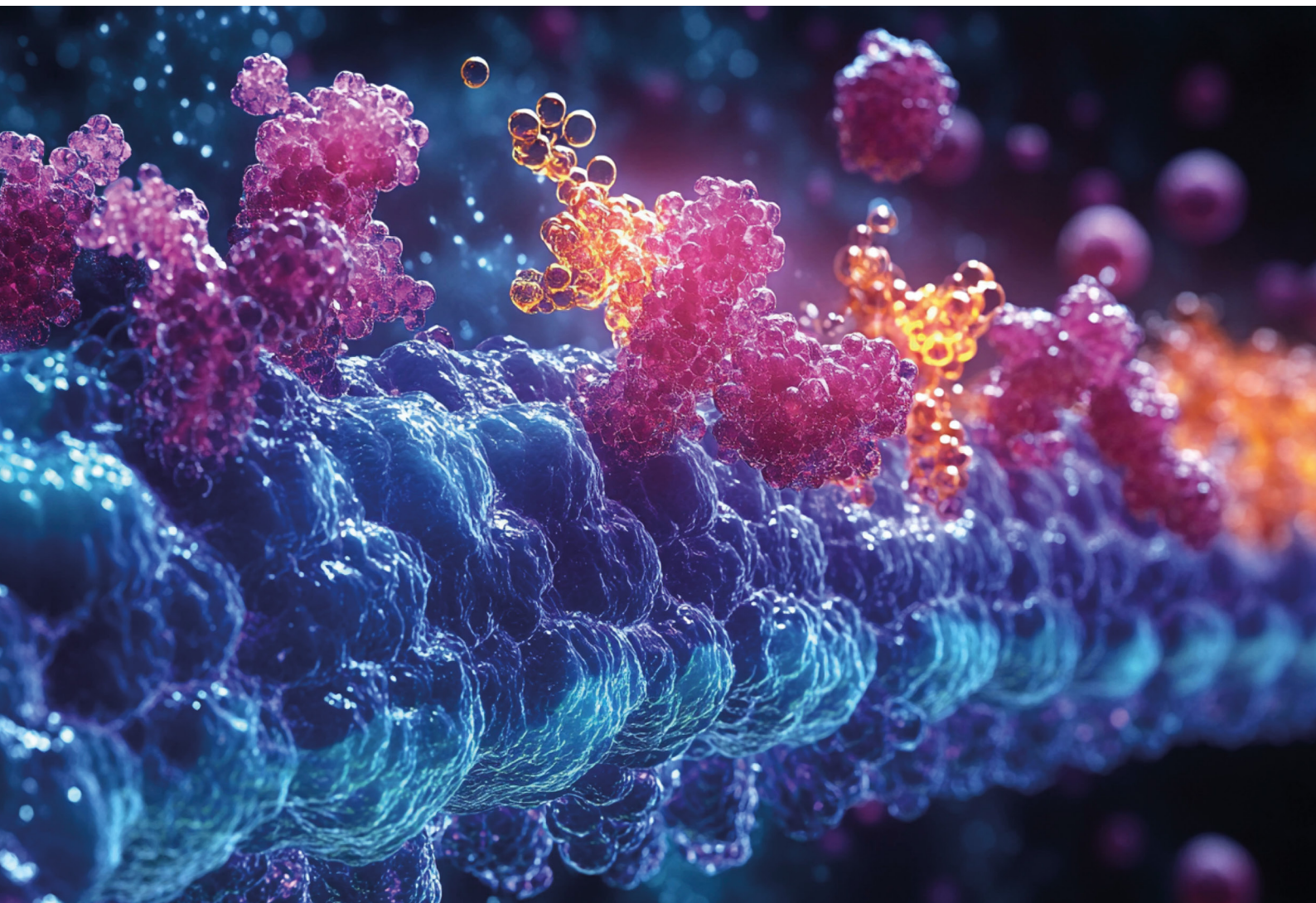


Histamine Intolerance



IDENTIFY UNDERLYING CAUSES AND PROVIDE TARGETED
TREATMENT USING ADVANCED DIAGNOSTIC METHODS.

DIAGNOSTIC POSSIBILITIES AT A GLANCE

At biovis, we provide a diverse spectrum of histamine-related tests and panels to assess histamine intolerance, including:



SA760A HIT Basic Profile

more info
under
EBS-
Profiles



SA760B HIT Midi Profile

more info
under
EBS-
Profiles



SA760C HIT Complete Profile

more info
under
EBS-
Profiles



C385 Histamine Degradation Capacity



C390 Diaminooxidase



C395 Co-factors of DAO



C410 Methylhistamine in Urine



C415 Histamine in Urine



A410 Histamine in Stool



Histamine is a naturally occurring tissue hormone in the human body that plays a vital role in several biological processes, including blood circulation, intestinal peristalsis, gastric acid secretion, and bronchoconstriction. It also contributes to inflammatory and immune responses. When histamine metabolism is disrupted, as seen in histamine intolerance, it can lead to symptoms such as heart palpitations, diarrhoea, skin rashes, and shortness of breath. Since there is no specific marker for a definitive diagnosis, identifying the condition can be challenging for healthcare providers. However, dietary adjustments often provide significant relief for those affected by histamine intolerance.

Histamine intolerance may cause the following symptoms:

- Heart palpitations
- Diarrhoea
- Skin rashes
- Shortness of breath



A112 Histamine Producing Bacteria



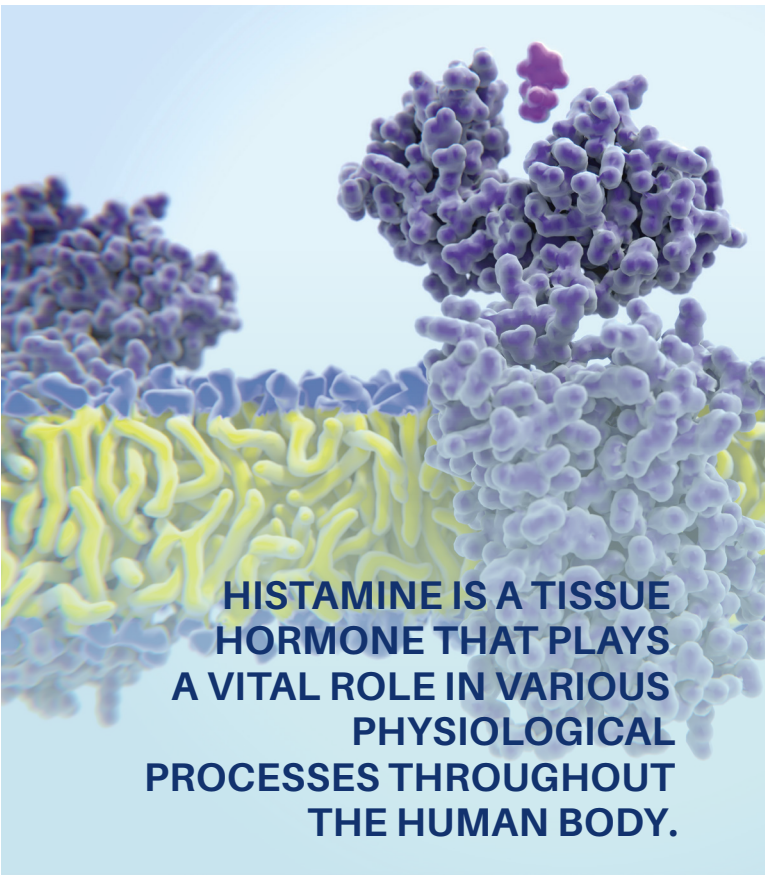
H420 Histamine Intolerance Profile

WHAT IS HISTAMINE?

Histamine is a tissue hormone derived from the **amino acid histidine**. It belongs to the group of biogenic amines and exhibits chemical similarities with compounds such as spermidine, ornithine, and cadaverine [1]. In the human body, histamine is synthesized through the decarboxylation of histidine, a process catalysed by the enzyme histidine decarboxylase [2].

WHAT IS THE ROLE OF HISTAMINE IN THE HUMAN BODY?

Histamine can be absorbed from food but is also released by mast cells, which are part of the immune system. So far, **four different histamine receptors** have been identified, all of which belong to the class of G-protein-coupled receptors. Depending on which of these receptors the biogenic amine interacts with, histamine can have a wide range of effects throughout the body [2,3].

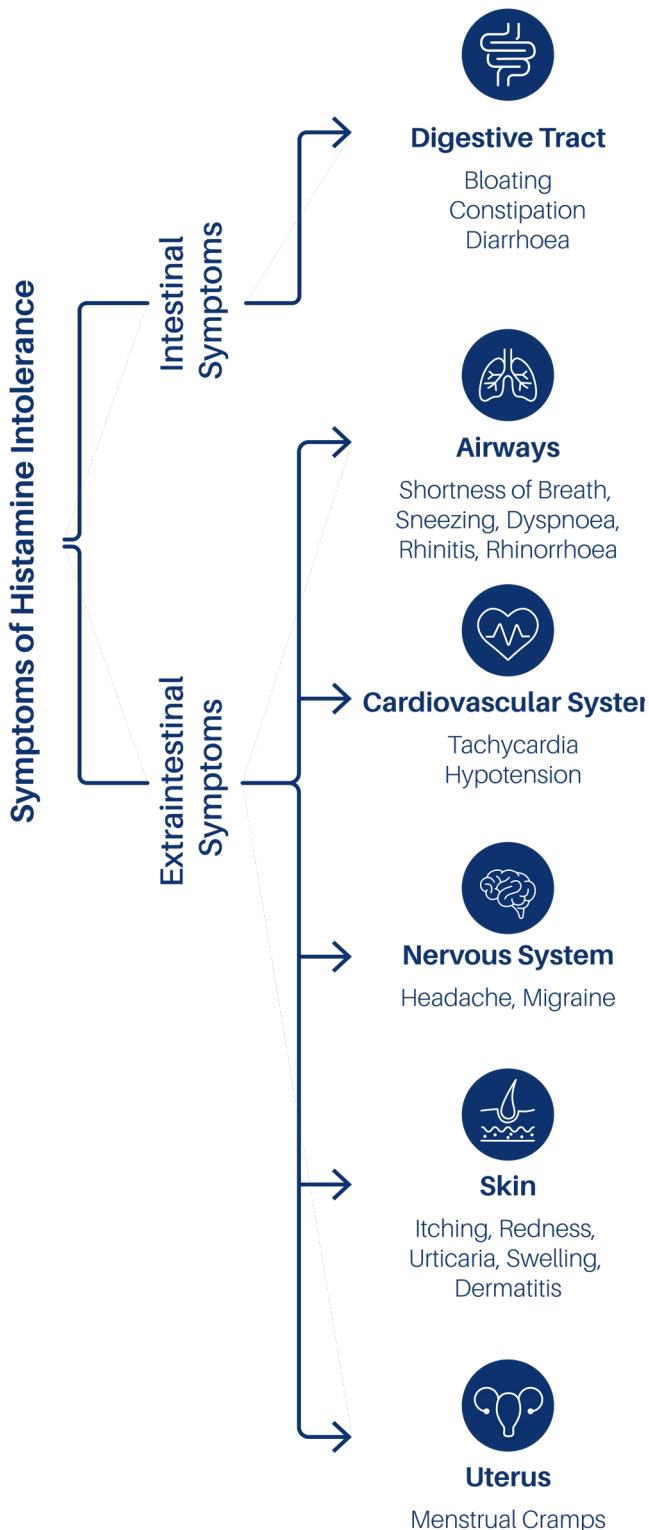


Receptor Type	Occurrence	Effects
Type 1 receptor	Ubiquitous	Increased vascular permeability, bronchoconstriction, vasodilatation, itching, hives
Type 2 receptor	Stomach, heart, small intestine	Gastric acid secretion, increase in heart rate and cardiac output
Type 3 receptor	Nervous system	Regulation of neurotransmitter release and sleep-wake cycle
Type 4 receptor	Skin, tonsils	Itching, chemotaxis, immunoregulation

Table 1: Types, occurrence, and effects of histamine receptors [2,3].

WHAT CAUSES HISTAMINE INTOLERANCE?

Histamine intolerance (HIT), also referred to as **histaminosis**, occurs when the body reacts to physiological levels of histamine, particularly those obtained from food, with symptoms that do not affect individuals without this condition [4]. The prevalence of HIT is estimated to be around **1% of the population**, with women being affected around four times more frequently than men [5].



WHICH SYMPTOMS MAY OCCUR?

Since histamine affects a wide range of cell types, excess histamine can lead to a wide variety of symptoms. Although the immune system is not involved in HIT, its symptoms closely resemble an allergic reaction and can be categorized as intestinal or extraintestinal. Digestive symptoms typically include bloating, nausea, vomiting, flatulence, and diarrhoea, though constipation is occasionally reported. Beyond the digestive system, HIT can also affect other parts of the body. Respiratory symptoms may include difficulty breathing, rhinitis, rhinorrhoea, and sneezing. Cardiovascular effects can manifest as tachycardia and hypotension, while nervous system symptoms often present as headaches or migraines. Some individuals experience menstrual cramps, and skin-related reactions such as itching, redness, hives, swelling, and dermatitis. Said symptoms usually occur after the consumption of histamine-rich foods [4].

CAUSES OF HISTAMINE INTOLERANCE

In patients suffering from HIT, even relatively small amounts of histamine, which are found in everyday foods such as sauerkraut or red wine, can trigger symptoms. This is thought to be due to an imbalance between histamine intake and its breakdown by enzymes such as diamine oxidase (DAO) and histamine N-methyltransferase (HMNT). The **reduced ability to degrade histamine** may be caused by several factors, including overall lower enzyme production or less efficient enzyme variants due to genetic variability. When the body becomes deficient in micronutrients, this can also lead to less efficient enzymatic activities as these enzymes are dependent on an adequate supply of these substances in order to function optimally.

Causes of excess histamine

- Diminished enzyme production
- Genetically less efficient enzymes
- Deficiency in cofactors



HISTAMINE INTOLERANCE IS DIFFERENT FROM CLASSIC TYPES OF FOOD POISONING.

HISTAMINE INTOXICATION:

Histamine intolerance should not be confused with histamine intoxication, a type of food poisoning that can occur after consuming improperly stored fish. In this case, large amounts of histamine are produced, which can cause symptoms of intoxication even in individuals who can typically tolerate high-histamine foods such as raw milk cheese or dry-cured meats without issues [6,7].



DIAGNOSTICS

In contrast to many other conditions where specific diagnostic markers, such as ferritin for diagnosing iron deficiency, are used, diagnosing HIT is more challenging. Laboratory values and test results must always be interpreted in relation to the patient's symptoms [8]. Currently, the most reliable signs of HIT are the development of symptoms after consuming histamine-rich foods (keeping a symptom diary is advised) alongside abnormal laboratory findings.

PLEASE NOTE

There is no single laboratory test that can definitively diagnose histamine intolerance. Test results should always be interpreted in conjunction with the patient's symptoms. Keeping a symptom diary can be a useful tool for identifying foods that may trigger symptoms.



**KEEPING A SYMPTOM
DIARY IS CRUCIAL.**



SA760A HIT Basic Profile

more info
under
EBS-
Profiles

Material: T909, EDTA, Heparin, Serum

The HIT Basic Profile includes measuring the patient's serum DAO concentration, determining the blood levels of key DAO cofactors (vitamin B6, zinc, and copper), and analysing faecal histamine concentrations.



SA760B HIT Midi Profile

more info
under
EBS-
Profiles

Material: T909, EDTA, Heparin, Serum

In addition to the parameters included in the basic profile, our HIT Midi Profile also measures the patient's histamine degradation capacity in the serum.



SA760C HIT Complete Profile

more info
under
EBS-
Profiles

Material: T909, T928, EDTA, Heparin, Serum

In addition to the parameters included in the Midi Profile, the HIT Complete Profile also measures the patient's S-adenosylmethionine (SAME) levels, a cofactor of the enzyme HMNT, which is critical to the intracellular degradation of histamine.





C390 Diaminooxidase

Material: Serum

Measuring the concentration of the histamine-degrading enzyme diamine oxidase (DAO) in the patient's faeces or blood can be helpful if an enzyme deficiency is suspected. Reduced DAO concentrations may indicate a decreased ability to break down histamine. Therefore, assessing DAO levels can assist in identifying the cause of impaired histamine degradation. However, if DAO levels are normal, enzyme activity may still be reduced due to genetic factors or a lack of necessary cofactors. In such cases, evaluating DAO cofactors and analysing the genetics of histamine degradation can provide additional insight.



C395 Co-factors of the DAO

Material: EDTA, Heparin

The cofactors for DAO include vitamin C, B6, zinc, and copper. A subclinical or overt deficiency of these micronutrients can impair enzyme activity, leading to reduced histamine breakdown. If such deficiencies are identified, they should be addressed through dietary improvements or supplementation to optimize enzyme function and minimize the body's exposure load.



A410 Histamine in Stool

Material: T909

Elevated faecal histamine levels may result from reduced DAO enzyme activity or increased histamine production by intestinal bacteria. If a deficiency in DAO cofactors is also present, impaired enzyme activity could be a contributing factor. In this case, DAO cannot function at its full capacity, and addressing the deficiencies through dietary improvements or supplementation is recommended to restore optimal enzyme activity.



C385 Histamine Degradation Capacity

Material: Serum

The body's capacity for histamine degradation depends on the total number, activity, and availability of all enzymes involved in the process. It reflects how much histamine the body can break down within a given time frame. Reduced values indicate insufficient histamine degradation. If the value falls within the normal range, it is unlikely that the patient has a systemic issue with histamine degradation.



C410 Methylhistamine in Urine

Material: T908

In the human body, histamine is excreted in the form of methylhistamine. Elevated levels may indicate increased histamine load. However, when interpreting urinary methylhistamine levels, it is important to consider that a high-protein diet can impact the results, as such diets generally increase the excretion of methylhistamine.



C415 Histamine in Urine

Material: T908

Elevated urinary histamine levels may indicate an increased histamine load. However, reduced or normal levels do not necessarily rule out HIT, as histamine excretion is not elevated in every HIT.



A112 Histamine Producing Bacteria

Material: Native Stool

Certain bacteria in the gut can convert the amino acid histidine, obtained from food, into histamine, thereby increasing the body's histamine load. These include species like *Hafnia alvei*, *Klebsiella pneumoniae*, and *Morganella morganii*. However, it is important to note that elevated numbers of these bacteria do not necessarily correlate with increased histamine production in the gut. For a more accurate assessment, faecal histamine levels should be measured as well alongside other relevant histamine parameters to provide a comprehensive picture.



H420 Histamine Intolerance Profile

Material: EDTA

The degradation of histamine is influenced by several factors, including the enzymes DAO and HNMT. However, the efficiency of these enzymes can be influenced by genetic polymorphisms. This panel includes five gene variants linked to a decreased ability to metabolise histamine which may result in reduced activity of histamine-degrading enzymes.



DIFFERENTIAL DIAGNOSES

Gastrointestinal symptoms indicative of HIT can also occur in other conditions. For example, diarrhoea may result from malabsorption or maldigestion, as seen in lactose intolerance or fructose and sorbitol malabsorption. Other potential differential diagnoses include chronic inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, as well as coeliac disease. For skin-related symptoms, a wheat allergy should also be considered as a possible cause [8]. Additionally, hyperthyroidism can trigger symptoms such as hot flushes and diarrhoea, so it should be ruled out when these symptoms are present. Conversely, hypothyroidism, along with its associated hypothermia, can reduce DAO activity, while Hashimoto's thyroiditis may lead to increased histamine release from mast cells [9]. When evaluating unclear gastrointestinal symptoms, it is essential to consider these differential diagnoses. Furthermore, if symptoms persist after the patient has been treated, one of these conditions may coexist with HIT as an underlying disease.

Possible differential diagnoses for histamine intolerance:

- Lactose intolerance
- Fructose malabsorption
- Sorbitol malabsorption
- Crohn's disease
- Ulcerative colitis
- Irritable bowel syndrome
- Hyperthyroidism
- Hypothyroidism
- Hashimoto's thyroiditis
- Non-coeliac gluten sensitivity
- Food allergies
- Irritable bowel syndrome
- Coeliac disease

THERAPY

Nutritional Therapy

Nutritional therapy for HIT is based on a three-phase approach. The first phase, lasting 10 to 14 days, involves a strict low-histamine diet to alleviate the patient's symptoms. This is followed by the testing phase, during which histamine-containing foods are gradually reintroduced to assess individual histamine tolerance. In the final phase, based on the patient's personal histamine tolerance, a long-term dietary plan is developed to achieve lasting symptom relief or complete resolution [8].

More detailed information on nutritional therapy for HIT patients can be found on our homepage.

DISCOVER:



biovis
nutrition flyer

DAO Inhibitors

A high dietary intake of histamine is not the only factor that can trigger HIT. The inhibition of diamine oxidase (DAO), the enzyme responsible for breaking down histamine in the intestine, also plays a significant role. Certain substances and medications can reduce DAO activity, exacerbating symptoms. Notable examples include the blood pressure medication verapamil, the painkiller diclofenac, and the antibiotics clavulanic acid and isoniazid. Additionally, alcohol inhibits DAO activity. Hence, it is recommended to limit or avoid alcoholic beverages whenever possible [2,4].

**CERTAIN SUBSTANCES AND
MEDICATIONS CAN REDUCE
DAO ACTIVITY.**



Histamine-Containing Foods (Selection):

Food	Average histamine content (mg per kg)
Raw milk cheese	59,37
Aubergine	39,42
Dry-cured sausage	32,15
Spinach	31,77
Pasteurised cheese	18,05
Canned fish	14,42
Smoked meat products	12,98
Tomatoes	2,51

Table 2: Histamine content of selected foods. Own representation [2,7]

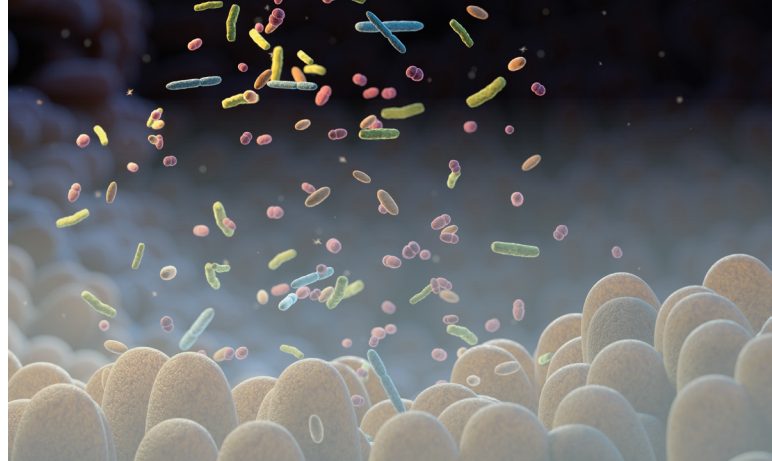
Histamine Liberators

Some foods can trigger symptoms in certain individuals despite containing little to no histamine. It is suspected that these foods stimulate the body's own histamine release, earning them the term histamine liberators. Examples include otherwise healthy foods such as strawberries, kiwis, citrus fruits, and nuts [10]. Permanent avoidance of these foods is advised only if they are clearly associated with symptoms during the reintroduction phase after an initial period of histamine restriction, as recorded in a symptom diary.



The Importance of Other Biogenic Amines

In addition to histamine, other biogenic amines – such as putrescine and cadaverine – are also broken down by DAO. If DAO becomes overloaded, reducing the intake of these amines may help free up its enzymatic capacity, allowing for a more efficient breakdown of histamine [11].



VITAMINS AND ENZYME SUPPLEMENTS CAN HELP OPTIMISE DAO FUNCTION.

Dietary Supplements and Phytochemicals

For patients with micronutrient deficiencies with regards to DAO cofactors (such as vitamin C, B6, zinc, and copper), increasing intake through natural foods or supplements can help restore optimal DAO function. Enzyme preparations containing DAO (e.g., Daozym, Daosin, or DAOfood) may provide additional support in breaking down histamine-rich foods when taken just before meals [11]. However, these should be used occasionally rather than as a permanent therapy. Quercetin, a phytochemical known to stabilise histamine-containing mast cells, may also be beneficial. To support this effect, regular consumption of quercetin-rich foods – such as unpeeled apples, onions, broccoli, and green beans – is recommended [12].

Pharmacological Therapy

In addition to nutritional therapy, antihistamines may be considered as an experimental drug treatment. However, it's important to note that this use is off-label, as there are no clinical studies to date that prove the effectiveness of antihistamines for treating HIT. H1 blockers such as cetirizine or loratadine may help alleviate symptoms like hot flushes, while H2 blockers such as famotidine or roxatidine may relieve nausea and vomiting. However, caution is advised with certain H2 blockers like cimetidine, as they inhibit DAO and could potentially worsen HIT symptoms [2]. Additionally, because the enzyme monoamine oxidase (MAO) is involved in histamine degradation, antidepressants from the MAO inhibitor class may interfere with the breakdown of histamine [3].



DID YOU KNOW?

The enzyme diamine oxidase (DAO) is primarily responsible for the extracellular breakdown of histamine and other biogenic amines, particularly in the digestive tract. In contrast, the enzyme histamine N-methyltransferase (HNMT) facilitates intracellular histamine degradation.

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