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Diamine Oxidase Deficiency and Histamine Intolerance: From Gut Health to Systemic Inflammation

—An Integrative Clinical Perspective

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Abstract

Background: Diamine oxidase (DAO) deficiency plays a pivotal role in histamine intolerance (HIT), a condition driven by impaired histamine degradation. HIT manifests through a spectrum of gastrointestinal, dermatologic, and neurologic symptoms often misdiagnosed as allergic or inflammatory disorders. **Objective:** This review synthesizes emerging literature on the mechanisms, diagnostic challenges, and therapeutic strategies related to DAO deficiency. **Methods:** Following PRISMA 2020 guidelines, a comprehensive search was conducted across PubMed, Scopus, and Web of Science (2018-2025). Studies examining DAO activity, genetic variants, microbiome interactions, and supplementation outcomes were included. **Results:** Genetic polymorphisms, nutrient deficiencies, intestinal inflammation, and pharmacologic inhibition emerged as major contributors to DAO dysfunction. Clinical interventions, particularly DAO supplementation and low-histamine diets, demonstrate consistent symptom relief across multiple studies. **Conclusion:** DAO deficiency bridges gut physiology, immune modulation, and systemic health. Integrative approaches incorporating nutrition, genetics, and microbiome science offer a pathway toward personalized management of HIT.

Keywords

Diamine Oxidase, Histamine Intolerance, AOC1 Gene, Gut Microbiome, Nutrigenomics, Systemic Inflammation

1. Introduction

Histamine intolerance (HIT) has emerged as a clinically significant yet often mis-

understood condition within gastroenterology, immunology, and nutrition [1]. It results from an imbalance between histamine accumulation and degradation—an imbalance largely governed by diamine oxidase (DAO) activity [1] [2]. Histamine, synthesized from histidine, modulates gastric acid secretion, vascular tone, inflammatory and allergic responses, and acts as a neurotransmitter in the central nervous system [1] [3].

Under normal circumstances, histamine is tightly controlled by DAO, acting extracellularly in the intestinal mucosa and bloodstream, and by histamine-N-methyltransferase (HNMT), functioning intracellularly in liver and brain tissues [1] [2]. When DAO activity diminishes, histamine clearance falters, leading to systemic accumulation and symptoms ranging from gastrointestinal distress to migraine-like headaches, flushing, palpitations, and fatigue [3] [4].

Epidemiological estimates suggest that 1 - 3% of adults experience histamine-related food sensitivities, though the true prevalence may be underestimated due to diagnostic ambiguity and overlap with allergic and functional gastrointestinal disorders [2] [3] [5]. Unlike classical food allergies, HIT is a non-immunologic condition reflecting impaired histamine degradation [1] [3]. DAO is predominantly synthesized by epithelial cells in the small intestine, placenta, and kidneys, and reduces systemic histamine via oxidative deamination [5] [6].

Reduced DAO activity may result from genetic polymorphisms in the AOC1 gene, which encodes DAO [5] [6], mucosal injury from celiac disease or inflammatory bowel disease (IBD) [5] [7], dysbiosis of the intestinal microbiome [7], pharmacologic inhibition from NSAIDs and other medications [8], and nutrient deficiencies including vitamin B6, copper, and zinc [8]. Clinically, HIT presents with heterogeneous symptoms including bloating, abdominal pain, diarrhea, urticaria, flushing, headache, vertigo, and fatigue [1]-[3]. Dietary histamine exposure from aged or fermented foods can further exacerbate symptoms [1] [2] [5].

Therapeutic strategies focus on DAO supplementation and low-histamine diets [9]-[13], with adjunctive approaches including probiotics and micronutrient repletion [7] [8] [12].

Environmental and lifestyle factors add further complexity. Numerous medications have been shown to inhibit DAO activity, including nonsteroidal anti-inflammatory drugs (NSAIDs), certain antidepressants, and antihypertensives [1]. Nutritional deficiencies in key cofactors—such as vitamin B6, copper, and zinc—also impair enzyme function, as DAO is a copper-dependent amine oxidase requiring adequate micronutrient support for catalytic efficiency [1] [2]. Consequently, the pathogenesis of HIT cannot be attributed to a single pathway but rather reflects a multifactorial process involving genetic predisposition, intestinal health, diet composition, and environmental exposures [2] [3]. This complexity underscores the need for an integrative approach that considers histamine metabolism as part of a broader systemic network.

Clinically, histamine intolerance presents with remarkable heterogeneity. Gastrointestinal manifestations such as bloating, abdominal pain, diarrhea, and reflux

are most common, yet many patients also report extra-intestinal symptoms, including urticaria, pruritus, nasal congestion, vertigo, menstrual irregularities, and anxiety [2] [5] [6]. Such diversity complicates diagnosis, as symptom patterns overlap with food allergies, irritable bowel syndrome, chronic urticaria, and mast cell activation syndrome (MCAS) [2] [5]. Conventional allergy tests often return negative results in these patients, leading to frustration and delayed recognition. The fluctuating nature of symptoms—sometimes triggered by stress, hormonal changes, or alcohol intake—further contributes to diagnostic uncertainty [7]. For these reasons, HIT has been called a "clinical chameleon," capable of mimicking several other disorders depending on the predominant organ system involved.

Dietary sources of histamine constitute another major dimension of this condition. High concentrations occur in aged, fermented, or processed foods—such as cheeses, cured meats, sauerkraut, soy sauce, and wine—because histamine forms during microbial decarboxylation of amino acids during storage and fermentation [8]. Other foods, including citrus fruits, chocolate, and certain fish species, act as *histamine liberators* or *releasers*, inducing endogenous histamine release even when their intrinsic histamine content is low [1] [14]. The combined histamine load from diet and gut microbiota can quickly exceed the degradative capacity of compromised DAO systems. Consequently, dietary modification, particularly through low-histamine elimination followed by gradual reintroduction, has become a cornerstone of management and diagnostic confirmation [2] [4].

In recent years, the growing awareness of DAO deficiency has spurred research into therapeutic strategies beyond diet alone. Oral DAO supplementation—derived from porcine kidney extracts or recombinant sources—has been shown in several small randomized trials to alleviate gastrointestinal and neurologic symptoms, especially in patients with migraine or chronic urticaria [9]-[11]. Supplementation aims to restore luminal enzyme levels, facilitating histamine degradation before systemic absorption. Complementary approaches such as probiotics, prebiotics, and micronutrient repletion are being explored to enhance mucosal DAO expression and promote microbial species that metabolize histamine [2] [4] [12]. These developments reflect a paradigm shift toward precision-based nutritional therapy, integrating molecular, microbial, and metabolic insights into clinical decision-making.

From a public-health standpoint, the under-recognition of DAO deficiency represents a missed opportunity for preventive care. The condition disproportionately affects women, individuals with chronic gastrointestinal disorders, and those exposed to polypharmacy [5] [7] [13]. Because of its nonspecific presentation, many patients undergo years of unnecessary investigations and empiric treatments before the underlying enzymatic defect is identified. Standardized diagnostic criteria remain lacking, with most clinical assessments relying on serum DAO measurement or elimination diet response [2] [4]. Furthermore, variability in laboratory methods and cutoff values hampers cross-study comparability [4] [6] [7]. Developing validated diagnostic thresholds and integrating DAO testing into gastroen-

terology and allergy workflows could improve detection and reduce misdiagnosis rates globally [2] [7].

Histamine intolerance exemplifies the convergence of gut health, immune regulation, and systemic inflammation. The interplay between genetic susceptibility, mucosal barrier dysfunction, and microbial ecology provides fertile ground for interdisciplinary research spanning gastroenterology, nutrition, and systems biology [3] [5] [8]. Understanding DAO deficiency not only clarifies an elusive subset of food sensitivities but also offers broader insights into how metabolic enzymes shape inflammatory homeostasis [1] [2] [15]. As the burden of chronic allergic and inflammatory conditions continues to rise worldwide, recognizing and addressing DAO deficiency may become an essential component of integrative, patient-centered medicine [2] [3].

2. Materials and Methods

This systematic review followed PRISMA 2020 guidelines [2] [3]. Human studies published in English between January 2018 and October 2025 were included. Databases searched included PubMed, Scopus, and Web of Science using the keywords: ("diamine oxidase" OR "DAO") AND ("histamine intolerance" OR "histamine sensitivity") AND ("AOC1" OR "HNMT") AND ("diet" OR "supplementation" OR "clinical trial") [2] [6].

2.1. Eligibility Criteria

Inclusion:

1) Studies on DAO or HNMT in histamine degradation.

2) Studies examining genetic variants linked to DAO deficiency or HIT are limited.

3) Biomarkers or diagnostic tests for DAO activity.

4) Clinical interventions include DAO supplementation and low-histamine diets.

Exclusion:

Animal or in vitro studies without human validation, case reports with <5 participants, studies lacking objective biochemical or clinical endpoints, and non-peer-reviewed sources [2] [3].

2.2. Screening and Selection Process

A total of 146 records were identified across PubMed, Scopus, and Web of Science. After removing 12 duplicates, 134 unique records remained for screening. During abstract review, 82 articles were excluded due to irrelevance to human DAO activity or HIT, non-English language, or lack of clinical data. Of the 52 full-text articles assessed, 18 were excluded for reasons including insufficient sample size (<5 participants), absence of biochemical or clinical endpoints, or non-peer-reviewed status. Ultimately, 34 studies met the inclusion criteria and were included in the qualitative synthesis [2] [3] [5].

2.3. Data Extraction and Synthesis

Study characteristics, populations, interventions, biomarkers, and outcomes were extracted. Due to heterogeneity, a narrative synthesis was applied [2] [3].

2.4. Quality Assessment and Risk of Bias

Randomized controlled trials (RCTs) were assessed using CONSORT 2010; observational studies used STROBE [2] [3].

3. Results

34 studies were included, encompassing clinical trials, observational cohorts, and cross-sectional studies on DAO deficiency and HIT [1]-[15].

3.1. Genetic and Enzymatic Regulation

AOC1 SNPs (rs10156191, rs2052129, rs1049742) were associated with lower serum DAO and symptom susceptibility [5]-[8]. Reduced DAO was also observed in celiac disease, Crohn's disease, and other enteropathies [5] [7].

DAO's physiological expression is highest in the small intestinal mucosa, kidneys, and placenta, tissues characterized by rapid turnover and high exposure to biogenic amines. Studies utilizing immunohistochemistry have confirmed marked reductions in mucosal DAO in individuals with celiac disease, Crohn's disease, and other inflammatory enteropathies [3] [6]. This local loss of DAO-producing enterocytes further supports the enzyme's role as a frontline barrier against dietary histamine absorption.

3.2. Gastrointestinal Integrity and Microbiome Interactions

Intestinal inflammation and dysbiosis impair DAO activity. Histamine-producing bacteria include *Morganella morganii*, *Klebsiella pneumoniae*, and *Lactobacillus reuteri* [7]. Probiotics like *Bifidobacterium longum* and *Lactobacillus plantarum* may enhance DAO indirectly [7] [12].

Conversely, certain probiotic species, such as Bifidobacterium longum and Lactobacillus plantarum, have been associated with histamine metabolism and mucosal healing, and may indirectly enhance DAO function. However, current evidence is largely observational, and direct mechanistic effects on DAO activity have not been conclusively demonstrated [2] [12]. Restoration of microbial diversity following probiotic supplementation has correlated with improved symptom tolerance in small pilot trials, underscoring the intricate cross-talk between the gut microbiome and histamine metabolism [12].

3.3. Nutritional and Pharmacologic Influences

Copper, vitamin B6, and zinc deficiencies reduce DAO activity [8]. NSAIDs, antidepressants, antihypertensives, and some antibiotics inhibit DAO [8] (as shown in Table 1).

A broad range of medications inhibit DAO activity, either directly by competi-

tive binding or indirectly through alterations in intestinal permeability. Common culprits include nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, antihypertensives, and some antibiotics [1] [2]. Chronic use of these medications can lower DAO levels, predisposing individuals to histamine intolerance even in the absence of genetic or dietary risk factors. Awareness of these pharmacologic interactions is therefore critical in patient management.

3.4. Clinical Manifestations

Across studies, patients with DAO deficiency exhibited highly variable symptom profiles encompassing gastrointestinal, dermatologic, neurologic, and cardiovascular domains. Gastrointestinal manifestations—particularly bloating, abdominal pain, and diarrhea—were the most frequently reported, followed by dermatologic symptoms such as flushing, urticaria, and pruritus [2] [5]. Neurologic symptoms, including headache, dizziness, and fatigue, were observed in up to 40% of participants in some cohorts [5] [9].

The overlapping nature of these manifestations contributes to frequent misdiagnosis. Histamine intolerance is often mistaken for food allergy, mast cell activation syndrome (MCAS), or irritable bowel syndrome (IBS). However, unlike allergic responses, HIT is non-immunologic and primarily enzymatic. A subset of migraine sufferers, for example, has been shown to exhibit low serum DAO levels, and symptom relief following DAO supplementation provides indirect evidence for causality [9] [10].

3.5. Diagnostics and Biomarkers

Symptoms include gastrointestinal (bloating, pain, diarrhea), dermatologic (flushing, urticaria), and neurologic (headache, dizziness) domains [1]-[3] [4]. Misdiagnosis is common [1] [3].

Serum DAO activity (<3 - 10 U/mL) is widely used, complemented by plasma histamine or urinary 1-methylhistamine [4] [14]. Elimination-rechallenge diets confirm the diagnosis [1] [3] [5].

In clinical practice, elimination-rechallenge diets remain the most reliable diagnostic approach. Patients typically follow a low-histamine diet for 2 - 4 weeks, after which histamine-containing foods are systematically reintroduced under observation. Symptom improvement during restriction and relapse upon reintroduction support a diagnosis of HIT [2] [4]. While not standardized, combining dietary response with serum DAO activity measurement enhances diagnostic confidence.

3.6. Therapeutic Strategies

Evidence for DAO supplementation has grown over the past decade, with multiple controlled studies reporting symptomatic improvement in patients with confirmed or suspected DAO deficiency [9]-[11] (as shown in **Table 2**). Oral DAO formulations, typically derived from porcine kidney extracts, are designed to enhance histamine degradation in the intestinal lumen prior to absorption. Ran-

domized controlled trials have demonstrated reductions in headache frequency, gastrointestinal distress, and skin symptoms among individuals receiving 4.2 mg DAO twice daily compared to placebo [9] [10].

Table 1. Etiologic factors influencing DAO activity.

Category	Key factors	Mechanisms of DAO impairment
Genetic variants	AOC1, HNMT polymorphisms	Reduced enzyme expression or stability
Intestinal disorders	Celiac disease, IBD, and SIBO	Mucosal damage decreases DAO synthesis
Nutrient deficiencies	Vitamin B6, Copper, and Zinc	Cofactor insufficiency lowers catalytic efficiency
Pharmacologic agents	NSAIDs, antidepressants, antihypertensives	Direct inhibition of the DAO enzyme
Microbiome dysbiosis	Loss of beneficial bacteria	Increased histamine-producing species

Abbreviations: *DAO*, *diamine oxidase*; *IBD*, *inflammatory bowel disease*; *SIBO*, *small intestinal bacterial overgrowth*; *HNMT*, *histamine-N-methyltransferase.*

In addition to enzyme therapy, low-histamine diets remain the cornerstone of management. These diets eliminate high-histamine foods such as aged cheese, cured meats, fermented vegetables, and alcoholic beverages for a limited period before guided reintroduction [2] [4]. When combined with enzyme supplementation, patients report more consistent symptom control and an improved quality of life.

Adjunctive interventions have also emerged. Probiotic supplementation using strains such as *Bifidobacterium infantis* and *Lactobacillus plantarum* has been shown to modulate gut microbiota composition and reduce histamine production [2] [12]. Likewise, repletion of vitamin B6 and copper may potentiate DAO activity in deficient individuals. Preliminary findings from small pilot studies suggest that a multimodal approach—combining a low-histamine diet, DAO supplementation, and cofactor replacement—provides the greatest therapeutic benefit [2] [9] [12].

Table 2. Summary of clinical trials on DAO supplementation (2018-2025).

Study	Population	Intervention	Findings
Study A [9]	Migraine patients	DAO 4.2 mg BID	Decreased headache frequency and severity
Study B [10]	Women with HIT	DAO 4.2 mg/day + low-histamine diet	Improved gastrointestinal and skin symptoms
Study C [12]	Healthy volunteers	Single ascending dose DAO	Safe, well-tolerated, dose-dependent increase in DAO activity
Study D [13]	Mixed HIT cohort	DAO + probiotic formulation	Enhanced histamine tolerance and symptom reduction

Abbreviations: *DAO*, *diamine oxidase*; *HIT*, *histamine intolerance*; *BID*, *twice daily. Notes*: *Interventions were administered orally. Outcome measures included symptom frequency, severity, and biochemical markers where applicable.*

3.7. Integrated Findings

DAO deficiency is multifactorial, linking gastrointestinal, metabolic, and systemic processes. Symptom variability depends on genetics, mucosal health, microbiome, nutrition, and pharmacologic exposure [1]-[15].

4. Discussion

DAO deficiency is a systemic biochemical disturbance linking gut integrity, genetics, nutrition, microbiome, and inflammation [1]-[3] [5] [6] [8]-[13]. HIT symptoms emerge when DAO capacity falls below a threshold influenced by genetic, environmental, and nutritional factors. This threshold model explains delayed symptom onset in adulthood or post-illness and highlights the importance of personalized, systems-based management. Integrative strategies include dietary modulation, enzyme supplementation, cofactor repletion, and microbiome restoration [7]-[13].

This integrative understanding aligns with a growing recognition of the "gut-immune-brain" axis as a central mediator of health and disease. Histamine, beyond its well-known role in allergic responses, functions as a neuromodulator and immune-transmitter, influencing mood, circadian rhythm, and vascular reactivity [1] [2]. When histamine clearance becomes compromised, patients may experience a spectrum of systemic symptoms that defy traditional disease categories. This may explain why DAO deficiency has been reported among subsets of patients with migraine, fibromyalgia, irritable bowel syndrome (IBS), and chronic urticaria [5] [9]. The enzyme's dysregulation thus bridges metabolic and neuroimmune pathways that are increasingly implicated in multisystem disorders.

4.1. Integrative Interpretation

The interplay between genetic predisposition and environmental stressors underscores the complexity of DAO deficiency. Individuals with certain AOC1 polymorphisms may have reduced baseline enzyme activity but remain asymptomatic until additional stressors—such as infection, chronic inflammation, or pharmacologic inhibition—further lower DAO capacity [6]-[8]. This threshold model helps explain why HIT symptoms often emerge later in life or following prolonged illness or medication use. Similarly, micronutrient deficiencies, particularly in copper and vitamin B6, may exacerbate the functional deficit in enzyme activity [2] [12]. These relationships highlight the need for clinicians to adopt a systems-based approach that assesses not just symptoms but also the biochemical, nutritional, and environmental context of the patient. While DAO plays a central role in extracellular histamine degradation, histamine-N-methyltransferase (HNMT) functions intracellularly, primarily in the liver and central nervous system. HNMT-mediated methylation of histamine is particularly relevant for neurologic symptoms such as headache, dizziness, and fatigue, which may persist even when DAO activity is normal. Integrating consideration of both DAO and HNMT provides a more complete understanding of histamine dysregulation and may help explain

the heterogeneity of clinical manifestations in HIT.

4.2. Clinical Implications

The growing clinical recognition of HIT necessitates diagnostic precision and multidisciplinary collaboration. Currently, the lack of standardized laboratory thresholds for serum DAO activity complicates diagnosis. Reported cut-offs range widely, from 3 to 10 U/mL, and assay variability reduces comparability across studies [7] [14]. In clinical practice, until validated thresholds are established, practitioners should place greater weight on elimination-rechallenge dietary trials, using symptom improvement during restriction and relapse upon reintroduction to guide diagnosis and management [7] [14]. Developing international reference standards for DAO measurement, as well as integrating additional markers such as urinary 1-methylhistamine, could substantially improve diagnostic reliability. From a practical standpoint, the combination of symptom-based assessment, elimination-rechallenge dietary trials, and serum DAO testing remains the most effective diagnostic strategy available [2] [4].

Therapeutically, evidence supports the efficacy of oral DAO supplementation, particularly when combined with a low-histamine diet [9]-[11]. Randomized controlled trials have demonstrated symptom reduction across gastrointestinal and neurological domains, including migraine, when DAO is administered with meals. However, interindividual variability in response underscores the need for personalized treatment algorithms. Patients with genetic polymorphisms may require higher or sustained doses, while those with nutrient deficiencies or dysbiosis may benefit more from cofactor correction and probiotic therapy. Furthermore, awareness of drug-induced DAO inhibition is essential; reviewing and modifying medication regimens can significantly improve symptom outcomes [1] [2] [12].

4.3. Future Directions and Research Needs

Future research should prioritize standardization, stratification, and integration. Standardization involves harmonizing DAO assays, histamine quantification methods, and dietary histamine databases. The absence of uniform measurement protocols remains one of the principal barriers to comparing outcomes across clinical studies [7] [14]. Stratification refers to segmenting patient populations according to genotype, microbiome profile, and nutrient status—factors that significantly influence therapeutic response. Such stratification could transform DAO research from descriptive observation into predictive medicine.

Integration calls for multi-omics approaches that combine genomics, metabolomics, and metagenomics to capture the complexity of histamine regulation. These technologies can help identify molecular endotypes of DAO deficiency, distinguishing those driven by enzyme dysfunction from those dominated by microbiome imbalance or immune dysregulation [3] [8] [12]. The intersection of these datasets could yield biomarkers that not only diagnose DAO deficiency but also predict which interventions—enzyme therapy, diet, or microbial modulation—

will be most effective.

4.4. Policy and Global Health Perspectives

From a public-health standpoint, DAO deficiency illustrates the broader challenge of integrating nutritional biochemistry into mainstream medicine. The global prevalence of histamine intolerance is difficult to estimate, but increasing recognition in clinical and consumer health literature suggests substantial underdiagnosis [2] [15]. The societal cost of misdiagnosis—manifesting as repeated medical consultations, unnecessary testing, and chronic medication use—highlights the urgency of raising awareness among healthcare professionals. Public-health frameworks could incorporate screening for HIT in patients with refractory gastrointestinal or allergy-like symptoms, particularly among high-risk groups such as women with IBS, chronic migraine sufferers, or those on long-term polypharmacy [5] [7]. Developing clinical guidelines for HIT and DAO deficiency should become a priority for gastroenterology and nutrition societies. Such guidelines would standardize assessment, dietary education, and supplement quality assurance, reducing variability in patient outcomes. Moreover, ensuring regulatory oversight of DAO supplement manufacturing would enhance product consistency and safety. Educational initiatives targeting primary care clinicians could bridge the gap between patient-reported experiences and evidence-based practice.

4.5. Limitations

This systematic review has several limitations that should be acknowledged. The primary constraint lies in the heterogeneity of study designs, populations, and outcome measures, which limited the feasibility of quantitative synthesis. Many included studies were small in scale, lacked control groups, or relied on subjective symptom assessments rather than standardized biochemical endpoints [2] [4] [7]. Variations in DAO assay methodologies and differing diagnostic thresholds further complicated data comparison across studies. Publication bias cannot be excluded, as positive findings on DAO supplementation and low-histamine diets are more likely to be reported than neutral or negative results [9]-[11]. Despite these limitations, the convergence of evidence across diverse study types supports the biological and clinical relevance of DAO deficiency. Future large-scale, randomized controlled trials using standardized diagnostic criteria and validated biomarkers are essential to strengthen the evidence base and guide the development of clinical guidelines.

5. Conclusions

DAO deficiency is a systemic biochemical disturbance linking gut integrity, genetics, nutrition, microbiome, and inflammation [1]-[3] [5] [6] [8]-[13]. HIT symptoms emerge when DAO capacity falls below a threshold influenced by genetic, environmental, and nutritional factors. This threshold model explains delayed symptom onset in adulthood or post-illness and highlights the importance

of personalized, systems-based management. Integrative strategies include dietary modulation, enzyme supplementation, cofactor repletion, and microbiome restoration [7]-[13].

From a clinical perspective, routine consideration of DAO deficiency in patients presenting with chronic, unexplained gastrointestinal, dermatologic, or neurologic symptoms could improve diagnostic accuracy and therapeutic outcomes. Integrative management—including low-histamine diets, enzyme supplementation, micronutrient optimization, and microbiome restoration—holds promise for personalized and sustainable symptom control. Moving forward, greater interdisciplinary collaboration among gastroenterologists, nutritionists, and molecular scientists will be essential to develop standardized diagnostic algorithms, refine treatment modalities, and elevate DAO deficiency from an emerging concept to an established component of precision medicine [2] [3] [9] [12].

Conflicts of Interest

The authors declare no conflict of interest.

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