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Review

Enzymatic Patterns of Pancreatic Involvement in Celiac Disease: Pathophysiology, Diagnosis, and Clinical Significance

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Abstract

Celiac disease (CD) is a systemic immune-mediated disorder that extends beyond its classic intestinal manifestations to affect multiple organ systems, including the exocrine pancreas. While the association between CD and endocrine pancreatic disorders is well established, exocrine pancreatic involvement remains underappreciated despite its significant clinical implications. This review provides a comprehensive examination of pancreatic enzyme alterations in CD, focusing on three key biomarkers: serum amylase, serum lipase, and fecal elastase-1. The pathophysiological mechanisms linking intestinal injury to pancreatic dysfunction involve impaired enteroendocrine hormone secretion, inflammatory and mechanical obstruction of pancreatic drainage, and immune-mediated pancreatic injury. Hyperamylasemia in CD predominantly reflects macroamylasemia rather than true pancreatic inflammation, occurring through the formation of amylase-immunoglobulin complexes. Hyperlipasemia, detected in approximately twenty percent of untreated patients, typically presents as mild elevations that normalize with gluten-free diet (GFD) adherence. Reduced fecal elastase-1 levels indicate functional exocrine pancreatic insufficiency secondary to villous atrophy and impaired pancreatic stimulation, rather than structural pancreatic disease. Recognition of these enzyme patterns is essential for accurate diagnosis and appropriate clinical management. Most pancreatic abnormalities in CD are reversible with strict GFD adherence, emphasizing the functional rather than structural nature of pancreatic involvement in this condition.

Keywords: celiac disease; pancreatic enzymes; macroamylasemia; exocrine pancreatic insufficiency

Introduction

Celiac disease (CD) is a chronic, systemic immune-mediated disorder triggered by dietary gluten ingestion in genetically susceptible individuals. While classically recognized for its hallmark intestinal manifestations, including villous atrophy, crypt hyperplasia, and malabsorption, CD is now understood as a multisystem condition with diverse extraintestinal complications [1,2]. Its pathophysiology involves an aberrant immune response to gluten peptides, generating T-cell-mediated inflammation and autoantibodies such as anti-tissue transglutaminase (tTG) [3]. This inflammatory cascade not only damages the duodenal and jejunal mucosa but also disrupts the intricate network of enteroendocrine cells embedded within the intestinal epithelium [4,5]. These specialized cells play a critical role in orchestrating digestive processes through the secretion of regulatory hormones such as cholecystokinin and secretin, which are released in response to luminal

nutrients and coordinate the function of distant organs involved in digestion [6]. The architectural destruction of the intestinal mucosa in untreated CD results in quantitative and qualitative alterations in these enteroendocrine cell populations, leading to impaired hormone secretion and subsequent downstream effects on organs that depend on these signals for proper function [7]. Furthermore, the chronic inflammatory state characteristic of CD extends beyond the intestinal epithelium, with immune dysregulation, autoantibody production, and cytokine release potentially affecting various organ systems [8]. As the only currently effective therapy, strict lifelong adherence to a gluten-free diet (GFD) leads to mucosal healing and recovery of these regulatory pathways in most patients [9].

This systemic nature of CD underscores the importance of recognizing and understanding its extraintestinal manifestations, which can significantly impact clinical outcomes, nutritional status, and quality of life in affected individuals. Among the organs potentially affected, the pancreas is of particular interest. While the association between CD and endocrine pancreas disorders, especially type 1 diabetes mellitus, has been well characterized [10], the exocrine pancreas has been comparatively underexplored despite its clinical significance [11]. The exocrine pancreas is responsible for secreting digestive enzymes essential for carbohydrate, protein, and lipid digestion, and its activity is tightly regulated by neurohormonal signaling originating from the duodenum and proximal jejunum [12,13]. Because pancreatic stimulation depends heavily on cholecystikinin and secretin-mediated signaling from healthy mucosa, damage to the proximal small intestine in CD provides a biologically plausible mechanism for secondary pancreatic dysfunction [14]. This intimate functional relationship between the intestinal mucosa and pancreatic secretory activity provides a mechanistic foundation for understanding how intestinal pathology in CD can lead to pancreatic dysfunction. Assessment of pancreatic function relies on various biomarkers, with serum amylase and lipase serving as indicators of acute pancreatic inflammation, while fecal elastase has emerged as a reliable non-invasive marker for evaluating exocrine pancreatic sufficiency [15,16].

Given the growing recognition that pancreatic involvement in CD may be more common than previously appreciated and can significantly influence clinical outcomes and nutritional status, a comprehensive understanding of pancreatic enzyme alterations in this condition is essential [17]. This review aims to provide a detailed examination of the three major pancreatic enzymes, amylase, lipase, and fecal elastase-1, specifically focusing on their diagnostic utility, clinical patterns, mechanistic alterations, and prognostic implications in patients with CD.

Search Strategy

We conducted a comprehensive review of research focusing on pancreatic enzyme abnormalities in CD. To achieve this, we searched the electronic databases PubMed, EMBASE, and Scopus for relevant literature available up to December 2025. Our search strategy combined terms related to pancreatic enzymes ("pancreatic enzyme" OR "amylase" OR "hyperamylasemia" OR "macroamylasemia" OR "lipase" OR "hyperlipasemia" OR "fecal elastase" OR "fecal elastase-1" OR "pancreatic elastase" OR "exocrine pancreatic insufficiency" OR "pancreatic function" OR "pancreatic dysfunction") with terms related to CD ("celiac" OR "celiac disease" OR "CD" OR "CeD" OR "coeliac" OR "coeliac disease" OR "gluten enteropathy" OR "Gluten-Sensitive Enteropathy" OR "Nontropical Sprue" OR "Celiac Sprue").

To refine the selection of articles, we applied inclusion and exclusion criteria to ensure that the studies were relevant and methodologically sound. We included human studies investigating pancreatic enzyme patterns in CD, such as clinical trials, observational studies, cohort studies, case-control studies, and clinically relevant case reports. Studies examining the pathophysiological mechanisms linking CD to pancreatic involvement were prioritized. We excluded studies not focused on CD or pancreatic enzymes, as well as editorials, conference abstracts, and opinion pieces lacking original data. Articles published in languages other than English were excluded if no translation was available.

Pancreatic Involvement in Celiac Disease: Pathophysiological Mechanisms

The pancreas serves essential endocrine and exocrine functions, with the exocrine pancreas secreting digestive enzymes in response to neurohormonal signals from the duodenum and proximal jejunum [18]. Because this regulatory axis depends heavily on the integrity of the small intestinal mucosa, CD can secondarily impair pancreatic stimulation. Although the endocrine associations of CD, particularly type 1 diabetes mellitus, are well recognized, exocrine pancreatic involvement remains comparatively underappreciated despite increasing evidence of functional disturbances in untreated or poorly controlled disease. Understanding the mechanisms linking intestinal injury to altered pancreatic secretion provides important context for interpreting the enzyme abnormalities commonly observed in CD [17,19].

CD and pancreatic exocrine dysfunction are linked through multiple interconnected pathophysiological mechanisms. While direct evidence for some of these proposed pathways remains limited and further investigation is needed, current research suggests three primary mechanisms through which intestinal pathology in CD may lead to pancreatic dysfunction: impaired enteroendocrine hormone secretion, inflammatory and mechanical obstruction, and immune-mediated dysregulation. These mechanisms are not mutually exclusive and may act synergistically in individual patients.

At the cellular and molecular level, the most prominent mechanism involves impaired secretion and release of critical pancreatic-stimulating hormones from the damaged proximal small intestine. The enteric endocrine system, particularly within the duodenum and proximal jejunum, plays an indispensable role in regulating pancreatic exocrine secretion through the release of cholecystokinin and secretin in response to luminal nutrients [6]. Immunohistochemical studies performed on small intestinal biopsies from untreated celiac patients have demonstrated significant quantitative and qualitative alterations in enteric endocrine cells, including a notable absence or marked reduction of secretin-producing cells [4]. Similarly, studies have documented impaired secretion of cholecystokinin-pancreozymin, resulting in diminished pancreatic acinar cell stimulation [5]. The mechanistic basis for this enterohormonal dysfunction lies in the destruction and architectural distortion of the intestinal mucosa, where enteroendocrine cells are either depleted or rendered dysfunctional by the ongoing inflammatory process [7].

A second proposed mechanism involves inflammatory and mechanical factors affecting pancreatic secretion. The inflammatory microenvironment created by CD may extend beyond the intestinal mucosa, with chronic duodenal inflammation potentially involving the ampullary and papillary regions where the pancreatic duct enters the duodenum, potentially causing papillary stenosis and impaired drainage of pancreatic secretions. This mechanical obstruction, even if partial, can lead to intraductal pressure changes within the pancreatic ductal system and contribute to both acute and chronic pancreatitis [20]. However, the frequency and clinical significance of this mechanical pathway in CD patients remain unclear, and more research is needed to establish whether inflammatory changes at the ampulla represent a common pathophysiological mechanism or occur only in select cases. The observation that some CD patients develop clinically overt pancreatitis while others show only functional enzyme abnormalities suggests that mechanical factors may contribute in a subset of patients, but are unlikely to explain the majority of pancreatic involvement.

The third proposed mechanism involves immune-mediated dysfunction of the pancreas itself. Intense immune activation characteristic of CD, involving both innate and adaptive immune responses with production of various autoantibodies and inflammatory cytokines, may have direct or indirect effects on pancreatic tissue. The documented presence of pancreatic enzyme-specific autoantibodies in some celiac patients, manifesting as macroamylasemia, suggests that immune dysregulation extends beyond the intestine to target pancreatic components [21]. Additionally, the possibility of autoimmune pancreatitis developing in the context of CD, though rare, indicates that shared immunological mechanisms may link these conditions [22]. However, it remains uncertain whether these immunological phenomena represent primary pathogenic mechanisms or secondary epiphenomena. The rarity of autoimmune pancreatitis in CD and the lack of systematic studies

examining pancreatic autoantibodies in large cohorts limit our understanding of this mechanism's contribution to pancreatic dysfunction. Further research is needed to determine whether immune-mediated pancreatic injury occurs commonly in CD or represents an uncommon complication in select patients.

Studies examining the correlation between the severity of intestinal mucosal damage and pancreatic function have provided important mechanistic insights. Research has demonstrated an inverse relationship between the degree of villous atrophy and pancreatic enzyme levels, with more severe mucosal damage corresponding to greater pancreatic dysfunction [23]. This dose-response relationship supports the concept that pancreatic impairment in CD is predominantly secondary to intestinal pathology rather than representing an independent primary pancreatic disorder. The reversibility of pancreatic dysfunction following implementation of a GFD provides compelling evidence for the functional and potentially reversible nature of this complication. As the intestinal mucosa heals and enteroendocrine cell populations recover, pancreatic stimulation normalizes, and enzyme production improves [24]. However, the timeline for pancreatic recovery may lag behind intestinal healing, and some patients may require temporary pancreatic enzyme replacement therapy during the recovery period [25]. Figure 1 illustrates the three proposed mechanisms linking CD to pancreatic dysfunction and highlights the potential for reversibility with GFD implementation.

The prevalence of pancreatic exocrine insufficiency in CD varies considerably depending on the diagnostic methods employed, with estimates suggesting that over twenty percent of patients with CD demonstrate defective exocrine pancreatic function [26]. This impairment has been documented both in newly diagnosed celiac patients and in treated individuals who remain symptomatic despite adherence to a GFD [17]. The clinical implications are substantial, as unrecognized pancreatic exocrine insufficiency can perpetuate malnutrition by impairing the digestion and absorption of nutrients, particularly fats and fat-soluble vitamins, creating a vicious cycle that compounds the nutritional deficits already present due to the enteropathy itself. In treated celiac patients experiencing persistent diarrhea, steatorrhea, and weight loss despite dietary compliance, pancreatic exocrine insufficiency should be considered. Current guidelines acknowledge this possibility and recommend assessment for pancreatic dysfunction in non-responsive CD [27]. However, the relative contributions of the three proposed mechanisms to the observed prevalence of pancreatic dysfunction remain unclear. Most evidence points to hormonal disruption as the primary driver, with inflammatory/mechanical and immune-mediated mechanisms potentially contributing in select cases. Future research should aim to characterize which patients are most likely to develop each type of pancreatic involvement and whether specific clinical or serological features can predict the underlying mechanism.

Given the clinical significance of pancreatic involvement in CD and its potential impact on nutritional outcomes and treatment response, a comprehensive understanding of pancreatic enzyme alterations in this condition is essential. The measurement of specific pancreatic enzymes provides valuable diagnostic and monitoring information in celiac patients. The following sections will provide a detailed review of the three major pancreatic enzymes, amylase, lipase, and fecal elastase-1, specifically examining their diagnostic utility, clinical patterns, mechanistic alterations, and prognostic implications in patients with CD.

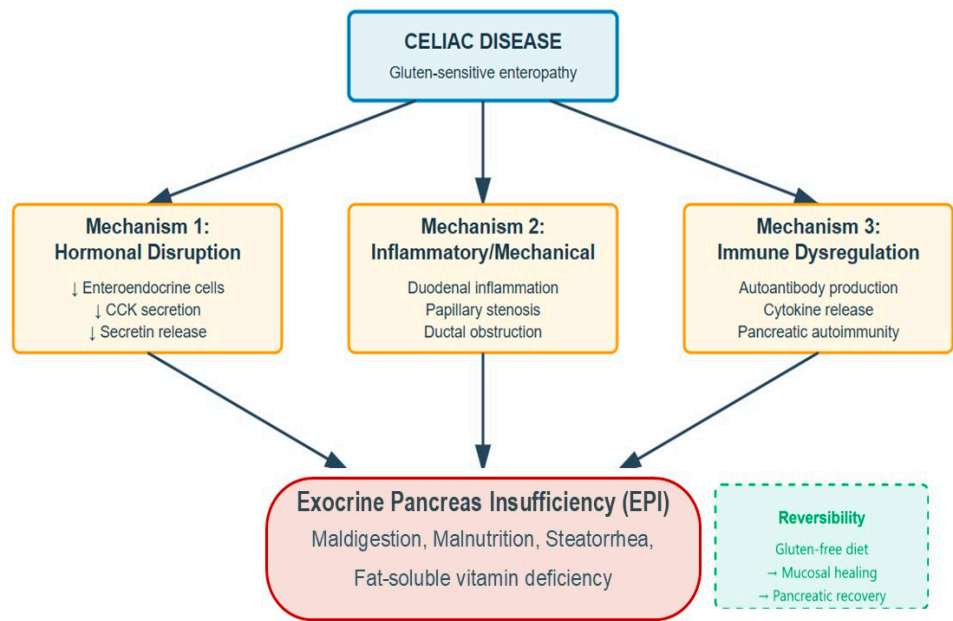


Figure 1. Proposed Pathophysiological Mechanisms Linking Celiac Disease to Exocrine Pancreatic Insufficiency. This schematic diagram illustrates three proposed mechanisms through which celiac disease may lead to exocrine pancreatic insufficiency. Mechanism 1 (Hormonal Disruption): Depletion of enteroendocrine cells in damaged intestinal mucosa reduces cholecystokinin (CCK) and secretin secretion, impairing pancreatic stimulation. Mechanism 2 (Inflammatory/Mechanical): Chronic duodenal inflammation causes papillary stenosis and pancreatic duct obstruction, impairing enzyme drainage. Mechanism 3 (Immune Dysregulation): Systemic immune activation produces pancreatic autoantibodies and inflammatory cytokines, which may directly affect pancreatic tissue. These mechanisms may contribute individually or synergistically to exocrine pancreatic insufficiency, resulting in maldigestion, steatorrhea, and malnutrition. The green dashed box indicates potential reversibility with gluten-free diet implementation.

Serum Amylase Abnormalities and Macroamylasemia in Celiac Disease

Amylase is a hydrolytic enzyme primarily produced by the pancreas and salivary glands, catalyzing the breakdown of complex carbohydrates into simpler sugars during digestion. Clinically, serum amylase serves as an essential biomarker for detecting pancreatic and salivary gland disorders, with elevated levels commonly indicating acute pancreatitis, though various pathological conditions can alter its concentration [28]. The enzyme exists in two principal isoforms: pancreatic amylase (P-type) and salivary amylase (S-type), each contributing distinct diagnostic information. Measurement of serum amylase remains fundamental in clinical practice for evaluating digestive system pathology [29]. However, the interpretation of elevated amylase levels becomes particularly complex in the context of CD, where multiple mechanisms may contribute to hyperamylasemia, ranging from macroamylase complex formation to true pancreatic involvement.

A major nationwide study by Sadr-Azodi and colleagues [30] established that patients with biopsy-verified CD demonstrate an almost three-fold increased risk of developing true pancreatitis compared to the general population, with an absolute risk of 126 per 100,000 person-years. Analyzing data from 28,908 CD patients across Sweden, the authors used robust diagnostic criteria combining enzymatic markers with clinical presentation to confirm this clinically important association. However, they acknowledged that the positive predictive value of elevated serum enzymes for diagnosing acute pancreatitis in CD patients remained unknown, as many CD patients may have enzyme elevations unrelated to pancreatic inflammation. Indeed, the study revealed that hyperamylasemia in CD more commonly reflects macroamylasemia (MA) than true pancreatitis. MA,

a condition characterized by high molecular weight amylase complexes in the blood, occurs five times more frequently in patients with active CD compared to healthy controls [30]. This finding highlights that, while CD patients face an increased risk of pancreatitis, the majority of amylase elevations in this population stem from mechanisms other than acute pancreatic inflammation.

Further research has focused on MA as a specific biochemical consequence and potential initial presentation of CD. MA represents complexes of amylase bound to immunoglobulins (typically IgA or IgG) or other macromolecules, resulting in reduced renal filtration and isolated hyperamylasemia. These high-molecular-weight complexes have impaired glomerular filtration, resulting in a characteristically low amylase-creatinine clearance ratio (ACCR), which distinguishes MA from other causes of hyperamylasemia [31]. This condition, which can be idiopathic, is also associated with several inflammatory and autoimmune disorders, including CD. Rabsztyn and colleagues [21] systematically investigated this relationship by measuring total amylase and macroamylase fractions in newly diagnosed celiac patients, patients on a GFD, and healthy controls. The study demonstrated that 17.7% of active CD patients exhibited hyperamylasemia, but when the macroamylase fraction was removed, pancreatic and salivary amylase levels did not differ among groups, indicating that elevated amylase in CD is primarily attributable to increased MA rather than true pancreatic or salivary hypersecretion. Notably, 16.8% of active CD patients and 7% of those on GFD demonstrated MA, compared with only 3.4% of healthy controls, suggesting persistent alterations in amylase handling even after dietary treatment. Although the authors proposed that MA may relate to immunologic mechanisms, they did not find correlations between MA levels and celiac serology or total IgA concentrations [21].

The importance of recognizing MA as an extraintestinal manifestation of CD is underscored by case reports, demonstrating variable clinical presentations and treatment responses. Depsames et al. [32] described a case where MA was the first clinical manifestation of CD in a 52-year-old woman presenting with markedly elevated serum amylase, very low urinary amylase, and a reduced ACCR, strongly indicative of MA, but without classic gastrointestinal symptoms. Serologic testing confirmed CD, and initiation of a GFD led to rapid and complete normalization of serum amylase and clinical recovery within two months. This reversibility supports the hypothesis that immune dysregulation in untreated CD may facilitate the macromolecular complex formation [32]. Conversely, Al-Rufayi et al. [33] reported a case of a young woman with persistent hyperamylasemia ultimately diagnosed with CD. Despite markedly elevated serum amylase and a reduced ACCR consistent with MA, she had consistently normal lipase, normal imaging, and no clinical features of pancreatitis. Although a GFD led to clinical improvement and normalization of celiac serology, her serum amylase levels remained persistently elevated over a three-year follow-up, suggesting that in some patients, macroamylase complexes may persist despite successful treatment [33].

These contrasting outcomes highlight the heterogeneity of MA in CD and raise important questions about the underlying mechanisms. While many patients, like the case reported by Depsames et al. [32], demonstrate complete reversibility with GFD, suggesting an active gluten-driven immune process, others show persistent MA despite dietary treatment and mucosal healing. Several explanations for this heterogeneity warrant consideration. First, some patients may have irreversible antibody formation or long-lived plasma cells producing amylase-specific autoantibodies that persist even after gluten withdrawal. Second, persistent MA could indicate ongoing subclinical inflammation despite apparent dietary adherence, either due to inadvertent gluten exposure or slow mucosal recovery. Third, some patients may have coexisting idiopathic MA unrelated to their CD, which would not be expected to resolve with GFD. The observation by Rabsztyn and colleagues that 7% of treated patients maintained MA despite being on a GFD supports this clinical heterogeneity and suggests that persistent MA does not necessarily indicate treatment failure [21]. These findings emphasize the need for individualized interpretation of amylase elevations in CD patients and caution against using persistent hyperamylasemia alone as a marker of ongoing disease activity.

The immunological mechanisms underlying MA in CD have been most comprehensively explored through pediatric case studies. Barera et al. [34] investigated an 11-year-old girl with chronic

abdominal pain, growth retardation, and persistent hyperamylasemia, finding markedly elevated serum amylase with normal lipase and severely reduced ACCR. After GFD initiation, progressive normalization of serum amylase occurred. Using immunoprecipitation assays, the authors demonstrated that in this single patient, >94% of the serum amylase activity precipitated with protein A Sepharose, confirming immunoglobulin-bound macroamylase complexes. ELISA testing revealed strikingly elevated IgA and IgG autoantibodies to α -amylase, levels far exceeding those of untreated celiac controls, along with autoantibodies to exocrine pancreatic tissue. Importantly, both amylase-specific and pancreas-specific autoantibodies declined progressively after GFD initiation. Notably, autoantibodies to amylase were not found in untreated celiac controls, indicating that such antibodies are not a universal CD feature but may occur in a subset of patients who develop MA. The authors concluded that MA in some pediatric patients may arise as part of a gluten-related autoimmune response, with amylase-binding antibodies serving as the pathogenic basis for impaired renal clearance [34].

Despite these compelling associations, the clinical utility of amylase screening for CD detection remains controversial. Migliori et al. [35] investigated whether asymptomatic pancreatic hyperenzymemia, including elevated serum amylase, pancreatic isoamylase, and lipase, might serve as a marker for occult CD. Evaluating 65 subjects with chronic, asymptomatic elevations of pancreatic enzymes, the study found that none tested positive for tTG antibodies, the serologic hallmark of CD. The authors concluded that screening for CD in individuals with benign pancreatic hyperenzymemia is not justified, as the enzymatic alterations did not correlate with undiagnosed CD.

However, this study examined a different clinical question than the prevalence studies described above. Rather than determining how common hyperamylasemia is among patients with established CD, Migliori's study asked whether hyperamylasemia in the general population predicts undiagnosed CD. The negative findings indicate that while hyperamylasemia occurs commonly in established CD, it has poor positive predictive value for detecting occult CD in asymptomatic individuals with isolated enzyme elevations. This distinction has important clinical implications. The study does not diminish the significance of hyperamylasemia as a manifestation of diagnosed CD, nor does it refute the finding that some patients present with MA as their initial CD manifestation. Rather, it suggests that routine CD screening based solely on asymptomatic enzyme elevation, in the absence of other clinical features or risk factors, is unlikely to be cost-effective. The authors further suggested that in patients diagnosed with CD who also present with variable amylase elevations, these abnormalities may reflect coexisting benign hyperenzymemia rather than celiac-associated pancreatic involvement in some cases, emphasizing the importance of clinical context in interpretation [35].

Overall, the relationship between amylase abnormalities and CD is complex and multifaceted. While CD patients demonstrate an increased risk of pancreatitis, hyperamylasemia predominantly results from MA rather than true pancreatic hypersecretion. The formation of amylase-immunoglobulin complexes, potentially driven by gluten-related autoimmune mechanisms, causes impaired renal clearance and persistent serum amylase elevation. Although many patients achieve normalization following GFD initiation, considerable heterogeneity exists. Isolated hyperamylasemia does not reliably indicate undiagnosed CD; however, in cases of unexplained persistent hyperamylasemia with normal lipase and reduced ACCR, CD should be considered, as dietary treatment may lead to complete biochemical resolution. A summary of the key studies evaluating amylase abnormalities and MA in CD is provided in Table 1.

Table 1. Summary of Studies on Amylase Abnormalities in Celiac Disease.

Author / Year	Study Design	Amylase Findings	Proposed Mechanism	Clinical Relevance	Ref
Sadr-Azodi et al. (2012)	Nationwide cohort study (n = 28,908 CD, n =143,746 controls)	CD patients exhibited higher rates of hyperamylasemia ; MA was about 5-fold more common in active CD.	Amylase abnormalities are not due to pancreatic hypersecretion; macroenzyme formation is suspected.	CD is associated with about a 3-fold increased pancreatitis risk; amylase/lipase alone has unclear PPV for pancreatitis in CD.	[30]
Al-Rufayi et al. (2025)	Single case report	Persistent hyperamylasemia with normal lipase; reduced ACCR indicative of MA.	Formation of macroamylase–immunoglobulin complexes	Hyperamylasemia may be the first clue to CD; MA may persist despite strict GFD.	[33]
Depsames et al. (2008)	Single case report	Markedly elevated serum amylase with very low urinary amylase; confirmed MA.	Amylase–IgA/IgG macromolecular complexes driven by CD-related immune activation.	MA can normalize rapidly with GFD; CD should be considered in unexplained hyperamylasemia .	[32]
Barera et al. (2001)	Pediatric case study with mechanistic immunologic analysis	Persistent hyperamylasemia ; low ACCR confirming MA.	Demonstrated autoantibodies to α -amylase and exocrine pancreas; macroamylase complexes >94% of circulating amylase.	CD-driven autoimmunity may cause MA; GFD leads to biochemical and immunologic normalization.	[34]

Rabsztyn et al. (2001)	Case-control and comparative study (n = 124 CD, n = 100 on GFD, n = 89 controls)	17.7% of active CD patients had hyperamylasemia ; MA present in 16.8% of active CD and 7% of those on GFD.	Elevated total amylase driven mainly by MA	MA relatively common in CD; may persist after GFD; not correlated with serology.	[21]
Migliori et al., (2011)	Prospective cohort of asymptomatic pancreatic hyperenzymemia (n = 65)	Persistent hyperamylasemia not associated with CD; no positive CD serology.	Hyperenzymemia unrelated to gluten exposure; benign pancreatic hyperenzymemia independent of CD.	Routine CD screening is not recommended for isolated asymptomatic enzyme elevation.	[35]

Abbreviations: CD, celiac disease; MA, macroamylasemia; PPV, positive predictive value; ACCR, amylase creatinine clearance ratio; GFD, gluten-free diet; ACCR, amylase-creatinine clearance ratio; IgA/IgG, immunoglobulin A/G.

Serum Lipase Elevations in Celiac Disease: Prevalence, Mechanisms, and Diagnostic Utility

Serum lipase is a highly specific marker of pancreatic injury, with elevated levels commonly indicating acute pancreatitis [36]. Compared to amylase, lipase has superior sensitivity and specificity for pancreatic pathology and remains elevated longer, making it the preferred biomarker in current clinical practice [35]. However, hyperlipasemia, defined as elevated serum lipase, is not exclusive to structural pancreatic disease and can occur in various systemic conditions, including renal failure, abdominal emergencies, and autoimmune disorders [37,38]. In contrast to the relatively extensive literature on amylase abnormalities in CD, lipase elevations have received limited investigational attention, with available evidence consisting primarily of a single cohort study and scattered case reports. Given the known association between untreated CD and secondary pancreatic dysfunction, characterizing the frequency and clinical significance of hyperlipasemia in celiac patients remains an important but underexplored area [39].

One of the earliest and most comprehensive studies to investigate this association was conducted by Carroccio and colleagues [40], who analyzed serum lipase levels in 202 newly diagnosed adult and pediatric CD patients. They established a baseline prevalence of hyperlipasemia at approximately 20% in untreated CD patients, with elevated lipase detected in 21.1% of adults and 18.7% of children. Importantly, these elevations were typically modest, rarely exceeding twice the upper limit of normal, suggesting a mild, reproducible biochemical abnormality rather than overt pancreatic injury. The authors excluded common alternative causes, such as alcohol abuse, drug exposure, renal dysfunction, and structural pancreatic pathology, as abdominal ultrasonography was normal across the cohort, including in patients with persistent hyperlipasemia. Furthermore, the abnormalities were independent of the patient’s symptom profile (typical, atypical, or asymptomatic presentation). Crucially, the functional link to CD was supported by the normalization of serum lipase in nearly all patients after 12 months on a strict GFD; persistence was observed only in cases of poor dietary adherence. The study concluded that even mild, unexplained hyperlipasemia should prompt consideration of CD screening [40].

While Carroccio's findings described mild elevations, individual case reports highlight the potential for more dramatic increases. Sahin et al. [41] reported a 45-year-old woman with isolated hyperlipasemia exceeding tenfold the upper reference limit, despite normal amylase and absence of radiologic evidence of pancreatitis. Extensive evaluation, including imaging and tumor markers, was unremarkable, while endoscopy confirmed villous atrophy with high-titer tTG antibodies, establishing a CD diagnosis. Serum lipase normalized within one year following GFD initiation, suggesting a causal relationship. This case illustrates that marked isolated hyperlipasemia, though apparently rare based on limited published literature, can occur as a presenting manifestation of CD and may respond to dietary treatment [41].

In contrast, Migliori and colleagues [35] challenged this association in their prospective study of 90 patients with isolated or combined pancreatic enzyme elevations despite normal imaging. Although lipase was elevated in 25 patients (28%), systematic serologic screening and duodenal biopsies revealed only one case of CD, and notably, this patient's lipase had normalized before diagnosis, indicating the earlier elevation was unrelated. The authors concluded that CD was not a significant cause of persistent hyperlipasemia and did not support routine screening for CD based solely on asymptomatic enzyme elevation [35].

The mechanisms underlying hyperlipasemia in CD remain poorly understood, as no studies have specifically investigated lipase elevations at the pathophysiological level. In the absence of direct mechanistic evidence, it is reasonable to hypothesize that the same pathways proposed for pancreatic dysfunction in CD, namely, impaired enteroendocrine hormone secretion (particularly cholecystokinin and secretin), inflammatory involvement of the pancreatic duct, and immune-mediated pancreatic injury, may contribute to lipase abnormalities. However, these remain theoretical extrapolations from general pancreatic physiology rather than lipase-specific mechanisms demonstrated in CD. The normalization of lipase with GFD in Carroccio's cohort and the Sahin case supports a functional mechanism linked to active enteropathy, but whether this reflects primarily hormonal disruption, resolution of systemic inflammation, or improved nutritional status cannot be determined from available data. Future mechanistic studies are needed to clarify the specific pathways leading to hyperlipasemia in CD and whether they differ from those underlying amylase abnormalities.

In summary, the limited existing literature suggests that mild hyperlipasemia is a relatively common, reversible biochemical feature of untreated CD, likely reflecting a functional mechanism linked to active enteropathy. However, the available data are conflicting regarding the clinical utility of lipase elevation as a screening tool for occult CD, especially in patients referred for unexplained asymptomatic hyperenzymemia. The negative findings from Migliori et al. suggest that routine CD screening based solely on isolated asymptomatic enzyme elevation has limited diagnostic yield, consistent with findings for amylase in the same population. Further prospective studies are essential to fully characterize the underlying mechanisms and determine whether serum lipase levels can be reliably incorporated into the diagnostic pathway for CD. Additionally, research is needed to establish whether lipase measurements offer advantages over amylase in distinguishing macroenzyme formation from true pancreatic involvement, and whether combined enzyme patterns (elevated lipase with normal amylase, or vice versa) have specific diagnostic or prognostic implications in CD. Additionally, research is needed to establish whether lipase measurements offer advantages over amylase in distinguishing macroenzyme formation from true pancreatic involvement, and whether combined enzyme patterns (elevated lipase with normal amylase, or vice versa) have specific diagnostic or prognostic implications in CD. A summary of the key studies evaluating lipase abnormalities in CD is provided in Table 2.

Table 2. Summary of Studies on Lipase Abnormalities in Celiac Disease.

Author / Year	Study Design	Lipase Findings	Proposed Mechanism	Clinical Relevance	Ref
Sahin et al. (2021)	Single case report	Markedly elevated isolated lipase (>10× ULN) with normal amylase and normal imaging; lipase normalized after 12 months on GFD.	malnutrition-related pancreatic stress, neuroendocrine dysregulation, autoimmune pancreatic involvement	CD as an underrecognized cause of isolated hyperlipasemia; unexplained lipase elevation should prompt CD evaluation.	[41]
Carroccio et al. (2006)	Prospective clinical study (n = 202 newly diagnosed CD)	Hyperlipasemia present in about 20% of adults and children; mild elevations (<2× ULN); normalized after 12 months of GFD except in non-adherent cases.	Likely subclinical pancreatic inflammation rather than macroenzyme formation or impaired clearance.	Mild lipase elevation is common at CD diagnosis; unexplained hyperlipasemia may be a diagnostic clue for CD.	[40]
Migliori et al. (2011)	Prospective cohort of asymptomatic pancreatic hyperenzymemia (n = 65)	Lipase elevated in 28%; only 1 patient diagnosed with CD, and their lipase had already normalized.	Lipase elevations unrelated to CD; represent benign or idiopathic hyperenzymemia rather than gluten-driven pathology.	Asymptomatic hyperlipasemia does not warrant routine CD screening.	[35]

Abbreviations: CD, celiac disease; GFD, gluten-free diet; ULN, upper limit of normal.

Fecal Elastase-1 in Celiac Disease: A Marker of Functional Exocrine Insufficiency

Fecal elastase-1 (FE-1) is a well-established, non-invasive biomarker used primarily to assess exocrine pancreatic insufficiency (EPI) [15]. As a pancreatic-specific enzyme, elastase-1 is secreted

into the duodenal lumen and travels through the gastrointestinal tract virtually undegraded, with its concentration in stool directly correlating with pancreatic output [23]. This remarkable stability during intestinal transit distinguishes it from other pancreatic enzymes that undergo significant degradation, making FE-1 an ideal marker for clinical assessment [42]. The test demonstrates high specificity (90.2%) and moderate sensitivity (72.2%) for detecting EPI, establishing it as a cornerstone for diagnosing conditions such as chronic pancreatitis and cystic fibrosis [43]. Furthermore, FE-1 measurement offers several practical advantages: it is simple to perform, requires only a single stool sample, and remains unaffected by pancreatic enzyme replacement therapy, allowing accurate assessment even during treatment [44]. However, interpretation of FE-1 results requires careful clinical consideration, as various gastrointestinal conditions affecting the intestinal mucosa may influence enzyme levels independent of true pancreatic pathology [45].

Early and comprehensive studies established that a reduction in FE-1 can be observed in various intestinal disorders, including CD, even in the absence of primary pancreatic pathology. Carroccio and colleagues [46], in their assessment of FE-1's diagnostic utility, demonstrated that while the marker excelled at identifying pancreatic insufficiency, low levels also occurred in intestinal diseases, with one case of biopsy-proven CD falling below the normal threshold. This was attributed to secondary reductions in pancreatic enzyme output due to diminished secretion of pancreatic-stimulatory hormones resulting from intestinal mucosal injury. This initial observation underscored the need for careful interpretation of FE-1 in the context of mucosal damage [46]. Supporting this concept, Walkowiak et al. [47] specifically investigated FE-1 across various causes of villous atrophy and concluded that levels were significantly decreased in patients with mucosal damage, independent of the underlying diagnosis. They explicitly stated that villous atrophy impairs the release of enteric hormones like secretin and cholecystokinin, suggesting that low FE-1 in these patients reflects a functional, reversible change rather than intrinsic pancreatic disease, warning against a potential overdiagnosis of EPI [47].

The relationship between the severity of mucosal damage and exocrine pancreatic dysfunction was further clarified by Nousia-Arvanitakis et al. in a seminal pediatric study [48]. By comparing celiac patients on a GFD with those on a gluten challenge, they found a clear association: patients with intact intestinal mucosa (normal morphology) had enzyme levels comparable to healthy controls, while those with villous atrophy exhibited significantly lower enzyme activity. The inverse correlation between mucosal damage and enzyme output was further strengthened by the finding that pancreatic ultrasonography remained normal in all participants, regardless of enzyme levels or mucosal morphology, indicating the dysfunction was purely functional and not structural [48]. Rana et al. [49] provided strong corroborating evidence in adult patients, finding that 10 of 36 (28%) recently diagnosed celiac patients had reduced FE-1 levels, but these reductions did not correlate with significant pancreatic parenchymal abnormalities as assessed by endoscopic ultrasound and elastography [49]. Both studies concluded that the EPI observed in CD is typically a functional disturbance linked to villous atrophy-induced secondary pancreatic under-stimulation.

A critical finding across multiple investigations is the reversibility of reduced FE-1 levels following treatment of CD with a GFD. The initial hypothesis proposed by Carroccio and colleagues suggested that low FE-1 in untreated CD would likely improve after gut healing [46]. This was confirmed by Rana et al.'s follow-up: after at least three months on a GFD, FE-1 normalized in 6 out of 7 reassessed adult patients (86%), paralleling clinical improvement without the need for pancreatic enzyme supplementation [49]. Similarly, the study by Walkowiak et al. concluded that pancreatic function often normalizes after resolution of villous atrophy or adherence to an effective therapeutic regimen [47]. This reversibility supports the notion that the deficiency is secondary to enteropathy. A prospective longitudinal study by Evans and colleagues [25] in celiac patients with persistent diarrhea and low FE-1 at baseline documented a significant and progressive increase in FE-1 levels over time, with many individuals achieving normalization and allowing for the discontinuation of enzyme supplementation. Interestingly, this recovery occurred regardless of mucosal healing status on follow-up biopsy, suggesting a complex relationship between histological healing and functional

pancreatic recovery [25]. This apparent dissociation between FE-1 recovery and mucosal healing may reflect several factors: enteroendocrine cell function can potentially recover before complete villous reconstitution, variability in biopsy sampling and timing relative to FE-1 measurement, or involvement of mechanisms beyond villous architecture, such as peptide YY regulation, as Evans suggested. These findings indicate that while villous atrophy is a major driver of low FE-1, pancreatic function recovery can follow a timeline distinct from complete histological healing. Nevertheless, the consistent reversibility with GFD across studies strongly supports that FE-1 reduction in CD is predominantly a functional and treatable consequence of active disease.

While FE-1 is frequently reduced in untreated CD, its status in treated and non-responsive cohorts suggests that clinically relevant EPI is not a universal or major persistent issue. Gülcü Taşkın and Dilek [50] evaluated pancreatic function in 106 pediatric celiac patients stratified by growth status and found no statistically significant differences in fecal elastase levels between any of the growth subgroups. This led them to conclude that functional impairment may not be universal among pediatric patients, even those with growth retardation. The potential for dietary adherence or other patient-related factors to mitigate potential enzyme reductions was proposed as an explanation for the predominantly normal FE-1 values observed [50].

The clinical relevance of EPI in treated CD was examined by Yoosuf et al. [51] in a randomized, double-blind, placebo-controlled trial investigating pancreatic enzyme supplementation in adults with non-responsive CD. Only one participant had low FE-1 at baseline, and baseline FE-1 levels did not correlate with symptomatic response to enzyme therapy. Given the predominance of normal FE-1 values and lack of symptomatic benefit from enzyme supplementation, the authors concluded that EPI is unlikely to be a major driver of persistent symptoms in non-responsive CD populations, emphasizing that empiric enzyme therapy should not be routine [51].

In conclusion, the collective evidence strongly suggests that the presence of reduced FE-1 in CD is typically a secondary, functional disturbance directly linked to villous atrophy and subsequent impairment in the release of pancreatic-stimulatory hormones like secretin and cholecystokinin. Crucially, FE-1 levels often normalize rapidly upon adherence to a GFD and mucosal healing, reinforcing its functional nature. Therefore, in the clinical management of newly diagnosed CD, low FE-1 should be interpreted cautiously as a transient finding, and the routine, empiric use of pancreatic enzyme supplementation is generally unnecessary, especially since FE-1 is rare and poorly predictive of symptom response in non-responsive CD. A summary of the key studies evaluating FE-1 abnormalities in CD is provided in Table 3.

Table 3. Summary of Studies on Fecal Elastase-1 Abnormalities in Celiac Disease.

Author / Year	Study Design	Fecal Elastase Findings	Proposed Mechanism	Clinical Relevance	Ref
Walkowiak et al. (2001)	Comparative observational study of patients with various causes of villous atrophy (n = 16 CD, n = 18 SMS, n = 20 FA, n = 70 HC, n = 131 CF)	FE-1 significantly reduced in patients with villous atrophy, independent of underlying diagnosis	Villous atrophy decreases secretin/CCK release → reduced pancreatic stimulation → secondary functional PEI	Low FE-1 in CD may be falsely low due to mucosal damage; pancreatic function often normalizes after mucosal healing	[47]

Gülcü Taşkın & Dilek (2023)	Prospective single-center pediatric study (n = 106 diagnosed with CD)	Wide FE-1 range but no significant differences across growth-based SD groups	Variability may reflect dietary adherence or patient factors; many children may not develop meaningful PEI despite mucosal atrophy	FE-1 often normal in pediatric CD; PEI is not universal and may not explain growth differences	[50]
Carroccio et al. (2001)	Diagnostic accuracy study including pancreatic and intestinal malabsorption cohorts (n = 49 CF, n = 43 with various small intestine disease, n = 45 without GI disease)	Some CD patients showed low FE-1; one CD child had FE-1 below threshold despite no pancreatic disease	Intestinal mucosal injury → reduced CCK/secretin → transient secondary pancreatic hypofunction	FE-1 has reduced specificity in intestinal diseases; low FE-1 in CD may reverse on GFD; interpret cautiously to avoid misdiagnosis	[46]
Rana et al. (2016)	Prospective evaluation with FE-1 and EUS/EUS elastography in adults with untreated CD (n = 36)	28% had reduced FE-1; FE-1 normalized in 86% after ≥3 months of GFD	Functional reduction due to impaired hormone secretion, malnutrition-related enzyme synthesis deficits, and villous atrophy	Low FE-1 common but reversible; structural pancreas usually normal; enzyme therapy generally unnecessary unless symptoms persist	[49]
Yoosuf et al. (2022)	Randomized, double-blind, placebo-controlled crossover trial in	Only 8% had low FE-1; FE-1 did not predict response to	Low FE-1 may be artifactual; PEI unlikely major driver of	Low FE-1 is rarely clinically meaningful in NRCD; enzyme therapy should	[51]

	adults with NRCD (n = 12)	pancreatic enzymes	NRCD symptoms	not be empirically used	
Evans et al. (2010)	Prospective 4-year longitudinal study with serial FE-1 measures of adults with CD (n = 20)	Low FE-1 at baseline; significant and progressive FE-1 improvement over time, often normalized	Mechanisms may include impaired CCK, peptide YY dysfunction; FE-1 recovery occurred even without mucosal healing	FE-1 is useful to track functional PEI; pancreatic dysfunction is often reversible, allowing discontinuation of enzyme therapy in many cases	[25]
Nousia-Arvanitakis et al. (1999)	Case-control study (n = 36 CD, n = 36 HC) with serial assessment of FE-1 (on GFD and after 6-month gluten challenge).	Villous atrophy is associated with significantly reduced FE-1; dysfunction recurred with gluten challenge	Strong correlation between mucosal damage and pancreatic hypofunction	Reversible, functional PEI in pediatric CD; relationship between mucosal status and FE-1	[48]

Abbreviations: CD, celiac disease; SMS, secondary malabsorption syndrome; FA, food allergy; HC, healthy control; CF, cystic fibrosis; FE, fecal elastase; CCK, cholecystokinin; PEI, Pancreatic exocrine insufficiency; GI, gastrointestinal; GFD, gluten-free diet; EUS, endoscopic ultrasound; NRCD, non-response celiac disease.

Conclusions

Pancreatic enzyme abnormalities represent an important yet underrecognized extraintestinal manifestation of CD with significant clinical implications. This review demonstrates that alterations in serum amylase, serum lipase, and fecal elastase-1 are common in untreated CD, reflecting predominantly functional rather than structural pancreatic involvement. Hyperamylasemia occurs primarily through macroamylase complex formation, hyperlipasemia affects approximately 20% of patients with mild elevations, and reduced FE-1 indicates secondary EPI driven by impaired enteroendocrine hormone secretion.

The reversibility of these abnormalities following GFD adherence underscores their functional nature and reinforces the critical importance of dietary compliance. Clinicians should recognize that unexplained pancreatic enzyme elevations may warrant CD screening, while patients with persistent symptoms despite treatment may benefit from pancreatic function assessment. However, routine empiric pancreatic enzyme supplementation is not recommended, as most patients experience spontaneous normalization with mucosal healing.

Future research should focus on identifying predictive biomarkers for persistent pancreatic dysfunction and characterizing the specific immunological mechanisms underlying these enzymatic alterations to optimize personalized management strategies for celiac patients.

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