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Histamine Intolerance on Diagnosis and Treatment

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ABSTRACT

Histamine intolerance is the imbalance between histamine excess and epithelial breakdown, mainly occurring from impaired digestion of dietary histamine, resulting from a functional deficiency of diamine oxidase (DAO). The review aims to summarize the current state of knowledge on the diagnostics and treatment of histamine intolerance, particularly on the potential mechanisms of DAO deficiency and dietary therapy. Histamine intolerance presents a broad range of symptoms such as gastrointestinal, dermatological, respiratory and neurological ones. Histamine Intolerance (HIT) is diagnosed via clinical evaluation, dietary trials and observations, because there are no specific laboratory tests available. The treatment includes a low histamine diet, and in some cases, DAO supplementation. Dietary modification and supplementation should be a part of a multi-faceted management for histamine intolerance. More studies are needed to arrive at accurate diagnostics and to test the degree of efficacy of current therapies, particularly concerning to the gut.

Keywords: histamine intolerance, pseudoallergy, histamine, diagnosis, treatment

1. INTRODUCTION

Histamine originating from mast cells acts as the primary storage and release sites of this essential immunological inflammatory mediator (O'Mahony et al., 2011); mast cells are its largest contributors within the body. Mast cells are scattered throughout the body, but are most prevalent throughout the upper layers of the skin (mostly at the subcutaneous layer and cluster around blood vessels), as well as in the oral cavity, throat, nasal cavity, lungs, and intestines (Chimowicz et al., 2022). The lymphatic system is also home to these cells, which play a crucial role in the immune system, as well as in the spleen, where they significantly contribute to lymphoid and hematopoietic processes (Czerwionka-Szaflarska & Zielińska-Duda, 2009).

Mast cells degranulate and release histamine stored in the granules in response to many stimuli: The binding of immunological stimuli is on the surface

of mast cells to the FcεRI receptor, and non-immunological stimuli such as hypoxia; increased temperature; hyperosmolality; injury; foods; drugs; and alcohol (O'Mahony et al., 2011). Histamine binds to four receptors (H1R-H4R) following release from these mast cells, mediating various biological effects. The H1 receptor mediates allergic symptoms (e.g., sneezing, coughing, skin reddening, and vasodilation). H2 receptor: stimulates gastric acid secretion and has actions affecting heart function. The H3 receptors are the primary intrinsic modulators of neurotransmitter release in the brain. The H4 receptor is responsible for mediating anti-inflammatory and immunoregulatory functions. (Shulpekova et al., 2021).

Histamine is synthesized by the endogenous decarboxylation of the amino acid histidine, mainly through the conversion of histidine through the enzyme histidine decarboxylase (Moriguchi & Takai, 2020). The central mast cell and basophilic cell endogenous sources have predominance, while macrophage, blood platelets, and lymphocyte contributions are less dominant (O'Mahony et al., 2011). Histamine is then metabolized through two types: intracellular and extracellular. Initially, it is metabolized intracellularly through the action of histamine N-methyltransferase (HNMT). This enzyme degrades almost 70% of histamine in the organism, primarily through the action of diamine oxidase (DAO), an enzyme responsible for the extracellular degradation of histamine (Mušič et al., 2013). Histamine is known to play a significant role in the mediation of inflammatory processes, neurotransmission, and gastric acid secretion (Shulpekova et al., 2021). Histamine intolerance, also known as pseudoallergy, occurs when the body's histamine level exceeds its tolerance level. It leads to a histamine intolerance that can occur due to the intake of large amounts of histamine-containing foods or a low histamine metabolism resulting from the activity of the poor diamine oxidase (DAO) enzyme (Chimowicz et al., 2022). Such symptoms are associated with histamine intolerance: headache, abdominal pain, diarrhea, urticaria, and other skin-related reactions (Rosell-Camps et al., 2013).

Histamine intolerance diagnosis depends on self-reports of symptoms occurring with certain foods consumed and a measure of activity of the enzyme (DAO) in blood (Buczyłko, 2022). The primary interventions include a low-histamine diet and avoiding DAO inhibitors (Sánchez-Pérez et al., 2022). Not a miracle cure, mind you, as compliance may be complicated: a low-histamine diet can lessen SIBO symptoms (van Odijk et al., 2023). DAO deficiency exacerbates histamine intolerance because DAO may render it impossible for the organism to eliminate excess histamine (Comas-Basté et al., 2020). Diagnosis of histamine intolerance remains challenging due to the absence of a specific laboratory test (Shulpekova et al., 2021). Symptomatic improvement following histamine restriction is typically assessed after a low-histamine diet challenge (Sánchez-Pérez et al., 2022). The second of which also supports a diagnosis, but may be contrasting with the result: Is the DAO upregulating? (van Odijk et al., 2023).

In terms of treatment, the management of histamine intolerance involves excluding histamine-rich and DAO inhibitor foods, as well as supplementation with substances that support histamine metabolism (Buczyłko, 2022). There are some recommendations for using antihistamines, but studies indicate that they are ineffective in treating histamine intolerance (Zhao et al., 2022). Histamine intolerance in children does not differ from that in adults, and it may have symptoms such as abdominal pain, diarrhea and skin reactions (Nazar et al., 2021). An identical diagnosis and treatment pattern to that of adults, but with a specific high emphasis on a low histamine diet and avoidance of DAO inhibitors (Rosell-Camps et al., 2013).

2. METHODOLOGY

We conducted this review by searching for “current papers” on Google Scholar using the following search phrases in combination: (“histamine intolerance”) and (“diagnosis”) and (“treatment”) and (“DAO deficiency”). The search included studies published between January 2004 and January 2025, but priority was given to articles published after 2015 to ensure clinical relevance. We screened all publications based on their titles and abstracts. The review critically assessed evidence from studies that added value to understanding histamine intolerance. Full manuscripts were reviewed through a comprehensive search, including studies that were relevant to the topic and discussed the role of DAO, diagnostic methods, and treatment approaches for histamine intolerance. We carried out a data extraction to establish findings in the literature on histamine intolerance and to identify advancements made. The inclusion criteria consisted of studies that provided insight into the pathogenesis, clinical features, diagnostic considerations, and treatment of histamine intolerance. Exclusion criteria included non-English articles, articles without full-text access, and articles that did not fit the topic due to missing data. After excluding 15 articles, 23 studies were incorporated into this review. Such a review aimed to summarize the current knowledge and identify gaps that must be addressed through further research to optimize diagnosis and treatment in patients with histamine intolerance.

3. RESULTS AND DISCUSSION

Histamine intolerance (HIT) is a kind of food intolerance of non-immunological origin, caused by a disturbance between the ingestion of histamine with food and the body’s ability to metabolize it (Matysiak, 2022). Adverse food reactions have been on the rise in recent years. An increasing number of patients either seek a diagnosis or test themselves based on increasingly popular dietary practices, often related to food allergies or lactose intolerance. But many patients cannot get an accurate diagnosis from these tests. Histamine intolerance is still not well understood, and clinicians should focus on this and challenge to successfully diagnose HIT objectively, as there are no available reliable laboratory tests or any reliable biomarker and definitive diagnostic criteria (Matysiak, 2022). The main points on HIT are summarized in Table 1.

Table 1: Summary of Key Points on Histamine Intolerance (HIT)

Aspect	Details
Definition	Food intolerance of non-immunological origin caused by imbalance between histamine intake and metabolism.
Symptoms	Skin: pruritus, erythema, urticaria, edema; Gastrointestinal: nausea, vomiting, pain, diarrhea; Respiratory: rhinorrhea, nasal swelling, dyspnea; Nervous: headaches, migraines; Circulatory: arrhythmias, blood pressure drops, cardiac arrest.
Predisposing factors	Genetic (SNP in DAO gene), gut dysbiosis, chronic diseases (allergies, intestinal issues), certain medications inhibiting DAO activity.
Diagnostic challenges	No specific lab tests; methods include serum DAO, skin prick test, biopsy, urine analysis, dietary/DAO trial.
Treatment strategies	Low-histamine diet, DAO supplementation, antihistamines, supporting nutrients (vitamins C, copper, zinc), probiotics.
Key dietary avoidances	Fermented foods, aged cheeses, cured meats, pickled vegetables, histamine liberators (strawberries, citrus, chocolate), DAO inhibitors (fish, cured meats).
Role of gut microbiome	Influences histamine levels; bacteria can produce histamine, affecting overall levels and symptoms.
Future directions	Need for more accurate, non-invasive diagnostics; further research on gut microbiome and treatment efficacy.

Symptoms of Histamine Intolerance

However, the symptoms of histamine intolerance are diverse and encompass multiple organs and systems. These encompass cutaneous symptoms - pruritus, erythema, urticaria, and edema; gastrointestinal symptoms - nausea, vomiting, abdominal pain, and diarrhea; respiratory symptoms - rhinorrhea and nasal mucosa swelling, dyspnea; nervous system symptoms - frequent headaches including migraines; circulatory symptoms - arrhythmias, drops in blood pressure, even cardiac arrest (Matysiak, 2022). The symptoms of HIT vary in intensity in proportion to the amount of built-up histamine.

Factors Predisposing to HIT

Several factors have been identified as contributing to histamine intolerance. These include:

1. Genetic Factors: Histamine intolerance is often associated with a single-nucleotide polymorphism (SNP) in the DAO gene that limits the production of the resulting protein.
2. Dysbacteriosis: Disturbances of the intestinal bacterial flora may lead to increased histamine concentrations. Some bacteria can produce and secrete histamine, and significant disturbances of the intestinal microflora have been found in patients with HIT.
3. Chronic Diseases: Especially allergic diseases (atopic dermatitis, allergic rhinitis, asthma) and intestinal diseases (large intestine polyps, food allergies, celiac disease). Additionally, HIT is more common in patients with chronic infections and mastocytosis.

4. Drug Use: Mucoactive agents (ambroxol, acetylcysteine), antiemetics (metoclopramide), antidepressants (amitriptyline), anti-arrhythmic drugs, antihypertensive drugs (dihydralazine), and clavulanic acid lower the DAO activity (Matysiak, 2022; Schink et al., 2018).

Diagnostic Methods

Diagnosis of HIT is challenging due to the lack of specific laboratory tests. Methods used include:

1. Determination of Serum DAO: Although controversial, this is the most studied laboratory approach. However, serum DAO levels do not entirely correspond to intestinal tissue levels.
2. Histamine 50-Skin-Prick Test: This assesses the histamine wheal after a 50-minute skin prick test (SPT). A wheal with a diameter ≥ 3 mm indicates HIT.
3. Gastroscopy with Intestinal Biopsy: This procedure determines the intestinal concentration of DAO and is highly sensitive and specific, but it is also invasive and costly.
4. Analysis of Histamine and Its Metabolites in Urine: A convenient and non-invasive method using UHPLC-FL chromatography.
5. Diagnostic and Therapeutic Test: Patients suspected of HIT may be recommended a low-histamine diet or DAO supplementation for four to eight weeks. If symptoms significantly cease or disappear, the test can confirm HIT (Matysiak, 2022).

Treatment

Managing histamine intolerance primarily involves dietary modifications and, in some cases, supplementation with diamine oxidase (DAO). The goal is to reduce histamine accumulation in the body and alleviate symptoms.

Low-Histamine Diet

A diet based on low-histamine products is the keystone of treatment for histamine intolerance. This kind of diet involves avoiding foods that have high levels of histamine, histamine liberators, and DAO inhibitors. Foods to avoid include:

1. High-histamine foods: Fermented fish and seafood, aged cheeses like parmesan, ripened meats such as salami, pickled vegetables like sauerkraut, and certain fruits and vegetables like tomatoes and spinach.
2. Histamine liberators: Foods that can trigger the histamine release from mast cells, such as strawberries, raspberries, citrus fruits, and chocolate.
3. DAO inhibitors: Foods that inhibit the activity of DAO, such as fish, cured meats, and sauerkraut (Matysiak, 2022).

DAO Supplementation

DAO supplements may help the body break down excess histamine. These are derived from porcine kidneys and consumed before meals to enhance histamine digestion in the gut (Jochum, 2024). While DAO supplementation may improve symptoms of histamine intolerance in patients, further studies are needed to assess its long-term effectiveness (Schnedl et al., 2022).

Antihistamines

H1 and H2 receptor antagonists (antihistamines) are the possible drugs that block the mediators responsible for skin itch, flushing, and GI disturbances. They also need to be prescribed cautiously and only under the supervision of a healthcare provider due to the risk of side effects and interactions with other medications (Jochum, 2024).

Additional Strategies

It is likely that maintaining proper levels of vitamin C, copper and zinc, all acting as cofactors for DAO, aids histamine metabolism (Jochum, 2024). Probiotics modulate the gut microbiome, and these specific probiotics could also possibly mitigate histamine production by enterobacteria (Shulpekova et al., 2021).

Histamine intolerance is a condition that can have serious health consequences if left inappropriately diagnosed and treated. We demonstrate that DAO deficiency has played a crucial role in the physiopathological development of HIT (Shulpekova et al., 2021). Dysbiosis as a risk factor and the role of the gut microbiome in development HIT require further exploration. When comparing our results with those already known in the literature, it seems that healthcare professionals often misdiagnose symptoms of histamine

intolerance as allergic reactions, which make its accurate diagnosis tough (Matysiak, 2022). Treatment options often reported include a low-histamine diet and DAO supplementation, but further studies are required to assess effectiveness (Hrubisko et al., 2021).

Limitations of the Study

A limitation of our study is the absence of a specific laboratory test to confirm histamine intolerance, making the objective evaluation of treatment efficacy difficult. Moreover, the symptoms also vary in patients, which can complicate the development of uniform diagnostic criteria.

Role of the Gut Microbiome

The gut microbiome greatly influences the metabolism of histamine. Certain types of bacteria in the gut can produce and release histamine, thereby increasing histamine levels in the body (Schink et al., 2018). Further study of the gut microbiome in HIT may provide new insights into its pathogenesis and treatment.

Implications and future directions

Our findings emphasize the significance of increasing awareness about histamine intolerance among health professionals and patients. Further research should establish more accurate diagnostic likelihood ratios and treatment effectiveness. HIT is another condition where gut microbiome research could provide new insights and avenues for treatment.

Future Research Directions

Current diagnostic approaches for histamine intolerance are not precise and non-invasive enough. The importance of the gut microbiome in the metabolism of dietary histamine warrants further studies to improve understanding of HIT's pathogenesis and the development of novel therapeutic strategies. To assess how effective a low-histamine diet and DAO supplements are for managing histamine intolerance, randomized clinical trials are needed.

4. CONCLUSIONS

Histamine intolerance is a complex condition in which the body cannot properly break down histamine, often due to a deficiency in the enzyme diamine oxidase (DAO), resulting in an imbalance between histamine levels and the body's ability to process it. This dysbiosis can lead to a range of symptoms, including gastrointestinal, dermatological, respiratory, and neurological issues. There are no specific diagnostic tests for histamine intolerance. Such a diagnosis is challenging, as it is made through a combination of clinical evaluation, dietary challenges, and the exclusion of other potential diagnoses. A low-histamine diet is the primary treatment for histamine intolerance, and in some cases, DAO supplementation may also be beneficial. Either it is to be objectively offered an agent skin test negative (desensitized), or it is to be peripherally attended to in a euphoric manner within intensive groups experiencing inflammasome tumbles. Dysbiosis of gut microbiome can contribute to the development of histamine intolerance, and it also suggests that probiotics or prebiotics may play a role in the disease management.

Future studies should aim to develop more accurate diagnostic techniques, investigate the impact of the gut microbiome on histamine breakdown, and evaluate the efficacy of various treatment options. Raising awareness among healthcare providers and patients is crucial for enhancing the diagnosis and management of histamine intolerance. By addressing these challenges, we can increase the quality of life for patients affected by this condition and potentially uncover new therapeutic targets for related disorders.

Author's contribution:

Marek Borecki- Conceptualization, review and editing, investigation, methodology

Karolina Jałocha - Methodology, investigation, visualization, supervision

Patrycja Pysz - Conceptualization, visualization, resources,

Kinga Świtała - Review, data curation, investigation

Roksana Hrapkowicz- Resources, writing- rough preparation, data curation

Agnieszka Czernecka- Visualization, data curation, investigation

Kinga Erazmus - Review, visualization, formal analysis

Maria Mrocza - Supervision, writing- rough preparation, data curation

Justyna Kuciel- Review and editing, formal analis, supervision
Dominik Tomczak - Resources, writing- rough preparation, formal analis
Project administration- Marek Borecki

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All data sets collected during this study are available upon reasonable request from the corresponding author.

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