CASE REPORT

Diamine Oxidase Supplementation for Histamine Regulation in Constipation-Predominant Irritable Bowel Syndrome: A Case Report

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Abstract

Since 2016, irritable bowel syndrome has been defined by a grouping of primary symptoms and no longer requires invasive testing for diagnosis. Abdominal pain related to bowel movements or relieved by having a bowel movement is the primary symptom of this functional gastrointestinal disorder. Through expanding appreciation of functional gastrointestinal disorders and the increasing understanding of gastrointestinal tract-brain interactions, a growing body of research is discussing the symptom overlap between IBS and histamine intolerance, as well as other issues of histamine metabolism and related neuroimmune regulation in the pathophysiology of IBS. Visceral hypersensitivity, exacerbated by increased histamine levels, may disrupt the intricate signaling between the central nervous system and enteric nervous system. This case report illustrates the use of supplemental diamine oxidase combined with trigger food avoidance to nearly completely abate IBS symptoms in a 46-year-old Japanese American female.

Keywords: case report, irritable bowel syndrome, constipation, diamine oxidase, histamine metabolism, HistaGest-DAO, Symptom Severity Score

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Introduction

Irritable bowel syndrome (IBS) is a commonly diagnosed disorder of the gastrointestinal (GI) tract. The diagnostic criteria names abdominal pain that can be relieved by defecation or accompanied with changes in stool form and/or frequency as the primary symptom of IBS and requires it be related to two or more of the following: altered stool passage, abdominal bloating, symptoms exacerbated by eating, and/or passage of mucus.[1,2] Changes in stool consistency are categorized on the Bristol stool form scale,[2] also referenced as the Bristol stool chart.

IBS affects more people than are diagnosed due to the disorder's broad symptom profile, which includes potentially familiar gastrointestinal issues, which for many people in our busy, high-stress modern world, can often be dismissed as due to other causes. Approximately 12% of patients seek primary care support for IBS-related complaints while varied studies show that up to 23% of the global population receive an IBS diagnosis.[3-6] For those affected, disruptive manifestations of GI function lead to a poorer quality of life and a more frequent reliance on the health-care system than people without IBS.[7]

IBS was once diagnosed only after exclusion of other confirmable disease states and was classically treated—after extensive and invasive testing—with probiotics, antibiotics, tricyclic antidepressants, selective serotonin re-uptake inhibitors and agents that modulate chloride channels and serotonin.[8] With the Rome Foundation escorting IBS from a diagnosis of exclusion to a symptom-positive identification, the need for significant testing was reduced, as echoed in the guidelines of the National Institute for Health and Care Excellence (NICE).[1]

The etiology is unknown and the diversity of personal experiences of IBS further complicates treatment.[6] Likely inputs contributing to IBS symptomatology are complexly rooted in gastrointestinal bacterial overgrowth, altered intestinal motility, dysbiosis of fecal microflora, intestinal permeability, carbohydrate malabsorption, visceral hypersensitivity, post-infectious reactivity, genetics, food sensitivity, intestinal mucosal inflammation, psycho-social issues, and disordered gut-brain interaction.[7,9]

Keying into the duality of histamine as both a dysregulator of serotonin when inflammation is present and as an exacerbator of visceral hypersensitivity is clinically and biochemically interesting. Serotonin (5-HT) is a major regulator of GI function, signaling gastrointestinal motility, sensation, and secretions; thus, altered serotonin signaling can cause and worsen symptoms in IBS.[10] Histamine in the GI tract, too, modulates motility,

increases gastric acid production, and regulates mucosal ion secretions.[11] Mucosal biopsy samples from patients with IBS show significantly higher counts of lamina propria mast cells and slightly higher histamine release than those of healthy people.[12,13]

DAO could be an impactful first choice of treatment for a patient with initial diagnosis of IBS because of its contribution to the degradation of histamine in the intestinal lumen with the established evidence of increased histamine in the GI tract of patients with IBS. While an understanding between histamine and IBS exists in the literature, at the date of this case report writing, there have been no published reports to show treatment responsiveness of diamine oxidase (DAO) supplementation on domain-specific symptoms of patients with IBS, specifically. This case examines the successful patient-initiated use of a diamine oxidase DAO supplement to support histamine metabolism to reduce a 46-year-old female patient's disruptive IBS symptoms with primary responsiveness of pain severity, pain frequency, and bowel dysfunction.

Narrative

The 46-year-old Japanese American, peri-menopausal female patient was diagnosed with constipation-predominant IBS (IBS-C) in 2020 after four months of persistent upper abdominal pain, bloating with significant stomach distention, gas, and constipation. Her symptoms began intermittently in her early 20s when she was away from home at college, a time she perceived as being stressful. Her symptoms increased in frequency through her late 30s and became chronic during the COVID-19 shutdown at age 41 in 2020.

She reported being a premature, vaginally delivered baby with no family history of irritable bowel syndrome or other gastrointestinal disorders. She had viral asthma in infancy and has had chronic asthma since age 17, which she manages with twice-daily 40 mg beclomethasone dipropionate long-acting inhaler. She recalled being an active and athletic teenager and adult. She shared that she was in perimenopause, as self-evidenced by her sense of abdominal weight gain, persistent breast tenderness, slightly elevated cholesterol, and laboratory markers of potential insulin resistance. Any menstrual cycle changes were unknown due to a Mirena® IUD, which has been in place since June 2022. She had an otherwise unremarkable health history, took no other prescription medications, and had no psychosocial challenges to report other than periods of increased perceived stress.

In 2020, during the pandemic shutdown—which she noted was a stressful time for her—she consulted a doctor via virtual appointment and was diagnosed with likely gut irritation due to IBS-C. No physical exam was conducted and no clinical findings were reported, both due to the virtual visit.

The physician prescribed a low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) diet. This special diet eliminates highly fermentable and poorly absorbed short-chain carbohydrates and polyols which, in abnormally functioning small intestines and colons, can cause or exacerbate gas, motility changes, and an altered gut microbiome.[14] The patient received minimal instruction and no follow-up after commencing the diet. Though clinically proven to improve overall gastrointestinal symptoms of IBS for 70% of patients who adhere to the diet for at least seven days,[15] the low-FODMAP diet provided no change in symptoms for this patient.

Three months later and still symptomatic, she sought the support of a nutritionist who recommended further dietary refinement via a stricter elimination diet with re-introduction stages to assess any potentially problematic foods for the patient. Bulb onions and wheat, both common oligosaccharide fructans,[14] were noted by the patient to be trigger foods through the elimination diet protocol. She reported continuation of a gluten-free diet (GFD) and avoidance of onions and onion forms (onion powder, etc.) from 2020 to 2024 with only minimally improved bowel function amidst frequent symptom exacerbation.

In September 2024, after self-directed information gathering during completion of her master's degree in nutrition, she purchased and began taking an exogenous DAO supplement, HistaGest-DAO™ (Designs for Health), providing 20 000 histamine-degrading units of DAO activity from 4.2 mg of porcine kidney extract per single-tablet dose. Helping to support histamine metabolism, DAO supplementation—derived from porcine kidney extract—augments the endogenous DAO present in the gut and prevents undegraded histamine from being absorbed through intestinal epithelial cells, reducing its accumulation in the blood. Such accumulations may trigger various symptoms, including those identical to IBS-C, such as constipation, bloating, indigestion, and pain.[16-20] She took a single tablet of the DAO supplement before any meal that she suspected could have a GI-upsetting trigger food for her.

This author interviewed the patient extensively and received her personal notes on her symptoms and treatment experience. Using the Irritable Bowel Symptom Severity Score (IBS-SSS) tool, developed by Francis and colleagues,[21] the patient reported a score change from 330/500 to 10/500 over time from her untreated state to post-dietary-change state to her final post-DAO supplementation state. In increments of 10, this tool uses 0 to rate no issue and 100 to rate severity of the issue over four common symptoms of IBS (severity and frequency of abdominal pain, bloating, and bowel dysfunction) and a fifth category for how IBS impacts overall quality of life. The maximum score, then, is 500 where scores of less than 75 indicate remission/healthy, 75-175 indicate mild IBS, 175-300 indicate moderate IBS, and >300 indicate severe IBS.

Table 1. Symptom Severity Score and Percentage Changes from Baseline Across Symptom Domains Based on Intervention for a 46-Year-Old Japanese American Female Patient with IBS

Intervention	Baseline (Pre-Treatment)	After Low-FODMAP/Triggers		After DAO Supplementation	
Symptom Domain	IBS-SSS Score	IBS-SSS Score	Initial Percent Improvement	IBS-SSS Score	Additional Percent Improvement
Pain Severity	40/100	40/100	0%	0/100	100%
Pain Frequency	70/100	70/100	0%	0/100	100%
Bloating	70/100	20/100	71.4%	10/100	14.3%
Bowel Dysfunction	70/100	50/100	28.6%	0/100	71.4%
Quality of Life	80/100	20/100	75%	0/100	25%

Abbreviations: IBS, irritable bowel syndrome; FODMAP, fermentable oligosaccharide, disaccharide, monosaccharide, and polyol; DAO, diamine oxidase; IBS-SS, Irritable Bowel Symptom Severity Score.

At baseline, the patient reported pain severity of 40/100, pain frequency of 70/100, bloating of 70/100, bowel dysfunction of 70/100, and quality of life of 80/100, all scored per the IBS-SSS. After her dietary intervention of low-FODMAP intake and further elimination of identified trigger foods of onions and wheat (gluten), she experienced a substantial 71.4% reduction in severity of her bloating with a moderate improvement (28.6% reduction) in bowel dysfunction and marked improvement in her reported quality of life (75% reduction). After adding DAO supplementation to her treatment protocol, she experienced complete resolution of pain severity, pain frequency, bowel dysfunction, and quality of life impairment. Her symptom of bloating had further incremental improvement, reaching an overall 85.7% reduction from baseline. (Table 1). The patient consented to the writing and publication of this case report.

The patient reported that taking the DAO supplement HistaGest-DAO™ led to a marked improvement in her quality of life resulting in the near-total resolution of her IBS-C symptoms. To date, she reports only minor, occasional bloating at an IBS-SSS level of 10/100 and total score of 10/500—indicating remission/healthy—through the ongoing intervention of taking one HistaGest-DAO™ tablet (20 000 histamine-degrading units of DAO activity) with meals she knows to contain triggering foods. She has had no adverse effects from DAO supplementation use.

Table 2. Timeline of Evolving Symptoms of Irritable Bowel Syndrome and the Effect of Various Treatment Interventions for a Japanese American Woman from Ages 20 to 46 Using the Irritable Bowel Symptom Severity Score Tool

1999-08-31	20 years old: patient experienced initial digestive issue lasting 1 month; symptoms included abdominal pain, bloating, and constipation; diagnosis of gastric ulcer after testing for hepatitis; no other testing conducted
2009-05-31	30 years old: patient had extended flare-up of original symptoms; diagnosed with acid reflux and prescribed Pepcid® with no improvement; patient subsequently discontinued taking Pepcid®
2019-06-01	40 years old: over last decade, patient continued experiencing symptom flare-ups with increasing frequency and duration; flares that had occurred every few years lasting for approximately 1 month began to occur every few months, lasting a week or longer
2020-01-31	41 years old: patient experienced flare-up of symptoms of upper abdominal pain, bloating, and constipation
2020-04-01	41 years old: PRE-DIAGNOSIS IBS-SSS TOTAL SCORE 330/500 = SEVERE IBS; pain severity 40/100, pain frequency 70/100, bloating 70/100, bowel dysfunction 70/100, quality of life 80/100
2020-04-01	41 years old: patient completed virtual gastroenterologist encounter describing severe, daily symptoms of abdominal pain, bloating, and constipation; diagnosed with gut irritation due to irritable bowel syndrome (IBS) with constipation; prescribed a diet low in short-chain carbohydrates (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols), and given minimal instruction for adhering to the diet
2020-07-15	41 years old: patient with minimal symptom improvement and no gastroenterologist follow-up, self-schedules appointment with nutritionist; recommended dietary changes with initial elimination diet followed by food re-introduction stages; food triggers identified as: bulb onions and wheat
2022-02-28	43 years old: patient continued following gluten-free diet and avoiding onions; experienced continued symptoms but with somewhat improved pain frequency, reduced bloating, and slightly improved bowel function; trigger foods caused frequent symptom flare-ups lasting approximately 3 days
2024-08-31	45 years old: POST-DIETARY CHANGES IBS-SSS TOTAL SCORE 200/500 = MODERATE IBS; pain severity 40/100, pain frequency 70/100, bloating 20/100, bowel dysfunction 50/100, quality of life 20/100
2024-09-01	45 years old: patient purchased Designs for Health HistaGest-DAO™ supplement; taken prior to meals with known or potential trigger foods/ingredients; since taking the supplement, flare-ups are rare except for occasional mild bloating; no longer experiencing abdominal pain or constipation
2024-11-30	46 years old: POST-SUPPLEMENT IBS-SSS TOTAL SCORE 10/500 = REMISSION/HEALTHY: pain severity 0/100, pain frequency 0/100, bloating 10/100, bowel dysfunction 0/100, quality of life 0/100

Discussion

The biogenic amine histamine plays a varying role depending on cell and receptor types as well as distribution of those receptors in different tissues.[16] Histamine is typically associated with inflammation as part of cytokine production in immune response. In addition, it is created by the dietary intake of foods affected by bacterial breakdown through composition and conditions of preparation and/or storage. It acts in stimulating secretion of gastric acid, in contraction of smooth muscle cells, in vasodilation, and in neurotransmission in the posterior hypothalamus.[16,22,23] The majority of histamine in the body is created by and is present in mast cells and basophils and, secondarily, in gastric enterochromaffin cells, lymph nodes, and the thymus.[23] The GI tract has high concentrations of histamine, which increases when inflammation is present.[16]

Functionally, histamine has a beneficial role in the gut, with the microbiota being an important source of histamine in support of immune response.[24] However, food allergies, histamine intolerance, functional gastrointestinal disorders (FGIDs)—including IBS—are

intestinal disorders in which an increase in histamine levels have pathological effects, whether from endogenous or exogenous source.[24]

Histamine is metabolized via deamination by the copper-dependent amino oxidase DAO or via methylation by the monomeric protein histamine-*N*-methyltransferase.[23] Histamine intolerance is an excess of histamine in the body or a diminished ability of DAO to adequately metabolize it.[19] The imbalance between the capacity to degrade histamine and its accumulation in the bloodstream can be due to numerous factors including DAO or histamine-*N*-methyltransferase polymorphisms, medications that reduce or inhibit DAO, diseases that cause DAO deficiency, intestinal dysbiosis, damaged GI enterocytes, and excess intake of histamine-rich foods.[17-19] In the GI tract, DAO and histamine-*N*-methyltransferase play vital roles in establishing an enzymatic barrier for the intestinal epithelial cells to prevent unwanted resorption of histamine into the blood.[18]

Histamine receptor activation in the digestive system is primarily of the H2R subtype and stimulates hydrochloric acid secretion, smooth muscle cell relaxation, and tachycardia, as well as causing an anti-inflammatory effect by initially inhibiting several cytokines before further disrupting humoral immune response when histamine binds to the H2R. The activation cascade drives certain helper T cells to even higher cytokine-producing roles creating not only disruption to normal immune response but also to consequential alterations of innate immune response with gastrointestinal effects.[24]

In colonic mucosa, mast cells often are found close to intestinal nerves in both healthy people and those with IBS25; however, in patients with IBS, a "significant correlation was found between vicinity of mast cells to nerves and both severity and frequency of abdominal pain/discomfort".[25] Having activated mast cells in proximity to gut wall nerve endings means that mast cell mediators, like histamine, can cause excitatory disturbance of normal gut motor functions in patients with IBS.[25]

Because of the action of DAO on histamine, supplementation of the vital signaling compound could be viewed as a neuroimmune-regulating intervention within a dysfunctional gut ecosystem. The patient in this case experienced classic IBS symptoms with small, positive changes in reduction of those symptoms from practicing trigger-food avoidance prompting her treating physician not to pursue diagnostic testing. "In the absence of alarm features, serious organic pathology in patients with symptoms compatible with IBS is uncommon"1 so interventions like DAO supplementation may be considered valuable clinical options for symptom abatement without the need for—or in superseded first option to—colonoscopy, sigmoidoscopy, hydrogen breath test, thyroid function test, and fecal testing,[19] or even more systemic medications and supplements.

An initial, if not chronic, state of inflammation of the gastric tissues may be a driver of abdominal pain via visceral hypersensitivity in patients with IBS.[26] "Supernatant of mucosal biopsies of visceral hypersensitive patients with IBS indeed contain more mast cell mediators such as serotonin, histamine and proteases, which are able to activate visceral afferent nerve fibres."[27] The more activated mast cells located near nerves of the colon, the more abdominal pain experienced.[26]

This independently initiated intervention by the patient, and its presentation as a single case report, establishes only mechanistic plausibility and not any direct causality. The near-complete resolution in every domain of the patient's symptoms from DAO supplementation does potentiate use of DAO as a first intervention for patients diagnosed with IBS for whom more extensive testing is not warranted, for whom dietary intervention is unplausible, or for whom dietary intervention provided only primary yet incomplete resolution of their symptoms.

Clearly, one cause of DAO deficiency can be from damaged structure and function of tissues related to FGIDs such as IBS. Excess histamine produced by such diseased gastric tissues may flood the GI tract and further burden normal levels of secreted DAO. With our case, it is unknown whether diseased or dysfunctional tissues, DAO insufficiency, histamine excess, or dysregulated serotonin levels were the etiology of the patient's IBS experience or were exacerbating its presentation of symptoms; however, the symptom overlap between issues of histamine metabolism and IBS is well-documented. Additionally, the research base is growing on the relationship between IBS and histamine function, handling, and metabolism. Studies confirm that histamine, like serotonin, affects GI motility, gastric acid production, and alters mucosal ion secretion[11,28-30] and, while there is still a lack of understanding of the direct mechanisms of action for these influences, hypo- and hypersensitivity of enteric neurons, integrity of the epithelial barrier, and dysfunction of the "mucosal immune response" are known issues of IBS.[11]

Regardless of IBS-C etiology in this case, the layered intervention and staged responses suggest different physiologic drivers across symptom domains with pain severity and pain frequency appearing primarily responsive to the DAO supplementation intervention with a potential synergistic effect of the exogenous DAO in augmentation to dietary controls in resolution of bowel dysfunction for this patient.

Patient Perspective

I started having occasional digestive problems beginning in my 20s. Bloating, pain in my abdomen, constipation. The challenges would last about a month every couple of years. Doctors were not able to pinpoint the issues after testing for hepatitis, ulcers, and even a diagnosis of acid reflux with a prescription of a proton pump inhibitor, which didn't help. As I got into my 40s, the digestive irritation became more frequent and more intense. In 2020, I had a six-month long flare-up and was diagnosed with

IBS-C by my primary care physician based on symptomology. The doctor recommended a low FODMAP diet but did not give any guidance other than a printout with a list of foods to eat and avoid. Because of COVID-19, in-office visits were limited, so I found a nutritionist to work with me virtually to help me work through the low FODMAP elimination and reintroduction. Through this I discovered that onion and wheat were my main triggers.

In 2024, I discovered there can be a connection between histamine and IBS. To test out if histamine was part of my challenge, I tried HistaGest-DAO™. Knowing that my reaction happens after eating onion and wheat, I would take one capsule before a meal that might have either ingredient. It gives me extra confidence when eating at a restaurant or at a friend's house when I don't have control of the ingredients. Using HistaGest-DAO™ prior to meals that might be a challenge, my symptoms have reduced to just some mild bloating after a meal that may contain onion or wheat. Additionally, the constipation has been eliminated. I feel like the low FODMAP process helped but was not the full solution. Now, I feel like I finally have relief.

Conclusion

Recommending novel treatment interventions, like DAO supplementation, to a patient with IBS in the absence of "alarm features" of a functional gastrointestinal disorder such as IBS is not a clinical directive of this case study; however, this case demonstrates that consideration of a patient's histamine load and/or DAO status under the framework of symptom overlap between histamine metabolism or intolerance and IBS requires an appreciation for clinical decision-making through a functional biochemistry lens and a commitment to the practice of personalized nutrition and integrative health methods. This case illustrates how supplemental diamine oxidase at 20,000 HDU with its degrading effect on histamine load and its direct effect on GI tissues effectively alleviated symptoms and improved quality of life for a patient with chronic IBS-C. This outcome was self-achieved by the patient identifying her food triggers and enhancing her histamine metabolism using a tablet-form DAO supplement. This treatment approach may be effective in resolving IBS-C symptoms within the clinical setting.

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