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THE ROLE OF ENZYME THERAPY IN THE TREATMENT OF NON-INFECTIOUS GASTROINTESTINAL DISORDERS IN CHILDREN

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Abstract: Non-infectious gastrointestinal disorders in children, including lactose intolerance, exocrine pancreatic insufficiency, and functional digestive disturbances, pose a significant burden on quality of life and nutritional status. Enzyme therapy—comprising lactase supplementation, pancreatic enzyme replacement therapy (PERT), and other digestive enzyme supports—has emerged as a key management strategy. In this review article, we systematically examined clinical studies and trials from 2000 to 2023 regarding the efficacy, dosing strategies, and safety profiles of enzyme therapy in the pediatric population. Our literature search revealed strong evidence supporting lactase supplementation for lactose intolerance and PERT in conditions such as cystic fibrosis-associated pancreatic insufficiency. In addition, emerging evidence suggests that enzyme-based approaches may improve outcomes in some functional gastrointestinal disorders. Limitations include variability in dosing regimens, product formulations, and patient adherence. Future studies should aim to standardize enzyme formulations and dosing guidelines as well as explore novel enzymes for other specific non-infectious gastrointestinal conditions. We conclude that enzyme therapy represents an effective, safe, and practical adjunctive treatment strategy for managing non-infectious gastrointestinal disorders in children.

Keywords: enzyme therapy, pediatric gastrointestinal disorders, lactase supplementation, pancreatic enzyme replacement, non-infectious diseases, children

INTRODUCTION

Non-infectious gastrointestinal (GI) disorders represent a significant and diverse group of conditions that affect children worldwide. These disorders, including lactose intolerance, exocrine pancreatic insufficiency (EPI), and a range of functional gastrointestinal disorders (FGIDs) such as irritable bowel syndrome (IBS), contribute to considerable morbidity and can severely impact growth, nutritional status, and overall quality of life [1]. Research indicates that up to 65% of the global population shows varying degrees of lactose maldigestion—a figure that tends to be even higher among certain ethnic groups—underscoring the high prevalence of enzyme-related digestive issues in children [2].

A critical component of these disorders involves deficiencies or dysfunctions in digestive enzymes, which are essential for the proper breakdown and absorption of nutrients. For example, lactose intolerance arises from insufficient production of lactase, the enzyme responsible for cleaving lactose into its constituent sugars, glucose and galactose. In children with genetic predispositions or secondary causes such as post-infectious enteropathies, the lack of adequate lactase activity results in unabsorbed lactose reaching the colon, where fermentation by gut microbiota produces gas and osmotic diarrhea. Meanwhile, conditions like cystic fibrosis or chronic pancreatitis lead to insufficient production of

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pancreatic enzymes—lipase, amylase, and protease—resulting in malabsorption syndromes that not only diminish caloric intake but also impair growth and development.

Enzyme therapy has emerged as a cornerstone in the management of these conditions. Lactase enzyme supplements, for instance, have consistently shown effectiveness in improving both subjective symptoms (bloating, abdominal pain, diarrhea) and objective markers (such as hydrogen breath test measurements) of lactose malabsorption when administered prior to dairy consumption. Likewise, pancreatic enzyme replacement therapy (PERT) has revolutionized the care of children with exocrine pancreatic insufficiency by improving fat digestion, nutrient absorption, and growth outcomes. Recent meta-analyses and randomized trials support that dosing regimens—typically calibrated to provide 500 to 2,500 lipase units per kilogram per meal—are linked with significant improvements in body mass index and overall nutritional status, albeit with cautious attention to the upper dose limits to mitigate risks such as fibrosing colonopathy [3].

In addition to these classical enzyme deficiencies, emerging research suggests that digestive enzyme supplementation might have a broader therapeutic scope. In functional GI disorders, where the etiology is often multifactorial and includes contributions from visceral hypersensitivity and dysmotility, a subset of patients appears to benefit from adjunctive enzyme therapy combined with dietary modifications. Although the clinical evidence in this area is still evolving, preliminary studies indicate that supplementing with enzymes that assist in the breakdown of proteins, carbohydrates, and fats may optimize digestive efficiency and improve overall symptomatology [4].

Moreover, the evolution of enzyme therapy is moving towards more personalized approaches. Variability in enzyme activity among individuals—and the role of the gut microbiome in modulating enzyme effectiveness—emphasizes the need for tailored dosing strategies. Standardizing formulations while considering patient-specific variables such as age, weight, and the severity of enzyme deficiency is critical for achieving the best therapeutic outcomes.

Taken together, these insights highlight the substantial impact that enzyme deficiencies have on pediatric gastrointestinal health and the promising role that enzyme therapy can play in alleviating these burdens. By addressing the underlying pathophysiology of impaired digestion, enzyme-based therapies not only reduce immediate GI symptoms but also support improved nutritional status and developmental outcomes over the long term. This article, therefore, aims to provide a comprehensive review of the current evidence on enzyme therapy in children with non-infectious gastrointestinal disorders, exploring clinical efficacy, dosing strategies, safety profiles, and future research directions [5].

METHODS

Literature Search Strategy - We conducted a systematic review of the literature using major databases, including PubMed, Scopus, and Google Scholar. The search period covered articles published from January 2000 to March 2023. Keywords used in the search included “enzyme therapy,” “digestive enzyme supplementation,” “lactase enzyme,” “pancreatic enzyme replacement therapy,” “non-infectious gastrointestinal disorders,” “lactose intolerance,” “exocrine pancreatic insufficiency,” and “children.”

Inclusion and Exclusion Criteria

Inclusion criteria: Original research articles, randomized controlled trials (RCTs), meta-analyses, and review articles in English. Studies involving pediatric populations (ages 0–18 years) with non-

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infectious gastrointestinal disorders. Studies evaluating the clinical efficacy, dosing, or safety profile of enzyme therapy.

Exclusion criteria: Studies focused exclusively on adult populations. Articles addressing gastrointestinal infections or inflammatory conditions of infectious etiology. Case reports with insufficient data for broader analysis.

Data Extraction and Synthesis - Data from eligible studies were extracted independently by two reviewers and included study design, population characteristics, type of enzyme therapy used, clinical outcomes (symptom reduction, nutritional status, growth parameters), dosing regimens, and reported adverse effects. Discrepancies between reviewers were resolved by discussion, and data were synthesized narratively under key thematic areas.

RESULTS

Lactase Supplementation in Lactose Intolerance - Lactose intolerance is one of the most common non-infectious gastrointestinal disorders in children. A series of randomized controlled trials (RCTs) have examined the efficacy of exogenous lactase supplementation in reducing symptoms of lactose malabsorption. In one notable trial including children aged 5–12 years, the administration of lactase enzyme tablets prior to dairy consumption resulted in significant reductions in symptoms of bloating, abdominal pain, and diarrhea compared with placebo. Hydrogen breath tests used as a surrogate marker showed a reduced peak hydrogen concentration when lactase was administered concomitantly with lactose. These studies uniformly demonstrated that a single oral dose, ranging from 5,000 to 10,000 lactase units, administered immediately before dairy ingestion, can enhance lactose digestion and minimize clinical symptoms [6].

Pancreatic Enzyme Replacement Therapy in Exocrine Pancreatic Insufficiency - Exocrine pancreatic insufficiency (EPI), particularly in children with cystic fibrosis (CF) or chronic pancreatitis, requires lifelong enzyme supplementation to ensure adequate digestion and nutrient absorption. Several meta-analyses and clinical trials have established that pancreatic enzyme replacement therapy (PERT) improves weight gain, stool consistency, and overall nutritional status in pediatric populations. For instance, an RCT involving CF patients reported that tailored dosing of PERT not only improved fat absorption (as evidenced by reduced fecal fat excretion) but also enhanced growth velocity and body mass index (BMI) in children. Typical dosing recommendations suggest around 500–2,500 lipase units per kilogram per meal, with the upper limit often capped at 10,000 units per kilogram per day to minimize the risk of adverse events such as fibrosing colonopathy.

Enzyme Therapy for Functional Gastrointestinal Disorders - Beyond classical enzyme deficiencies, emerging data suggest that enzyme therapy may benefit children with functional gastrointestinal disorders (FGIDs) where the role of enzyme insufficiency is less clear but clinically relevant. Some studies have evaluated the use of supplemental digestive enzymes—such as proteolytic, lipolytic, and amylolytic enzymes—in children with irritable bowel syndrome (IBS) or functional dyspepsia. Although the quality of evidence in this area remains variable, preliminary findings indicate that these supplements can improve digestion and reduce symptom severity in selected patient subsets [7]. However, further research is needed to define optimal formulations and identify biomarkers to predict response.

Safety and Adherence - Across several studies, enzyme therapies have been well tolerated by children. Adverse effects reported were mild and transient, including occasional gastrointestinal discomfort, nausea, or bloating. The ease of oral administration and the noninvasive nature of these supplements

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promote adherence. Nevertheless, variability in product formulation and dosing regimens continues to pose challenges in standardizing therapy protocols. Patient education and caregiver involvement remain crucial to ensure proper dosing and timing—especially with products like lactase tablets that require administration shortly before lactose intake [8].

DISCUSSION

Interpretation of Findings - Our review indicates that enzyme therapy is a valuable treatment modality for a range of non-infectious gastrointestinal disorders in children. In lactose intolerance, the administration of lactase supplements clearly reduces both subjective symptoms and objective markers of lactose malabsorption. Similarly, in conditions involving exocrine pancreatic insufficiency—where enzyme production is reduced or absent—PERT is essential for optimizing nutritional status and promoting growth. The consistent benefits observed across multiple RCTs and systematic reviews support the clinical utility of these therapies.

In the context of functional gastrointestinal disorders, enzyme therapies are emerging as adjuncts to dietary modification. Although the mechanisms in these conditions are not solely related to enzyme deficiency, enhanced digestion may alleviate symptoms in a subset of children. Given the complex etiology of FGIDs, enzyme supplementation should be considered within an individualized therapeutic approach that also incorporates dietary modification, psychosocial support, and lifestyle changes.

Limitations - Despite the positive findings, our review also identifies several limitations. First, dosing regimens and product formulations vary considerably among studies, which may affect the comparability of outcomes. Second, many studies have relatively short follow-up periods; long-term safety and sustained efficacy data, particularly regarding risks such as fibrosing colonopathy with high-dose PERT, are still needed. Finally, while research in lactose intolerance and CF is robust, investigations into enzyme therapy for other functional disorders are sparse, and large-scale RCTs are warranted.

Future Directions - Future research should focus on standardizing dosing protocols and product formulations to ensure consistent and reproducible outcomes. Additional large-scale, long-term studies are needed—especially for the use of enzyme supplements in functional gastrointestinal disorders—to better define patient selection criteria and identify predictive biomarkers of therapeutic response. Furthermore, the integration of enzyme therapy with complementary treatments such as probiotics, dietary interventions, and behavioral therapies may offer synergistic benefits that warrant exploration.

CONCLUSION

Enzyme therapy has emerged as an essential and transformative treatment option for a variety of non-infectious gastrointestinal disorders in children. The robust body of evidence reviewed in this article demonstrates that the strategic use of exogenous enzymes—especially lactase for lactose intolerance and pancreatic enzyme replacement therapy (PERT) in cases of exocrine pancreatic insufficiency—can significantly alleviate symptoms, improve nutrient absorption, and enhance overall growth and quality of life in the pediatric population.

In the case of lactose intolerance, clinical trials consistently show that administering lactase supplements at appropriate doses immediately before the ingestion of dairy products reduces both subjective symptoms (such as bloating, abdominal pain, and diarrhea) and objective markers of malabsorption (e.g., hydrogen breath test levels). Similarly, for conditions associated with pancreatic enzyme insufficiency—most notably in children with cystic fibrosis—the use of PERT has not only improved stool characteristics and reduced steatorrhea but has also led to better weight gain and

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improved body mass index scores. These benefits directly translate to a more favorable nutritional status and overall well-being.

Beyond these well-established applications, emerging evidence suggests that enzyme therapy might also play a beneficial role in managing functional gastrointestinal disorders where the etiology is multifactorial and not solely based on a single enzyme deficiency. For such disorders, supplemental digestive enzymes may work synergistically with dietary modifications and other therapeutic strategies to relieve symptoms and improve digestive efficiency in select groups of children.

Despite these promising outcomes, several limitations must be acknowledged. Variability in enzyme formulations, dosing regimens, and the timing of administration poses challenges to standardizing treatment protocols. Moreover, while short-term safety profiles are generally favorable—with adverse effects being mild and transient—the long-term implications of chronic enzyme supplementation, especially at higher doses, require further investigation. There is also a need for more extensive randomized controlled trials focusing on enzyme therapy in less clearly defined functional gastrointestinal disorders to establish both efficacy and optimal patient selection criteria.

Looking forward, future research should aim to refine the dosage and formulation of enzyme products to ensure a uniform, reproducible therapeutic response across diverse pediatric populations. Integration of enzyme therapy with other treatment modalities—such as probiotics, dietary interventions, and behavioral therapies—could also yield synergistic benefits, paving the way for a more personalized and holistic approach to managing non-infectious gastrointestinal disorders in children. Greater emphasis on long-term studies will be essential to better understand the chronic safety of these treatments and to monitor potential complications such as fibrosing colonopathy in high-dose PERT regimens.

In summary, enzyme therapy remains a cornerstone in addressing nutritional deficiencies and digestive inefficiencies stemming from non-infectious gastrointestinal disorders in children. Its proven efficacy in conditions such as lactose intolerance and exocrine pancreatic insufficiency, combined with emerging applications in functional gastrointestinal disorders, underscores its significance in pediatric gastroenterology. Continued research, standardization of treatment protocols, and the development of personalized therapeutic strategies will help maximize the potential of enzyme therapy to improve clinical outcomes and quality of life for affected children.

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