grains.

CD – Celiac disease; GFD – Gluten-free diet; GFP – Gluten-free product; PUFA – Polyunsaturated fatty acids; LDL – Low-density lipoprotein; HDL – High-density lipoprotein.

3. Specific Micronutrient Deficiencies in Pediatric CD

Micronutrients are essential to physiological homeostasis, yet many must be acquired through diet as they cannot be synthesized endogenously. In CD, deficiencies commonly observed at diagnosis result from malabsorption and may partially improve following adherence to a GFD. However, persistent or newly emerging deficiencies have also been reported, reflecting both incomplete mucosal recovery and suboptimal dietary quality. Notably, many studies evaluating nutrient intake in CD rely on nutritional data derived from commercial GFP labels, yet the inconsistent reporting of micronutrient composition introduces the potential for underestimation of actual intake in the literature.

3.1. Iron Deficiency

Iron deficiency is one of the most common extraintestinal manifestations of CD, presenting either as overt iron deficiency anemia (IDA) or as subclinical depletion. Ferritin is the most reliable biomarker of iron status, though its interpretation may be confounded by inflammation. Iron deficiency, with or without anemia, is frequently observed in pediatric CD, particularly at diagnosis. One study reported that 73.3% of affected children showed some degree of deficiency, with the highest prevalence among infants and older children [60]. Similarly, Mt et al. (2016) found anemia in 30.1% of children with CD, of whom 21.6% had confirmed IDA, while a regional study from Southern Punjab, Pakistan, revealed that 17.4% of children with IDA were subsequently diagnosed with CD [60].

Iron deficiency may be overt or subclinical and can, in some cases, represent the sole manifestation of CD, especially in atypical or silent forms lacking gastrointestinal symptoms [61]. Serological testing for celiac-specific antibodies followed by duodenal biopsy remains the diagnostic standard. In one cohort of children with moderate-to-severe IDA, 10.5% tested positive for celiac serology, and 3.9% were confirmed histologically [62].

Strict adherence to GFD is the cornerstone of therapy, facilitating mucosal healing and restoring iron absorption. Most pediatric patients normalize ferritin levels within 12 months of GFD initiation, even without iron supplementation [63]. Persistent deficiency despite compliance may require pharmacologic iron replacement. Regular monitoring of hemoglobin, ferritin, and serum iron levels is essential for effective management and to prevent recurrence.

 doi:10.20944/preprints202510.1964.v1

3.2. Vitamin D Deficiency

Vitamin D deficiency is markedly more prevalent in children with CD than in healthy controls. Meta-analyses report that serum 25-hydroxyvitamin D_3 levels are, on average, 5.77 nmol/L lower in children with CD [64] . In a Kuwaiti cohort, 31% of affected children exhibited growth stunting and 20.8% had a low BMI-for-age, with vitamin D deficiency identified as a key factor [64]. Similarly, a cross-sectional study found that 31.5% of children positive for anti–tissue transglutaminase antibodies were vitamin D deficient, highlighting the need for systematic screening [65].

The primary mechanism is intestinal malabsorption secondary to villous atrophy, which reduces uptake of fat-soluble vitamins, including vitamin D [66]. Other contributors include insufficient dietary intake and limited sunlight exposure, both common in pediatric CD populations [67]. Socioeconomic factors, such as lower household income and maternal education, further increase the risk of vitamin D deficiency and growth impairment [63]. Routine measurement of serum 25(OH)D levels is therefore recommended at diagnosis and during follow-up to ensure sufficiency [67].

Adherence to GFD typically improves vitamin D status through restored intestinal absorption. Several studies have shown rising 25(OH)D_3 levels after GFD initiation [66,68]. Moreover, fortification of gluten-free foods with vitamin D has demonstrated additional benefits for serum vitamin D concentrations and bone health in children with CD [69].

3.3. Zinc

Zinc deficiency is highly prevalent among children with CD, including those adhering to a GFD. In one study, 91% of pediatric CD patients on a GFD exhibited low serum zinc levels, with median concentrations significantly lower than those of healthy controls [70]. The pathophysiology involves intestinal epithelial damage that impairs zinc absorption and increases fecal zinc losses [71]. Untreated CD is consistently associated with reduced serum zinc concentrations compared with non-celiac controls, indicating that the enteropathy itself drives systemic depletion [72]. Zinc plays an essential role in epithelial integrity, immune competence, and growth. Deficiency can cause stunted growth, immune dysfunction, and increased susceptibility to infections such as diarrhea and pneumonia [73]. The condition is further exacerbated in malnourished children, among whom zinc deficiency occurs up to four times more frequently than in well-nourished peers [74].

3.4. Magnesium

Children with CD, particularly those with concurrent malnutrition, are at elevated risk of magnesium deficiency due to both insufficient dietary intake and impaired intestinal absorption. This deficiency contributes to poor growth and overall health impairment [63]. Magnesium is crucial for bone mineralization, and its deficiency has been associated with osteoporosis and reduced bone density [75]. Severe cases may present with neuromuscular symptoms such as spasms, tremors, and convulsions, which resolve following repletion [75]. In addition to musculoskeletal and neurological effects, magnesium deficiency promotes systemic inflammation and oxidative stress, potentially worsening intestinal injury and metabolic disturbances in CD [76]. Ensuring adequate magnesium intake through diet or supplementation is therefore essential. Regular monitoring of serum magnesium levels is recommended, especially in children with persistent malabsorption or inadequate intake [77].

3.5. B Vitamins

Among the most clinically relevant micronutrient deficiencies in untreated CD are those of vitamin B_{12} and folate, both essential for hematopoiesis, neurological function, and cellular growth. Although the terminal ileum, the primary site of vitamin B_{12} absorption, is typically less affected in CD, deficiency has been reported in up to 41% of patients [78]. The underlying mechanisms include extensive villous atrophy and impaired pancreatic exocrine function, both of which compromise cobalamin absorption. In children, vitamin B_{12} deficiency can cause developmental delay, cognitive

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impairment, and megaloblastic anemia. Notably, up to 16.3% of children with severe acute malnutrition show vitamin B_{12} deficiency, aggravating clinical outcomes.

Folate deficiency is equally concerning in pediatric CD and primarily results from the restrictive nature of GFDs. Many gluten-free products lack mandatory folate fortification, as observed in countries such as Canada, where folate intake among GFD consumers is significantly lower than in those consuming fortified wheat-based foods [79]. Folate deficiency impairs DNA synthesis and cell division and elevates homocysteine levels, a known risk factor for cardiovascular and skeletal disorders [80]. Autoimmune enteropathy in CD further reduces folate absorption [81]. Serum and erythrocyte folate assessments are reliable for diagnosing deficiency in children with CD [82]. While adherence to a GFD generally improves absorption, persistent deficiencies require supplementation. A strict GFD remains the cornerstone of management, often leading to gradual normalization of vitamin B_{12} and folate levels [78,83]. Nevertheless, continued monitoring is essential, as deficiencies may persist despite mucosal recovery, and supplementation may be necessary to prevent anemia, growth failure, and neurocognitive impairment [84].

Table 2 summarizes the principal micronutrient deficiencies identified in pediatric celiac disease, outlining their pathophysiology, prevalence, clinical implications, and evidence-based management strategies.

Table 2. Specific micronutrient deficiencies in pediatric CD: prevalence, mechanisms, and clinical implications.

Micronutrient	Mechanism of Deficiency	Prevalence / Key Findings	Clinical Consequences	Management and Monitoring
Iron	Villous atrophy leading to impaired iron absorption; chronic mucosal inflammation; low intake from unfortified gluten-free products (GFPs).	Iron deficiency (ID) or anemia in 30–73% of children with CD; ID may be sole presentation in atypical CD.	Iron deficiency anemia, fatigue, impaired growth and cognition.	Gluten-free diet (GFD) restores mucosal absorption; ferritin and Hb should be monitored; oral/IV supplementation if persistent.
Vitamin D	Fat malabsorption from villous atrophy; limited intake and sunlight exposure; socioeconomic and cultural factors.	$25(OH)D_3$ levels ↓ by 5.77 nmol/L vs. controls; 31–32% deficient in pediatric cohorts; linked to low BMI and stunting.	Rickets, osteopenia, delayed growth, increased fracture risk.	Routine 25(OH)D testing; GFD improves absorption; supplementation and fortified GFDs recommended.
Zinc	Enterocyte damage impairs absorption; fecal loss of zinc complexes; chronic inflammation.	Deficiency in up to 91% of CD children on GFD; lower serum zinc vs. controls.	Growth retardation, impaired immunity, recurrent infections.	Dietary counseling, zinc supplementation, and serum level monitoring.
Magnesium	Malabsorption and low dietary intake; loss via diarrhea; oxidative stress increases demand.	Frequent in malnourished CD children; associated with bone and neurological complications.	Muscle spasms, tremors, convulsions, reduced bone density, inflammation.	Dietary enrichment (legumes, nuts, seeds) or supplements; serum magnesium monitoring.
Vitamin B_{12}	Villous atrophy and pancreatic insufficiency impair absorption; low intake in GFD.	Deficiency in up to 41% of pediatric CD cases; higher prevalence in severe malnutrition.	Megaloblastic anemia, neurocognitive impairment, developmental delay.	GFD improves absorption; persistent cases require supplementation and monitoring.
Folate (Vitamin B_9)	Reduced intake from non-fortified GFPs; malabsorption due to enteropathy.	Low dietary folate in GFD consumers; associated with ↑ homocysteine and anemia.	Megaloblastic anemia, growth failure, cardiovascular and skeletal risk.	Encourage folate-rich foods (legumes, leafy greens) or supplementation;

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	monitor serum folate and homocysteine.

CD – Celiac disease; GFD – Gluten-free diet; GFP – Gluten-free product; ID – Iron deficiency; Hb – Hemoglobin; 25(OH)D – 25-hydroxyvitamin D.

4. Biomarker in CD

Many patients, including children, continue to experience deficiencies even after adopting a strict GFD, highlighting the need for comprehensive nutritional monitoring. Traditional nutritional assessment methods, such as anthropometry and dietary recall, are limited in chronic conditions like CD, where inflammation and malabsorption distort results. Biomarkers have thus emerged as valuable tools for assessing malnutrition, providing early and precise detection of deficiencies before clinical manifestations occur.

4.1. Liver Biomarkers

Human serum albumin (HSA) and prealbumin are key indicators of nutritional status in both obesity and CD. In obesity, mild hypoalbuminemia becomes more pronounced in the presence of diabetes [85], while the urinary albumin-to-creatinine ratio (UACR) is elevated, reflecting early metabolic renal dysfunction [86]. In CD, distinct hepatic alterations are observed: elevated transferrin levels due to iron deficiency anemia and mild hypoalbuminemia, generally less severe than in other malabsorptive disorders. Prealbumin, a sensitive marker of acute malnutrition, is often reduced, reflecting impaired protein metabolism [87]. These differences underscore the contrasting hepatic profiles of obesity-related metabolic dysfunction and CD-associated malabsorption.

4.2. Inflammatory and Metabolic Biomarkers

Chronic inflammation in untreated CD alters metabolic demands and nutrient utilization. Elevated C-reactive protein (CRP) and interleukin-6 (IL-6) indicate persistent inflammation, potentially interfering with absorption even after gluten withdrawal. Hyperhomocysteinemia, linked to B-vitamin deficiencies, serves as an emerging biomarker of cardiovascular risk in CD [90].

4.3. Advances in Biomarker Research

Recent advances in metabolomics and proteomics have enhanced molecular detection of malnutrition. These approaches identify early metabolic alterations, such as changes in branched-chain and aromatic amino acids, enabling preclinical intervention. Digital biomarkers, including wearable devices tracking diet and activity, complement biochemical measures by providing real-time data, though challenges such as data security and compliance remain [92].

4.4. Genetic Damage

Telomere-associated DNA damage is increasingly recognized in both obesity and CD. In children and adolescents, obesity correlates with accelerated telomere shortening in 85.71% of studies [93–95]. Weight loss interventions promote telomere elongation, suggesting partial reversibility [96,97], while improved glucose tolerance similarly correlates with increased telomere length [96,98]. Conversely, CD exhibits a distinct, irreversible telomere shortening pattern associated with chronic inflammation. A telomeric gene in the HLA class I region (6p21.3) has been identified as a CD susceptibility locus [99], supporting the concept of immune-mediated genomic instability [100,101].

4.5. Adipose Tissue Biomarkers

Adipose tissue dysfunction plays a central role in both obesity and CD. In obesity, hypertrophic adipocytes alter adipokine secretion, particularly leptin and adiponectin, thereby disrupting energy balance and insulin sensitivity [102]. Leptin levels rise in obesity, correlating with insulin resistance

 doi:10.20944/preprints202510.1964.v1

[103], and fall with caloric restriction. Adiponectin, which exerts anti-inflammatory effects, is reduced in obesity [104]. In CD, the link between adipokines and disease activity remains unclear; leptin receptors are present in the intestinal mucosa, but no consistent association has been demonstrated [103]. Hypothyroidism, a common comorbidity in both obesity and CD, further modulates adipokine profiles. El Amrousy et al. reported elevated leptin and reduced adiponectin in obese hypothyroid children, while lean hypothyroid subjects showed milder alterations [103]. These findings emphasize the complex interplay between adipokines, metabolic health, and autoimmune disease.

Table 3 summarizes the principal biomarkers associated with celiac disease, outlining their physiological relevance, characteristic alterations, and potential clinical utility for nutritional and metabolic assessment.

Table 3. Biomarkers in Celiac Disease and Their Clinical Significance.

Biomarker Category	Specific Biomarkers	Physiological / Clinical Role	Alterations in Celiac Disease (CD)
Liver Biomarkers	Human serum albumin (HSA), Prealbumin, Transferrin	Indicators of nutritional and hepatic status; prealbumin is a sensitive marker of acute malnutrition	↓ Albumin and prealbumin in active CD (protein malabsorption); ↑ Transferrin due to iron-deficiency anemia
Inflammatory & Metabolic Biomarkers	C-reactive protein (CRP), Interleukin-6 (IL-6), Homocysteine	Reflect systemic inflammation and metabolic stress; hyperhomocysteinemia linked to B-vitamin deficiency	↑ CRP and IL-6 in active CD; persistent low-grade inflammation even after GFD; ↑ Homocysteine due to folate, B_6, B_{12} deficiencies
Metabolomic & Proteomic Biomarkers	Branched-chain amino acids (BCAAs), Aromatic amino acids	Reflect nutritional and metabolic alterations; early indicators of malnutrition	Altered amino acid profiles in untreated CD; normalization after GFD; potential for early malnutrition detection
Digital Biomarkers	Dietary intake and activity sensors (wearables)	Real-time tracking of lifestyle and nutrition	Provide dynamic assessment of adherence and energy balance; limited clinical implementation
Genetic Damage Biomarkers	Telomere length, HLA-linked telomeric gene loci (6p21.3)	Indicators of genomic stability; telomere attrition reflects oxidative stress and inflammation	Persistent telomere shortening despite GFD; immune-mediated genomic instability distinct from metabolic-driven obesity effects
Adipose Tissue Biomarkers	Leptin, Adiponectin	Regulate energy balance, inflammation, and insulin sensitivity	Leptin receptor expressed in intestinal mucosa; inconsistent correlation with disease activity; thyroid comorbidity modulates adipokine levels

5. Consequences of Macro- and Micronutrient Malnutrition in Pediatric Celiac Disease

Children with CD are especially vulnerable to the adverse effects of macronutrient malnutrition. Chronic deficiencies can impair linear growth and delay puberty, with lasting effects on physical and psychosocial development [102]. During this critical developmental period, adequate macronutrient intake is essential, warranting more frequent nutritional monitoring in pediatric than in adult patients.

The growing consumption of ultra-processed gluten-free products, typically high in sugar and saturated fat but low in fiber and micronutrients, adds further metabolic risks. Even in children, such dietary patterns are associated with obesity, metabolic syndrome, and gut microbiota dysbiosis [36].

Therefore, dietary counseling should focus on limiting processed gluten-free foods and emphasizing naturally gluten-free whole foods.

Effective management of macronutrient malnutrition in CD requires a multidisciplinary approach involving dietitians, gastroenterologists, and primary care providers. Beyond gluten exclusion, nutritional education should promote: a) naturally gluten-free whole grains (e.g., quinoa, millet, buckwheat) to enhance fiber and complex carbohydrate intake; b) diverse, high-quality protein sources such as legumes, fish, and plant-based proteins to optimize amino acid balance and reduce inflammation; c) replacement of saturated fats with monounsaturated and polyunsaturated fats from olive oil, nuts, seeds, and fatty fish; d) reduced consumption of processed gluten-free products high in sugar and unhealthy fats. Personalized interventions should be guided by anthropometric, biochemical, and dietary assessments. When dietary adjustments are insufficient, targeted supplementation with key nutrients may be indicated.

A persistent concern in CD management is the link between strict GFD adherence and metabolic imbalance. Excessive intake of fat, sugar, and sodium increases the risk of cardiovascular disease and metabolic syndrome (MS). Several studies report rises in BMI and fat mass among pediatric CD patients after starting a GFD [105]. Więch et al. observed greater increases in weight, BMI, and fat mass in adherent children [106], while Kabbani et al. found that 15.8% of adults shifted from normal or low BMI to overweight following GFD initiation [107]. Conversely, Ukkola et al. noted normalization of weight in previously underweight patients, highlighting heterogeneity in outcomes [108].

The "compensatory hypothesis" suggests that improved absorption after mucosal healing restores caloric balance and promotes weight gain [109]. Additional factors include the higher fat, protein, and glycemic content of gluten-free products compared with gluten-containing equivalents [39]. Behavioral factors may also contribute, as gluten-free foods are often perceived as healthier, encouraging overconsumption. Recently, Papastamataki et al. reported gut–brain axis hormone alterations in children with CD, suggesting that disrupted appetite regulation may further influence post-dietary metabolic changes [110].

6. Nutritional Profile of Gluten-Containing and Gluten-Free Food Products

Adherence to a GFD induces symptom remission, normalization of antibody titers, and mucosal healing in CD [39]. However, its nutritional adequacy depends on both GFP composition and individual dietary habits. Population-based studies consistently report suboptimal nutritional status among GFD-adherent CD patients, implicating GFPs in perpetuating imbalanced nutrient intake.

Traditional gluten-containing (GC) staples such as wheat, barley, and rye breads provide essential macro- and micronutrients, including carbohydrates (42.7–51.9 g/100 g), protein (8.5–12.5 g/100 g), calcium, iron, zinc, magnesium, phosphorus, potassium, and B vitamins [111–113]. In contrast, rice- and corn-based GFPs are typically deficient in protein, fiber, and folate [39]. To replicate gluten's structural properties, manufacturers often add starches, fats, dairy or egg proteins, and hydrocolloids [114], thereby increasing caloric density and glycemic index (GI) [114,115]], which may lead to adverse metabolic outcomes[116,117]. Moreover, most GFPs lack micronutrient fortification, resulting in reduced vitamin and mineral intake.

International surveys across multiple continents reveal substantial variability in GFP nutrient composition [118–125]. Energy content is inconsistent, some studies report equivalence with GC products [39], while others find lower or higher values depending on category [118,124]. Fat content is frequently elevated [39,122], though findings vary [121,126]. Saturated fat levels are similarly inconsistent [39,127]. Carbohydrate and sugar data are heterogeneous, with several studies reporting higher sugar content in GFP breads and flours [120,122].

Fiber and protein deficits remain the most consistent findings. Multiple analyses document lower fiber in GFPs [[119], while others note category-specific variation [120,124]. Protein content is uniformly reduced, with GFP bread containing up to 30% less protein than wheat bread [121,122,124,125]. Alternative ingredients such as quinoa, amaranth, buckwheat, and legumes can improve protein and micronutrient profiles, but their use remains limited. Reformulation with unsaturated fats and vitamin-mineral fortification is needed to align with WHO/FAO guidelines limiting saturated fats to <10% of total energy.

Despite recent improvements, most GFPs still contain more fat and carbohydrate, higher glycemic potential, and less protein and micronutrients than GC counterparts [128]. These imbalances, coupled with inadequate fortification, compromise dietary adequacy in CD patients, especially children and those with restrictive diets [129]. Bread and pasta exemplify these disparities: GFP bread is higher in fat but lower in protein [125], while GFP pasta, often made from rice or corn starch, has an elevated GI [129]. Consequently, GFPs cannot be considered nutritionally equivalent to GC products [130].

Reformulation efforts should focus on protein enrichment, improved lipid profiles, and micronutrient fortification, with increased use of pseudocereals and legumes. Until such strategies are widely adopted, clinicians should encourage patients to prioritize naturally gluten-free, nutrient-dense foods and to limit processed GFP consumption.

7. Gut Microbiota and Gluten-Free Diet in Celiac Disease

Diet plays a central role in modulating gut microbiota composition and function, thereby influencing host physiology through multiple mechanisms [131]. Microbiota development progresses from birth to adulthood, stabilizing in mature individuals, although dietary changes, gastrointestinal disease, and antibiotics can significantly alter microbial balance [131]. Two main mechanisms underlie dietary modulation: competition among microbial species for substrates and diet-dependent variations in pH, bile salts, and micronutrient availability [131].

Individuals with CD exhibit distinct microbial profiles compared with healthy controls, with dysbiosis often persisting despite adherence to a GFD [132]. Reductions in beneficial taxa such as *Bifidobacterium, B. longum*, and *Lactobacillus spp.* are accompanied by increases in *Enterobacteriaceae spp.* [132]. These alterations reflect reduced polysaccharide intake during GFD adherence [133]. Since undigested polysaccharides normally reach the distal colon as fermentation substrates, their absence promotes competition and overgrowth of opportunistic species [133]. De Palma et al. documented significant declines in *Bifidobacterium spp., Clostridium lituseburense* group, *Fecalibacterium prausnitzii, Lactobacillus spp.*, and *Bifidobacterium longum*, together with increases in *Escherichia coli*, Enterobacteriaceae, and *Bifidobacterium angulatum* after one month of GFD exposure, suggesting that the GFD may inadvertently promote dysbiosis rather than restore microbial balance. Dysbiotic patterns compromise mucosal defense and foster chronic inflammation [133]. Polysaccharide fermentation generates short-chain fatty acids (SCFAs) that inhibit enterobacteria; low fiber intake diminishes SCFA production, reducing this protective effect. Conversely, fiber enrichment supports SCFA synthesis and microbial diversity [133].

The gut microbiota influences nutrient metabolism, xenobiotic degradation, mucosal barrier integrity, pathogen defense, and immune regulation [134]. Microbial composition is shaped not only by diet but also by birth delivery mode and antibiotic exposure [135]. Notably, diet-induced microbial shifts occur rapidly: David et al. demonstrated that dietary modification alters microbiota within days [136]. Persistent dysbiosis despite gluten withdrawal remains a major concern. Golfetto et al. found that CD patients exhibit microbial imbalance even under a GFD [137]. Whether dysbiosis precedes CD onset or results from gluten exclusion remains uncertain [137,138]. De Palma et al. similarly observed microbial depletion after one month of GFD in healthy adults, emphasizing the microbiota-disruptive potential of gluten exclusion.

Adjunctive interventions are therefore needed to mitigate GFD-related dysbiosis. Probiotic supplementation may restore beneficial taxa and enhance microbial resilience [139]. Combining probiotics with fiber- and polysaccharide-rich naturally gluten-free foods could promote microbial diversity and functionality, thereby improving clinical outcomes in CD patients [140]. Table 4 compares the macronutrient and micronutrient composition of gluten-free and gluten-containing

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products, highlighting the consistently lower protein and micronutrient density, higher fat content, and elevated glycemic index commonly observed in gluten-free formulations.

Table 4. Comparative nutritional characteristics of GFPs and GC products.

Nutrient / Property	Gluten-Containing (GC) Products	Gluten-Free (GFP) Products
Energy (kcal/100 g)	230–280	Similar or slightly lower; varies by product type
Protein (g/100 g)	8.5–12.5 (wheat bread)	↓ 20–40%; average 5–8 g/100 g
Total Fat (g/100 g)	2.0–4.5	↑ 50–100% higher; often 5–9 g/100 g
Saturated Fat (g/100 g)	0.5–1.5	↑ or comparable depending on formulation; often >2 g/100 g
Carbohydrates (g/100 g)	42–52	Similar or ↑ (especially in starch-based GFPs)
Sugars (g/100 g)	1.0–3.5	Variable; ↑ in breads, cakes, and mixes
Dietary Fiber (g/100 g)	3–7 (wholegrain); 1–2 (white bread)	↓ in most GFPs; occasionally ↑ in fiber-enriched products
Glycemic Index (GI)	50–70 (moderate)	↑ High; often >80 for rice/corn-based GFPs
Micronutrient Content	Fortified with iron, folate, B vitamins, minerals	↓ Unfortified; lower levels of iron, calcium, zinc, folate
Fortification Status	Mandatory in most countries	Rarely fortified; labeling inconsistent
Pseudocereal / Legume Inclusion	Rare in standard formulations	Emerging use (quinoa, amaranth, buckwheat, legumes) improves protein and fiber content
Overall Nutritional Quality	Balanced macronutrient distribution; fortified	Often imbalanced: ↑ fat, ↑ GI, ↓ protein, ↓ micronutrients

GFPs – Gluten-Free Products; GC – Gluten-Containing Products; GI – Glycemic Index.

8. Addressing Malnutrition in Celiac Disease: Integrated Strategies and Future Perspectives

Malnutrition remains a critical clinical and public health issue in CD, driven by both intestinal malabsorption and the restrictive nature of the GFD. Effective management demands a multifactorial approach integrating clinical monitoring, supplementation, and policy initiatives to sustain metabolic health and support optimal growth. The adoption of standardized biomarker panels represents a pivotal advance in nutritional assessment. While traditional anthropometry and dietary recalls provide valuable insights, they are insufficient to capture the biochemical complexity of malnutrition. The incorporation of molecular and biochemical biomarkers, encompassing gut microbiota composition, systemic inflammatory mediators (e.g., IL-6, CRP), and metabolic indices, offers earlier and more precise detection of deficiencies, enabling tailored interventions. Longitudinal studies remain essential to elucidate the long-term effects of GFD adherence on bone density, body composition, and micronutrient balance in both pediatric and adult cohorts.

Dietary optimization continues to be the cornerstone of therapy. A nutritionally adequate GFD supported by fortified gluten-free foods and appropriate supplementation can mitigate common deficiencies. Prioritizing fortification with iron, folate, vitamin D, and calcium is particularly important to prevent complications such as anemia, osteopenia, and delayed growth. Emerging advances in precision medicine are redefining nutritional care in CD. Integration of genetic, microbiome, and metabolomic profiling enables identification of individuals predisposed to nutrient malabsorption or altered metabolism, facilitating personalized supplementation strategies. For instance, patients with genetic variants affecting vitamin D or folate metabolism may benefit from individualized dosing regimens.

Combating malnutrition in CD requires coordinated action among clinicians, researchers, policymakers, and the food industry. Mandatory fortification of gluten-free staples with key micronutrients could improve dietary adequacy and reduce deficiency prevalence. Reformulation of commercial gluten-free foods to enhance protein quality, fiber content, and lipid profiles remains essential for achieving nutritional equivalence with gluten-containing counterparts.

Ultimately, the integration of clinical, nutritional, and molecular data into comprehensive care frameworks represents the next frontier in CD management. Bridging precision diagnostics with dietary innovation will allow the transition from symptom control toward prevention of long-term nutritional and metabolic sequelae.

9. Limitations and Future Directions

Despite growing interest in the nutritional consequences of pediatric CD, current evidence is limited by methodological inconsistencies, product variability, and a lack of long-term data.

Macronutrient intake data remain inconsistent, particularly for protein and fat, due to regional dietary differences, evolving GFP formulations, and non-uniform assessment tools. While fiber intake is often lower in CD populations, this reflects a broader dietary inadequacy common to children overall, exacerbated in CD by reliance on refined GFPs.

Commercial GFPs frequently exhibit suboptimal nutritional profiles, high in saturated fats and simple sugars, yet low in protein, fiber, and key micronutrients (iron, folate, B vitamins). Fortification is uncommon, and labeling is often incomplete, limiting accurate intake assessment. The integration of nutrient-dense ingredients like legumes and pseudocereals is hindered by cost and processing constraints.

Longitudinal studies are critically lacking. The long-term impact of GFD on growth, bone health, body composition, and metabolic risk remains underexplored, particularly in high-risk subgroups such as children with concurrent type 1 diabetes. Persistent dysbiosis despite GFD adherence further raises questions about microbiota-related consequences.

Finally, while biomarkers offer promise for early detection, their validation in pediatric CD is limited. Multi-omics and precision nutrition approaches remain underutilized but represent key future directions for optimizing individual care and public health strategies.

10. Conclusion

Macronutrient and micronutrient imbalances remain critical challenges in the nutritional management of pediatric CD. Although adherence to GFD restores intestinal integrity and alleviates clinical symptoms, its nutritional adequacy cannot be presumed. GFPs are frequently suboptimal, characterized by low protein quality, excessive saturated fat, insufficient dietary fiber, and limited fortification with essential vitamins and minerals. These deficiencies, particularly involving iron, vitamin D, calcium, and B vitamins, contribute substantially to growth impairment, delayed pubertal development, and increased long-term metabolic and skeletal risk.

Precision-based nutritional strategies, integrating targeted supplementation, dietary diversification, and, when necessary, specialized nutritional support, should form the foundation of individualized management. Systematic use of biochemical and molecular biomarkers may further refine monitoring and enable early detection of subclinical deficiencies.

A coordinated, multidisciplinary approach involving clinicians, dietitians, researchers, and the food industry is essential to improve the nutritional quality of GFDs. Reformulation of GFPs through fortification and enhancement of protein and fiber content, guided by evidence-based recommendations, represents a key step toward achieving dietary adequacy. Ultimately, ensuring balanced macro- and micronutrient intake transcends symptom control, establishing a cornerstone for comprehensive, lifelong metabolic and developmental health in children with celiac disease.

Author Contributions: Conceptualization, V.N.D and R.F..; methodology, V.N.D. and N.S..; validation, V.N.D., F.C., M.B. and R.F..; formal analysis, V.N.D., R.F..; investigation, F.C., C.D., L.G., S.P.C. and L.P.; data curation,

doi:10.20944/preprints202510.1964.v1

F.C.,L.G.,S.P.C.,M.B., and L.P.; writing—original draft preparation, V.N.D., N.S., F.C.,G.L.G.,C.D,. and L.P; writing—review and editing, S.P.C. and R.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

BMI	Body Mass Index
CD	Celiac Disease
CRP	C-Reactive Protein
ESPGHAN	European Society for Paediatric Gastroenterology
FAO	Food and Agriculture Organization
GC	Gluten-Containing
GFD	Gluten-Free Diet
GFP	Gluten-Free Products
GI	Glycemic Index
Hb	Hemoglobin
HDL	High-Density Lipoprotein
HSA	Human Serum Albumin
ID	Iron Deficiency
IDA	Iron Deficiency Anemia
IL-6	Interleukin-6
LDL	Low-Density Lipoprotein
MS	Metabolic Syndrome
MUAC	Mid-Upper Arm Circumference
PUFA	Polyunsaturated Fatty Acids
SCFA	Short-Chain Fatty Acids
WHO	World Health Organization

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