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REVIEW ARTICLE

Histamine Intolerance: Unraveling the Complexities of Diagnosis and Management

[1]Dr. Pritayan Bhattacharjee, [2]Dr. Sarla Mahawar, [3]Dr. Kamlesh Kumar Tanwani, [4]Dr. Nitin Sharma

[1]Resident Doctor, [2]Senior Professor, [3]Associated Professor, [4]Professor, Department of Biochemistry, JLN Medical College, Ajmer, India

Corresponding Author
Dr. Nitin Sharma
Professor, Department of Biochemistry, JLN Medical College, Ajmer, India
Email: mailnkks@gmail.com

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ABSTRACT

Background: Histamine intolerance (HI) is a disorder caused by an impaired ability to degrade histamine, leading to an accumulation of the biogenic amine in the body.Histamine intolerance is frequently misdiagnosed or overlooked, partly due to its symptom overlap with other conditions such as food allergies, irritable bowel syndrome, and migraines. **Methods:** This review examines the current literature on histamine intolerance, focusing on its pathophysiology, diagnostic challenges, and therapeutic strategies. We conducted a comprehensive search of PubMed, Scopus, and other medical databases for relevant studies published in the past two decades. Key topics reviewed include the enzymatic breakdown of histamine (DAO and HNMT), clinical symptomatology, diagnostic methodologies (including dietary elimination and histamine challenge tests), and current treatment protocols such as dietary management, enzyme supplementation, and pharmacological interventions. **Results:** Histamine intolerance is linked to dysfunction or deficiency in the enzymes diamine oxidase (DAO) and histamine N-methyltransferase (HNMT). While diagnostic testing for HI remains challenging, many studies suggest that DAO activity levels can be a potential biomarker, though results are often inconsistent. Clinical symptoms vary widely, with gastrointestinal issues, neurological disturbances, and skin conditions (urticaria) being most commonly reported. Management typically involves a low-histamine diet and, in some cases, DAO supplementation or antihistamine therapy**.** **Conclusion:** Histamine intolerance is a complex and often underdiagnosed condition that requires a multifaceted approach for diagnosis and management. While a low-histamine diet remains the primary treatment strategy.

Keywords: Histamine intolerance, Histamine metabolism, Food triggers, Histamine-related symptoms, Gastrointestinal health, Histamine sensitivity

WHAT IS FOOD INTOLERANCE?

Any non-immune mediatedadverse reaction of the human body;towardsthe consumed food (or its components) in some individuals is referred to as food intolerance.[1]Nearly 15–20% of the population suffers from this kind of hypersensitivity towards certain foods triggering gastrointestinalcomplaints (like flatulence, abdominal bloating / distension, pain and diarrhea. Research outcomes have associated these potential intolerances to foodwith the pharmacological properties of food components, non-celiac gluten sensitivityor deficiency / transport defects of enzymes.[1]

Histamine intolerance:It occurs because of impaired histamine degradation processes, disturbing the equilibria between histamine levels in blood and the continuous degradation of histamine in the body.Diamine oxidase is the principal enzyme that catabolizes ingested histamine.Impaired activity of this enzyme results in an impaired histamine degradation leading to histamine buildup which in turn is responsible for various symptoms which mimic allergic reactions.[2]

It has been postulated that Diamine oxidaseserves as a secretory protein, which degrades extracellular histamine. In contrast, histamine N-methyltransferase, is another crucial enzyme involved in the metabolism of histamine, functions within the cytosol of cells and can only metabolize histamine in the intracellular compartment. An impairment in the rate of histamine degradation due to decreased activity of Diamine oxidase develops histamine excess resulting in various symptoms representing an allergic reaction.[2,3]

Histamine intolerance is characterized by a range of symptoms like headaches, digestive issues, and inflammatory skin conditions such as redness, itchiness, urticaria, flushed skin, etc. Despite its prevalence, histamine intolerance remains poorly understood and frequently misdiagnosed, leading to prolonged discomfort for many sufferers.

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In this article, we delve into the intricacies of histamine intolerance, shedding light on its symptoms, underlying causes, and effective management strategies. By gaining a deeper understanding of this condition, individuals can better navigate their symptoms and improve their quality of life.

Histamine

Histamine; chemical name,2-(1H-Imidazol-4-yl)ethanamineacts as a mediator of anaphylactic reactions.[2]Histamine is a biogenic amine synthesized by decarboxylation of histidine utilizinghistidine decarboxylase.[4]Histamine is produced as well as stored in significant amounts in the basophils and mast cells and gets rapidly released upon receiving a stimulus from various triggers.In basophils, histamine is associated with chondroitin-4-sulfate, while in mast cells, it is bound to anionic proteoglycans like heparin. This storage arrangement allows for rapid release of histamine upon activation, contributing to their role in allergic reactions and immune responses.[4] The biosynthesis and storage of histamine takes place primarily by mast cells and basophils[5].

Histamine conjugates with heparin (through its carboxyl group) and gets stored in the intracellular granules. Histamine gets released when allergens attach on the mast-cell-bound IgE antibodies.

Histamine Metabolism

Histamine is a biogenic amine that plays a crucial role in several physiological processes, such as modulating allergic reactions, regulating gastric acid production, facilitating neurotransmission, and influencing immune system responses. It is produced in the body by the decarboxylation of the amino acid histidine, a process catalyzed by the enzyme histidine decarboxylase. Once synthesized, histamine can be stored in granules of mast cells and basophils, where it plays a crucial role in allergic reactions, or it can be released from other cells like neurons or enterochromaffin-like cells.

Metabolism of histamine primarily occurs through two main pathways

1. **Diamine Oxidase (DAO) Pathway[10]**: This pathway primarily occurs in the gastrointestinal tract and involves the enzyme diamine oxidase. Diamine oxidase (DAO) facilitates the oxidative deamination of histamine, converting it into imidazole acetaldehyde. This intermediate is subsequently further metabolized into imidazole acetic acid through the action of aldehyde dehydrogenase. This pathway is particularly important for the degradation of histamine derived from ingested food and beverages.
2. **Histamine N-Methyltransferase (HNMT) Pathway[10]**: This pathway involves the enzyme histamine N-methyltransferase, which catalyzes the transfer of a methyl group from S-adenosylmethionine (SAM) to histamine, forming N-methylhistamine. N-methylhistamine is further metabolized into N-methylimidazole acetaldehyde by monoamine oxidase (MAO), and finally into Nmethylimidazoleacetic acid by aldehyde dehydrogenase. This pathway is primarily responsible for the inactivation of histamine in tissues, particularly in the brain.

Both pathways lead to the production of inactive metabolites, which are then excreted from the body. The balance between histamine synthesis, release, and metabolism is crucial for maintaining homeostasis and preventing the adverse effects associated with histamine excess, such as allergic reactions and inflammation. Dysfunction in histamine metabolism pathways can lead to histamine intolerance or other histamine-related disorders.

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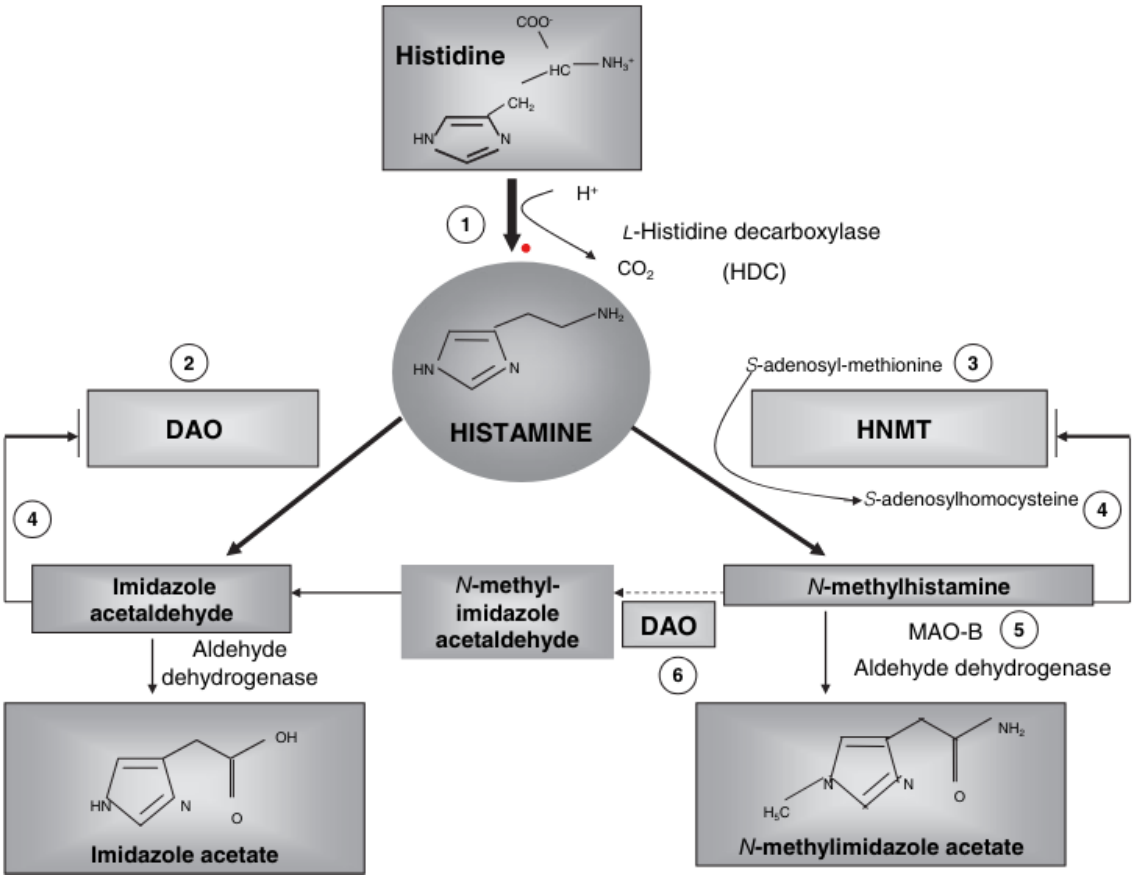

Fig 1: Histamine metabolism. Summary of the histamine metabolism. The biogenic amine histamine is synthesized by decarboxylation of the amino acid histidine catalysed by L-histidine decarboxylase (HDC) (1). Histamine undergoes metabolism through two main pathways: extracellular oxidative deamination of the primary amino group by diamine oxidase (DAO) and intracellular methylation of the imidazole ring by histamine-N-methyltransferase (HNMT). Both enzymes can be inhibited by their respective reaction products in a negative feedback loop (4). N-Methylhistamine is oxidatively deaminated to N-methyl-imidazole acetaldehyde by monoamine oxidase B (MAO B) (5) or by DAO (6).Because the methylation pathway takes place in the cytosolic compartment of cells, MAO B (5) has been suggested to catalyse this reaction in vivo.

ETIOPATHOGENESIS OF HISTAMINE INTOLERANCE

While the exact etiology of histamine intolerance is not fully understood, several factors may contribute to its development:

1. **Enzyme Deficiency:** One of the primary causes of histamine intolerance is a deficiency or dysfunction of the enzyme diamine oxidase (DAO) or histamine-N-methyltransferase (HNMT). These enzymes are responsible for breaking down histamine in the body. If they are deficient or not functioning properly, histamine levels can build up, leading to symptoms of intolerance.
2. **Genetic Factors:** There is evidence to suggest that genetic factors may predispose individuals to histamine intolerance. Variations in genes responsible for producing DAO or HNMT enzymes can affect their activity, potentially leading to impaired histamine metabolism. The human DAO gene spans 10 kbp and is located on chromosome 7q35.[10] Multiple single-nucleotide polymorphisms (SNPs) in the DAO gene have been linked to inflammatory and neoplastic gastrointestinal disorders. These include conditions such as food allergies, gluten-sensitive enteropathy, Crohn's disease, ulcerative colitis, and colon adenomas. These genetic variations can influence DAO enzyme activity, potentially affecting histamine metabolism and contributing to the pathogenesis of these diseases. No significant difference in the distribution of the investigated HNMT alleles could be shown between patients with gastrointestinal diseases and control subjects but a functional relevant polymorphism of the HNMT gene (chromosome 2q22) has been described for white asthma patients.[2]Therefore, histamine intolerance appears to primarily arise from reduced DAO activity due to gastrointestinal diseases or inhibition of DAO. However, significant interindividual variations in DAO expression within the gut, along with the presence of specific SNPs in the DAO gene associated with gastrointestinal disorders, suggest a genetic predisposition in certain patients with histamine intolerance.[10]

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3. **Gut Health:** The gut plays a crucial role in histamine metabolism. Conditions that disrupt gut health, such as small intestinal bacterial overgrowth (SIBO), leaky gut syndrome, or intestinal inflammation, may impair the body's ability to properly metabolize histamine, contributing to intolerance. Furthermore, histamine was recently named to act as a key mediator in IBS .Functional Dyspepsia with absence of an organic disease a disorder with heterogeneous symptoms in the epigastric region. Patients with histamine intolerance (HIT) commonly report abdominal pain and postprandial fullness as prominent symptoms. These symptoms are also described as main symptoms in functional dyspepsia (FD). SIBO occurs with an abnormal increase in the overall bacterial population in the small intestine. Bloating and abdominal pain are primary symptoms in SIBO, very much comparable to HIT complaints [3]
4. **Histamine-Rich Foods:** Certain foods are naturally high in histamine or can trigger the release of histamine in the body. Consuming large quantities of these foods, especially in individuals with reduced histamine metabolism capacity, can overwhelm the body's ability to process histamine efficiently, leading to intolerance symptoms. Here are some examples of histamine-rich foods:a.Fermented foods: Sauerkraut, kimchi, yogurt, kefir, and other fermented dairy products.b. Aged cheeses: Such as aged cheddar, parmesan, blue cheese, and Gouda.c.Processed meats: Salami, pepperoni, sausage, and other cured meats. d.Certain fish: Tuna, mackerel, sardines, anchovies, and some types of shellfish like shrimp.e.Certain vegetables: Spinach, tomatoes, and eggplant can have higher histamine levels when they are older or not fresh.f .Alcohol, particularly red wine, contains high levels of histamine and strongly inhibits DAO activity. Studies have demonstrated a correlation between wine consumption, elevated plasma histamine levels, and the onsetof symptoms such as sneezing, flushing, headaches, asthma attacks, and other anaphylactoid reactions. These symptoms have been shown to decrease with the use of antihistamines, indicating a potential role of histamine in these reactions triggered by alcohol consumption.However, among the multitude of substances contained in wine, other biogenic amines such as tyramine and sulphites have been supposed to contribute to symptoms summarized as “wine intolerance” or “red wine asthma.[2]Vinegar and foods containing vinegar: Pickles, mustard, ketchup, and mayonnaise. .Certain fruits: Strawberries, bananas, papayas, pineapples, and citrus fruits.

For individuals sensitive to histamine, consuming these foods can lead to symptoms such as headaches, hives, digestive issues, and nasal congestion. Managing histamine intolerance typically involves avoiding high-histamine foods and sometimes taking antihistamines under medical supervision.Furthermore, certain foods have been identified as histamine-liberators, capable of triggering the release of endogenous histamine. Scientific literature lists foods with suggested histamine-releasing capacity, which include citrus fruits, seafood, papaya, tomatoes, nuts, pineapple, spinach, chocolate, strawberries, and others. These foods may elicit histamine-related reactions in susceptible individuals. However, the mechanism responsible for this potential effect has not yet been elucidated.[11]

5. **Histamine-Blocking Medications:** Some medications, such as certain antidepressants, antipsychotics, and proton pump inhibitors (PPIs), can inhibit the activity of DAO or HNMT enzymes, leading to elevated histamine levels and exacerbating symptoms of intolerance.Several drugs and substances can influence the metabolism and distribution of histamine in the body, potentially by decreasing DAO (diamine oxidase) activity.

Antibiotics	clavulanic acid, isoniazid, cefuroxime, cefotiame, pentamidine, chloroquine, doxycycline, neomycin B, acriflavine, D-cycloserine
Antidepressants	amitriptyline, monoaminooxidase 1 inhibitors
Anxiolytics	diazepam, barbiturates
Antihypertensives	verapamil, dihydrazine, alprenolol
Local anaesthetics	lidocaine, prilocaine, marcaine, procaine

Fig 2: Table Showing group of drugs that might cause histamine intolerance .

6. **Other Health Conditions:** Certain underlying health conditions, such as mast cell disorders, autoimmune diseases, and allergies, may contribute to histamine intolerance or exacerbate its symptoms by increasing histamine release or impairing histamine metabolism.Overall, histamine intolerance is likely a multifactorial condition influenced by a combination of genetic, physiological, dietary, and environmental factors. Understanding these factors can help individuals manage their symptomsthrough lifestyle modifications, dietary changes, and targeted

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treatments aimed at improving histamine metabolism and reducing histamine exposure.

INTOLERANCE

Clinical Features: Clinical features related to histamine intake can manifest in complex ways, affecting multiple organ systems. Symptoms may appear unexpectedly and randomly following food ingestion, indicating a potential histamine-related origin. Typical signs include: Skin Manifestations: Such as flushing (erythema in the facial area), pruritus (itchiness), and urticarial rash on the body. Gastrointestinal Symptoms: These can include diarrhoea with or without vomiting, as well as constipation and abdominal pain. These manifestations highlight the broad range of symptoms that can occur due to histamine intake, reflecting its effects on various physiological processes and organ systems in susceptible individuals. Manifestations in the cardiovascular system, such as low blood pressure (counter-regulatory hypertension may subsequently occur) and tachycardia are less frequent, as are manifestations in the nervous and respiratory system.

TABLE 3

Symptoms of histamine intolerance

Organ	Symptoms
Skin	Flush Urticaria Itch
Gastrointestinal tract	Nausea/vomiting Abdominal pain Meteorism Diarrhea
Central nervous system	Headache Dizziness
Cardiovascular system	Hypotension Tachycardia Cardiac arrhythmia
Respiratory system	Nasal obstruction Rhinorrhea
Urogenital tract	Dysmenorrhea
Intolerance of histamine liberating/DAO blocking medications	
Intolerance of histamine rich food/alcohol	

Fig 3: Table showing Symptoms of Histamine Intolerance.

The challenge with a “diagnosis” of HIT is precisely the inconstancy and variety of the manifestations in the same individual following similar stimuli. In cross-over placebo-controlled trials assessing symptoms, subjects responded randomly to histamine provocation tests. While the total symptom score was clearly higher after histamine was given compared to the placebo, not everyone had the same response—many people showed no consistent pattern when it came to symptoms after taking histamine.[12]

Histamine and Headache: Histamines can cause headache both in migraine sufferers and migraine free patients, in adose-response relationship. Histamine induced headache is a vascular headache, causedprimarily by nitric oxide (NO). Histamine can induce the release of nitric oxide (NO) from the endothelium through the stimulation of histamine receptor (H1R), particularly in large intracranial arteries among other locations. Many patients with migraines exhibit decreased DAO activity, and these individuals often report that their migraines are triggered by histamine-rich foods such as wine or aged cheese. Conversely, they may experience complete relief from migraines when following a histamine-free diet.[13] [14] Pregnancy, which is associated with a high placental production of DAO, is associated with remission in some women who suffer fromdiet related headache .[15]

Histamine and gastrointestinum: Besides headache, gastrointestinal ailments including diffuse pain abdomen, colic, flatulence, and loose stool are leading symptoms of histamine intolerance. Elevated histamine levels and reduced DAO activity have been documented in several inflammatory and neoplastic conditions, including Crohn's disease, ulcerative colitis, allergic enteropathy, food allergies, and colorectal neoplasms. In patients with food allergies, there is often a simultaneous decrease in histamine-N-methyltransferase (HNMT) activity and impaired total histamine degradation capacity (THDC) within the colonic mucosa. This impaired enzyme activity prevents effective compensation between DAO and

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HNMT, potentially contributing to elevated histamine levels and associated symptoms in affected individuals. Therefore, an impaired histamine metabolism has been suggested to play a role in the pathogenesis of these diseases.[2]

Histamine and airways: During or soon after the ingestion of histamine-rich food or alcohol, rhinorrea or nasal obstruction may occur in patients with histamine intolerance; in extreme cases, asthma attacks also may occur. Reduced HNMT activity has been shown for patients with food allergy and Bronchial asthma.

Diagnosis

The wide ranging symptoms in various organ systems requires careful history taking including any precipitating foods or medications which may influence histamine metabolism. The accompanying gastrointestinal symptoms and allergies must also be borne in mind. It cannot be assumed that all clinical findings related to histamine are attributable to the underlying pathology. Allergy testing should also be carried out, using skin prick tests and identification of specific IgE, to exclude a true food allergy. Serum tryptase should also be assayed, to exclude an occult mastocytosis.[16]

Diagnosing histamine intolerance or sensitivity involves a combination of clinical evaluation, symptom assessment, and sometimes specific tests. Here's how it is typically approached

One of the primary methods to diagnose histamine intolerance is through an elimination diet. This involves avoiding foods high in histamine for a period (usually 2-4 weeks) and then reintroducing them one at a time while monitoring symptoms. If symptoms worsen upon reintroduction of histamine-rich foods, it suggests histamine intolerance.

Diagnostic Tests: In some cases, specific tests may be used to support the diagnosis:-DAO Activity Test: Measures the activity of Diamine Oxidase (DAO) enzyme in your blood. Low DAO levels suggest reduced ability to break down histamine. A DAO activity of < 3 U/ml is suggestive of histamine intolerance, with an activity of < 10 U/ml it is probable, whereas an activity greater than or equal to 10 U/ml makes the diagnosis unlikely .[17]

- Histamine Levels: Blood or urine tests to measure histamine levels may be done, although these are less commonly used and their interpretation can be complex. Histamine can be measured in plasma and, as its breakdown product, N-methyl histamine, in urine. A lack of DAO cofactors vitamin B6, copper and vitamin C can also occur.[16]

Where there is clinical suspicion of histamine intolerance, the activity of DAO in serum or in a biopsy specimen can be ascertained, using radio extraction assays (REA)developed for the ascertainment of enzymatic DAO activity. [3H]- or C14-labelled putrescinedihydro chloride are used as a substrate. The DAO activity in plasma is normally relativelylow. A heparin injection releases tissue bound DAO. Hence prior to the development ofnew, sensitive assays, heparin administration followed by plasma DAO measurement werethe main diagnostic method.[16]It's important to work closely with a healthcare provider, preferably one familiar with histamine intolerance, to ensure an accurate diagnosis and appropriate managementplan. Self-diagnosis based solely on symptoms or internet sources is not recommended, as it may lead to unnecessary dietary restrictions or treatments.The gold standard of diagnosis is a double-blind placebo-controlled provocation test following a histamine reduced diet (diagram 3) .It in done after a 4-wk histamine-free diet. The provocation can be performed with alternate administration of capsules containing increasing doses of histamine-dihydrochloride (0.75 and 1.5 mg/kg body wt, respectively) and placebo capsules.[2]It is essential to monitor blood pressure and heart rate continuously, particularly in cases where positive reactions such as hypotonia, tachycardia, urticaria, or other symptoms suggestive of an anaphylactoid reaction occur. Immediate medical attention should be sought for proper treatment by a physician. Subsequently, symptoms should be assessed using a standardized symptom-scoring system to evaluate the severity and responseto treatment.

The treatment for histamine intolerance focuses on managing symptoms by reducing histamine levels in the body and avoiding triggers. Here are the primary approaches used in treating histamine intolerance:

1. **Low-Histamine Diet:** The cornerstone of managing histamine intolerance is following a low-histamine diet. This involves avoiding foods that are high in histamine or that can trigger its release. Common high-histamine foods include aged cheeses, cured meats, fermented foods (like sauerkraut and soy sauce), alcohol (especially wine and beer), and certain vegetables (like tomatoes and spinach). Fresh foods are generally better tolerated than aged or processed ones.
2. **DAO Enzyme Supplements:** Recently, capsules containing DAO isolated from pig kidneys have been generated to supplement the lack of endogenous human DAO in patients with histamine intolerance. These capsules exclusively contain stabilizers such as cellulose, sucrose, solanum tuberosum, polyacrylic acid, cellulose gum, triethyl citrate, and potato starch.[2]
3. Oral supplements containing Diamine Oxidase (DAO) enzyme can assist in the breakdown. These supplements are typically taken before meals, especially meals that may contain higher histamine levels. DAO supplements are available over-the-counter in some countries. In individual cases of patients in whom a lack of DAO cofactors is etiological, the use of Vitamin B6 and Vitamin C has been reported.[17]
4. **Antihistamines:** Antihistamine medications can help block the effects of histamine in the body,

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providing relief from symptoms such as itching, hives, nasal congestion, and headaches. They do not directly reduce histamine levels but can alleviate symptoms caused by histamine release.

5. **Probiotics:** Certain probiotic strains, such as Lactobacillus rhamnosus, have been studied for their potential to improve DAO activity in the gut and may be beneficial in managing histamine intolerance. It can help stabilize the gut microbiome without significantly increasing histamine production.[18] Lactobacillus plantarum can aid in histamine breakdown, which is crucial for individuals with histamine intolerance. It supports a balanced gut microbiome while helping to manage histamine levels.[1]

It's essential to work closely with a healthcare provider, preferably one familiar with histamine intolerance, to develop a personalized treatment plan. They can help you navigate dietary restrictions, recommend appropriate supplements or medications, and monitor your response to treatment over time.

CONCLUSION

In summary, histamine intolerance (HI) is a complex condition characterized by an impaired ability to metabolize histamine, leading to a range of symptoms that overlap with various other disorders. This review has highlighted the multifactorial nature of HI, including the roles of enzymes like diamine oxidase (DAO), genetic factors, gastrointestinal health, and external triggers such as diet and environmental factors. While histamine intolerance is increasingly recognized in clinical practice, its diagnosis remains challenging due to the lack of specific biomarkers and the overlap with other conditions, including food allergies and gastrointestinal disorders. Effective management hinges on a multifaceted approach that includes dietary modifications, supplementation with DAO enzymes to aid histamine breakdown, and sometimes the use of antihistamines to mitigatesymptoms. Awareness of trigger foods and proactive lifestyle adjustments play pivotal roles in symptom control, underscoring the importance of individualized care and ongoing management strategies tailored to each person's unique sensitivities and responses.

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