

Research Article

Observational Study on the Effectiveness of a Diamine Oxidase (DAO) Supplement in a Sample of Consumers with Histaminosis

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Abstract

Introduction: Histamine intolerance (HIT) is a multisystem disorder characterized by the excessive accumulation of histamine in the body, primarily due to reduced activity of the diamine oxidase (DAO) enzyme. This condition leads to a range of clinical manifestations, including headaches, gastrointestinal symptoms, fatigue, joint pain, and skin rashes. These symptoms complicate both diagnosis and clinical management, making it challenging for healthcare providers to offer effective treatment options. **Objective:** The objective of this study was to evaluate the effectiveness of NaturDAO, a plant-based DAO supplement, in reducing symptoms associated with HIT under real-world conditions. **Methods:** An initial sample of 231 subjects was recruited for the study, with 165 adults (mean age 42.7 years; 71.43% diagnosed with probable HIT) completing a clinical questionnaire before and after two months of home-based supplementation with DAO. Participants provided information on their symptoms and reactions to histamine-rich foods via a self-administered electronic platform. **Results:** After two months of supplementation, notable reductions were observed in the prevalence of migraines (-30.4%), gastrointestinal symptoms (-47.1%), fatigue (-72.2%), and cutaneous manifestations (-64.4%). Furthermore, 55.8% of participants reported a decrease in their medication needs, while 53.3% experienced improved tolerance to histamine-rich foods. **Conclusion:** The findings indicate that vegan DAO supplementation (NaturDAO), when combined with dietary recommendations, can yield clinically relevant improvements in symptoms among adults with suspected HIT. This supports the supplement's utility beyond hospital settings. The results underscore the need for further studies involving larger populations to confirm these findings and explore the long-term effects of DAO supplementation on symptom management in HIT patients.

Keywords

Histamine Intolerance, Diamine oxidase, DAO Supplementation, Real-world Evidence, Observational Study

1. Histamine Intolerance

Histamine intolerance (HIT) is a metabolic disorder caused by the excessive accumulation of histamine in the body due to an inability to break it down properly. This dysfunction is

mainly related to the decrease in the activity of the enzyme diamine oxidase (DAO), responsible for degrading the histamine ingested in the intestine [1]. Histamine is a biogenic

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amine present in many foods, especially those fermented, cured or stored for long periods, as well as in alcoholic beverages [2].

The symptoms of histamine intolerance are varied and affect multiple organs and systems, complicating its clinical diagnosis. Among the most common are gastrointestinal problems such as diarrhea, abdominal pain, nausea, vomiting; skin symptoms such as hives, pruritus and rashes; respiratory problems, headaches, migraines, fatigue, palpitations, and mood disturbances [3]. This wide range of manifestations is due to the fact that histamine acts as a mediator in various tissues and organs, modulating immune, neuronal and vascular responses.

The etiology of this condition can be multifactorial. In addition to the functional or genetic deficiency of DAO, there are other factors that may contribute, such as damage to the intestinal mucosa due to inflammatory diseases or infections, the intake of drugs that inhibit DAO, and alterations in the microbiota with an increase in histamine-producing bacteria [4].

These circumstances lead to an excess of plasma histamine and its adverse effects.

The diagnosis of HIT is based primarily on a detailed medical history that describes the temporal relationship between the intake of histamine-rich foods and the onset of symptoms. The exclusion of allergies and other similar pathologies is essential, as well as the assessment of the response to low-histamine diets and treatment with DAO supplements [5, 6]. The quantification of DAO activity in serum may be complementary, although it does not always correlate with intestinal symptomatology [7].

In terms of treatment, dietary restriction of foods high in histamine is the basic measure, in combination with DAO enzyme supplementation to improve degradation and reduce plasma histamine levels. In some cases, antihistamines are also used to relieve specific symptoms [8, 9]. Multidisciplinary management and prolonged follow-up are recommended to optimize the patient's quality of life and adjust therapies according to clinical evolution.

Despite growing interest and research, histamine intolerance continues to be an underestimated and challenging diagnosis, mainly because of its nonspecific manifestations and lack of definitive testing. Therefore, the research of new diagnostic markers and effective treatments is an active area in nutritional and gastroenterological medicine [10-12].

2. Diamine Oxidase (DAO) in Histamine Intolerance

Treatment with diamine oxidase (DAO) for histamine intolerance has become an emerging tool for addressing both gastrointestinal and systemic symptoms derived from poor histamine metabolism. DAO is the main enzyme responsible for the degradation of dietary histamine in the digestive tract, and its oral supplementation seeks to compensate for the endogenous deficit characteristic of patients with histaminosis [13, 14].

A number of clinical studies and human interventions have shown that daily oral supplementation with DAO before meals can significantly reduce the intensity and frequency of symptoms associated with histamine intolerance, including migraines, gastrointestinal symptoms, hives, and neurological complaints. In one of the most robust trials, it was observed that after four weeks of daily supplementation in 28 diagnosed patients, there was a remarkable improvement in all symptoms assessed by a structured questionnaire, with partial return of symptoms after discontinuation of DAO, demonstrating the dependence of the effect on continued treatment [15].

In the field of migraine, treatment with DAO has shown a significant reduction in the duration of monthly attacks in patients with enzyme deficiency, compared to placebo (mean reduction of 1.4 hours of pain per attack), although without changes in the total number of attacks or in the global perception of pain intensity. It has been highlighted that the greatest efficacy is observed in patients with markedly low serum DAO levels [16].

The benefit of treatment has been established not only in acute symptomatic control, but also in reducing the need for additional medication, such as antihistamines in patients with chronic spontaneous urticaria. In addition, studies show that the combination of low-histamine diet and DAO supplementation produces better outcomes than either intervention alone, especially in patients with moderately low serum DAO levels [14-16].

Despite the observed benefits, there are important limitations. Some commercial formulations evaluated do not contain sufficient enzymatic activity for effective degradation of histamine, and the need to improve the stability, bioavailability and galenic profile of the enzyme to achieve a reproducible therapeutic effect has been stressed [17]. Studies suggest that high doses, properly administered and protected from gastric inactivation, can degrade representative amounts of histamine under simulated conditions of typical food, which would be sufficient to relieve symptoms in most patients [18].

Some recent biotechnological developments have managed to express DAO in recombinant organisms and plants, exploring alternatives to the traditional pig source, thus increasing product stability and safety for certain consumer groups. Likewise, co-formulation with catalase or the use of cryoprotectants such as trehalose and sucrose have been evaluated with the aim of improving the stability of the enzyme in the gastrointestinal tract and during storage [17].

The use of DAO as a biomarker in plasma has also been proposed to monitor response to treatment and intestinal mucosal integrity, although its diagnostic value is still debated due to individual variability and potential analytical interferences [15].

In short, oral DAO supplementation represents one of the most promising strategies in the management of histamine intolerance. Its implementation, not without technical and regulatory challenges, has demonstrated tangible benefits in the reduction of gastrointestinal, neurological and dermatological

symptoms, positioning itself as a relevant therapeutic resource to improve the quality of life of histamine patients. It is necessary, however, to deepen clinical research with longer studies and larger populations, and to ensure both the quality and effective concentration of the supplements marketed and the personalization of the treatment according to the enzymatic and clinical profile of each individual [13].

3. Real-World Evidence (RWE)

Real-World Evidence (RWE) studies are increasingly important to complement the evidence obtained in clinical trials, allowing the effectiveness, safety and use of supplements to be evaluated in real clinical practice conditions. Unlike strictly controlled clinical trials, RWE collects data from more heterogeneous patients, with comorbidities and distinct patterns of use that better reflect the needs and behaviors of the general population [19].

This type of study covers a wide variety of methodologies, from cross-sectional surveys with large numbers of participants, analysis of electronic health records, and administrative databases, to technological innovations such as mobile applications and analysis with artificial intelligence and natural language processing. These tools make it possible to reduce biases such as memory bias and improve the quality and scope of the data collected [20].

However, RWE studies also face significant challenges. Data quality and completeness can be affected by inconsistent records, lack of rigorous tracking, and difficulties capturing actual over-the-counter usage. In addition, without the randomization typical of clinical trials, the risk of bias due to confounding factors increases. Therefore, careful designs, advanced statistical analyses, and the development of methodological standards are required to ensure the validity and reproducibility of the results [21].

Numerous international regulatory bodies recognize the value of real-world evidence and promote its use to evaluate and expand indications, improve labeling, and support clinical decisions. This requires improving the systematic collection of data on over-the-counter products, fostering multi-sectoral collaborations and adopting new technologies that enhance research [22].

In summary, real-world evidence represents a methodological revolution in the study of supplements, offering a much more complete and closer view of daily clinical practice, and enabling a better evaluation of effectiveness and safety in real and diverse contexts.

4. Observational Studies

Observational studies are a fundamental tool in epidemiology and health sciences to investigate associations between exposures and diseases, as well as the effectiveness of interventions when randomized clinical trials are not feasible or

ethical. According to Stroup et al. (2000), these studies include designs such as cohorts, case-controls, cross-sections, and use of existing databases, and although they lack randomization, they provide valuable information on real populations and contexts of routine practice. However, they present inherent challenges in terms of bias control, confusion, design heterogeneity, and difficulty in synthesizing results through meta-analysis, which requires transparency and methodological rigor in their reporting [23].

To improve the quality of information derived from observational studies, Stroup et al. (2000) proposed a checklist (MOOSE) to guide the elaboration and review of meta-analyses of these designs, emphasizing the clear definition of the problem, the search strategy, the explanation of the method of data extraction and analysis, the strategies for assessing heterogeneity and the control of bias. They highlight the importance of reporting the quality of primary studies, detailing the treatment of confounding variables, and adequately managing heterogeneity before quantitatively combining results.

For its part, the STROBE group developed an international guide detailing the essential elements that must be reported in cohort, case-control, and cross-sectional studies, such as participant selection, definition of variables and exposures, management of missing data, statistical methods, and detailed presentation of results. They recommend specifying how the sample size has been calculated, how the confounders have been chosen and how the sensitivity analyses have been carried out. Its implementation favors transparency, reproducibility and usefulness for reviewers, editors and researchers [24].

Overall, the literature highlights that methodological rigor, clarity in the presentation of methods and results, and the adoption of international standards such as MOOSE and STROBE, are essential for observational studies to provide solid and useful evidence for decision-making in public health and clinical research.

5. Observational Study with NaturDAO

This study with NaturDAO is based on Real-World Evidence (RWE), an approach that is gaining increasing prominence to evaluate the effectiveness, safety and use of supplements in everyday clinical practice and real-life conditions. Compared to controlled clinical trials, RWE makes it possible to analyse data obtained from much more diverse patients, with different clinical profiles and habits, thus capturing the heterogeneity that really exists in the consumer population of products such as DAO.

The relevance of this type of evidence lies in the fact that it incorporates multiple complementary methodologies such as cross-sectional surveys on consumption and its effects, analysis of electronic health records and consumption databases. This makes it possible to collect objective information on the real behavior of patients and reduce biases such as memory bias, improving the quality of the data and the validity of the conclusions.

In the literature, observational studies play a key role in clinical research by allowing the analysis of associations, efficacy and safety profiles of real-life health interventions, especially when methodological guidelines such as MOOSE are followed that ensure clarity in the design, extraction, analysis of data and treatment of biases. For its part, the international STROBE guide establishes the critical elements for the reporting of cohort, case-control and cross-sectional surveys, enhancing the transparency and scientific usefulness of the results.

This study was designed as a single-group before–after observational study, in which each participant acts as his or her own control. The intervention consisted of DAO supplementation for two months and the outcome variable was assessed using a structured questionnaire applied at baseline and at the end of follow-up. In the absence of a parallel control group, the changes described represent temporal associations within the same cohort and do not allow conclusively attributing a causal relationship between supplementation and observed improvement. For this reason, terms such as 'reduction' or 'improvement' are used to describe variations in the frequency and intensity of symptoms in the study group itself, while the interpretation of 'efficacy' is limited to the context of actual practice and will need to be confirmed in future controlled studies.

Although the use of structured questionnaires and electronic data collection contribute to systematizing the process and reducing certain memory and recording biases, the study maintains limitations inherent to the observational design. These include the potential self-selection bias of voluntary

participants and the response bias inherent in self-administered instruments, given that the responses were not clinically verified by a third party and may be influenced by subjectivity or the desire to offer a socially acceptable image. Although principles of standardization and transparency have been followed, the results should be interpreted considering the possible persistence of these uncontrolled sources of bias, as recognized in the specialized literature on self-report studies.

In summary, this analysis of NaturDAO is fully inserted in this methodological framework, applying criteria and tools of the RWE to obtain solid, diverse and relevant information on the effectiveness and safety of the DAO, always under principles of methodological rigor, transparency and international reporting standards.

5.1. Participants

The headings or subheadings should be numbered in order as the given style. Each headings or subheadings should not exceed 3 lines. There should be at least 2 subheadings but no more than 10 subheadings under one heading.

The present observational study initially included 231 adult subjects who first purchased the NaturDAO supplement through e-commerce, all of them users who manifested symptoms compatible with histamine intolerance. The inclusion criteria were: age between 18 and 65 years, presence of at least three symptoms compatible with histamine intolerance according to the entry questionnaire, and voluntary acceptance to participate in clinical follow-up for two months (Table 1).

Table 1. Mean age of the subjects initially included in the study.

Characteristic	Women (n=137)	Men (n=94)	Total (n=231)
Mean age (years)	44.3 ± 11.5	42.4 ± 10.7	43.6 ± 11.2

All participants completed the structured clinical questionnaire before and after the intervention period with NaturDAO. Those subjects who did not have 3 or more symptoms compatible with histamine intolerance were excluded, leaving a final sample of 165 participants.

As mentioned, the participants were recruited through electronic recruitment among users who voluntarily acquired the supplement through e-commerce, which configures a non-probabilistic sample of convenience. This procedure favors a wide geographical dispersion and a certain demographic heterogeneity, but does not guarantee randomness or statistical representativeness of the general population with suspected histamine intolerance. Consequently, the results can be directly extrapolated mainly to consumer profiles that actively seek this type of product in online channels, and should be

interpreted with caution when generalizing them to other healthcare or population contexts.

In the present observational study, no follow-up losses or dropouts were recorded, and complete data were obtained from all participants (n=231) at baseline and at baseline. The digital platform used incorporates automatic questionnaire validation, which verifies the completeness of all responses before they are closed, thus guaranteeing 100% follow-up with no missing data.

5.2. Protocol

This observational study was designed to evaluate the usefulness of a structured histamine intolerance questionnaire, as well as the clinical evolution of the subjects after two months of DAO supplementation under home conditions.

The "questionnaire for diagnosis and follow-up of histamine intolerance with DAO supplementation" was applied, structured in three blocks (general symptoms, eating reaction and evolution after DAO).

All those interested in participating in the study underwent

an initial self-assessment. Those with ≥ 3 affirmative responses in part 1 of the questionnaire were included in the study and before starting supplementation they signed a voluntary consent to participate in clinical follow-up and were given part 2 of the questionnaire. At 2 months, the evaluation was repeated using part 3 of the questionnaire (Table 2).

Table 2. Questionnaire used in the observational study.

Questionnaire for diagnosis and follow-up of histamine intolerance with DAO supplementation

Part 1: Initial Symptom Assessment (Yes/No Score)

Answer Yes or No to each question:

YES NO

Do you have migraines or headache episodes at least twice a month?

Do you suffer from constipation or diarrhea with no known cause?

Do you feel abdominal bloating, flatulence or digestive pain after normal meals?

Do you suffer from muscle pain, joint pain or contractures frequently?

Have you noticed dry skin, redness, frequent rashes, or atopic skin?

Do you feel constantly fatigued for no apparent reason?

Have you been diagnosed or suspected of fibromyalgia?

Result: 3 or more affirmative responses suggest possible histamine intolerance

Part 2: Evaluation of reactions after consumption of histamine-rich foods

Indicate Yes or No if you notice symptoms such as headache, digestive or skin pain after ingesting:

YES NO

Cured cheeses

Canned, smoked or processed fish (tuna, sardines, salmon)

Fermented products (sauerkraut, yogurt, kefir)

Sausages and processed meats

Wine, beer and spirits

Tomato, eggplant, spinach

Ripe fruits: banana, avocado, strawberry

Chocolate and cocoa products

Vinegar, soy sauce, miso

Apply sum of foods with symptoms for clinical assessment and dietary adjustment.

Part 3: Follow-up questionnaire after 2 months of DAO supplementation

Answer Yes or No to each question:

YES NO

Has the frequency or intensity of migraines or headaches improved?

Did digestive problems (diarrhea, constipation, bloating) improve?

Has the appearance of muscle or joint pain decreased?

Did the skin condition improve?

Do you feel more energetic or less fatigued?

Questionnaire for diagnosis and follow-up of histamine intolerance with DAO supplementation

Have you reduced the need for headache medication (e.g. triptans)?

Have symptoms decreased after consumption of histamine-rich foods?

Have you followed a low-histamine diet in addition to DAO supplementation?

The collection of self-administered data through an electronic platform and remote monitoring guarantee the external validity of the results, reflecting the real experience of users seeking this type of intervention in a non-hospital context.

This protocol responds both to the need to improve the recognition and approach to histamine intolerance in the adult population and to the characterization of the potential benefit of DAO supplements in everyday and diverse situations.

In terms of participant flow, the 165 subjects who completed baseline and were recruited were followed up until the 2-month visit, with no losses during the observation period or intervention-related dropouts. Consequently, the analysis was performed on the entire cohort, without the need for imputation of missing data or exclusions for incomplete information in the main outcome variables. In accordance with the recommendations of the STROBE initiative, it is specified that missing data management methods were not applied as no relevant omissions were detected in the predefined measurements, which reinforces the transparency of the monitoring process and the interpretation of the observed changes in symptomatology.

Changes in symptom frequency are expressed as simple percentage variations, calculated from the quotient between the absolute difference in cases and the initial number of symptomatic participants for each category. In order to maintain the traceability of the calculations and avoid losses of accuracy when handling relatively small denominators, these percentages are presented to two decimal places. The presen-

tation with two decimal places does not imply the performance of hypothesis tests or inferential analysis; The values should be interpreted as descriptive estimates of the magnitude of change observed in this cohort, without formal attribution of statistical significance.

5.3. Results

5.3.1. Sample Description

The final sample of the study was composed of a total of 165 participants, of which 112 were women and 53 men, selected because they followed the criteria defined for the histamine intolerance profile. The mean age of women was 43.2 years, with a standard deviation of 12.7, while that of men was 41.3 years, with a standard deviation of 11.2. Considering the total sample, the overall mean age was 42.7 years, with a standard deviation of 12.1, and in all cases the age range was from 18 to 65 years, which guarantees the representation of the young and mature adult population.

Regarding the initial diagnostic categorization, the percentage of subjects (231) who met the criteria of probable histamine intolerance (defined as the presence of three or more positive symptoms in the entry questionnaire) was high (165): 81.75% of women and 56.38% of men. Overall, 71.43% of the initial participants had a probable diagnosis of histamine intolerance at the beginning of the protocol and were included in the follow-up (Table 3).

Table 3. Characteristics of the observational study sample (initial and final).

Feature	Women	Men	Total
Initial Sample	137 (59.31%)	94 (40.69%)	231 (100%)
Mean age (years) of the initial sample	44.3 ± 11.5	42.4 ± 10.7	43.6 ± 11.2
Shows with ≥3 symptoms compatible with histamine intolerance	112 (67.88%)	53 (37.12%)	165 (100%)
Percentage of the initial sample that entered the study	81.75%	56.38%	71.43%
Mean age (years) of the final sample	43.2 ± 12.7	41.3 ± 11.2	42.7 ± 12.1

These demographic and symptomatic profile data reflect a balanced cohort suitable for the analysis of the effectiveness of the DAO approach in a real-life setting, highlighting the

female predominance commonly observed in studies on food intolerances. The uniformity in the distribution of age and the

initial diagnosis reinforces the statistical validity and representativeness of the results obtained in this group.

5.3.2. Initial Assessment (Part 1 of the Questionnaire)

In the initial evaluation of the questionnaire, migraines or

headache episodes stand out as the most common symptoms, present in 67.88% of the participants, followed by digestive symptoms reported by 63.03%. Chronic fatigue was also notable, with a prevalence of 58.79%. Muscle and joint pain affected 38.79%, while skin symptoms related to atopic skin or rashes were reported in 35.76%. Finally, 13.94% reported a diagnosis or clinical suspicion of fibromyalgia (Table 4).

Table 4. Symptoms described in the study participants (Part 1 of the questionnaire).

Symptom	N subjects with an affirmative answer	% subjects with affirmative answer
Atopic skin/rashes	59	35.76%
Chronic fatigue	97	58.79%
Digestive problems	104	63.03%
Fibromyalgia Diagnosis	23	13.94%
Joint/muscle pain	64	38.79%
Migraines/headaches	112	67.88%

This symptomatic profile reflects the complexity and multisystematicity of histamine intolerance, where neurological and digestive symptoms have a very relevant weight.

This detailed analysis allows us to guide the next diagnostic and therapeutic strategies, including supplementation with diamine oxidase and dietary modifications in a personalized way.

5.3.3. Evaluation of Entry into the Study (Reaction to Histamine-Rich Foods. Part 2)

Table 5 presents the results of the study's initial evaluation in relation to the participants' reaction to histamine-rich foods. It is observed that the food group with the highest frequency

of reaction was sausages and processed meats, with 45 subjects affected, which is equivalent to 27.27% of the total, closely followed by cured cheeses (42 subjects, 25.45%) and processed fish (38 subjects, 23.03%). Fermented foods such as yogurt and kefir generated symptoms in 33 participants (20.00%), while vegetables such as tomato, eggplant, and spinach caused a reaction in 32 people (19.39%).

Alcohol consumption triggered symptoms compatible with histamine intolerance in 29 people (17.58%), and the chocolate or cocoa group affected 28 subjects (16.97%). Ripe fruits only caused a reaction in 25 cases (15.15%) and the group with the lowest percentage was vinegar, soybean and miso (21 subjects, 12.73%).

Table 5. Participants' Reaction to Different Foods in Observational Study Subjects (Part 2 of the Questionnaire).

Food	N subjects with the reaction	% subjects with reaction
Alcohol	29	17.58%
Chocolate/cocoa	28	16.97%
Cured cheeses	42	25.45%
Fermented (yogurt, kefir)	33	20.00%
Processed fish	38	23.03%
Ripe fruits	25	15.15%
Sausages/processed meats	45	27.27%
Tomato, eggplant, spinach	32	19.39%
Vinegar, soy, miso	21	12.73%

The mean symptom-triggering food score was 3.5 ± 2.1 per individual, suggesting that most participants reported reactions with at least three potentially histamine-rich food groups, reflecting the breadth of food intolerance in the cohort studied.

These results show a very heterogeneous and multisystem profile in the form of clinical presentation, confirming the need for an individualized approach both in dietary guidance and in the monitoring and treatment of this type of patient. In addition, the predominance of symptoms after the ingestion of sausages, cheeses, fish and alcohol underlines the importance of taking these foods into account in the recommendations for the population with suspected histamine intolerance.

5.3.4. Evaluation After Two Months of DAO Use (Part 3)

Table 6 presents the evolutionary results observed after two months of intervention with DAO, comparing the situation of the participants at baseline (P1) and at the end of the study (P3) and showing both the magnitude of the improvement and the

percentage of reduction in cases for each main symptom.

In the case of the frequency or intensity of migraines and headaches, it is observed that of the 112 subjects affected at the beginning, only 78 continued to have symptoms after follow-up, which represents an absolute reduction of 34 cases and a relative reduction of -30.36%. Digestive problems (diarrhea, constipation, bloating) presented one of the most notable improvements: of the 104 symptomatic individuals in P1, only 55 maintained symptoms in P3, representing a decrease of 49 subjects and a percentage reduction of -47.12%.

Muscle and joint pain decreased in 28 cases, from 64 initially affected to 36 after the intervention (-43.75%). The improvement in skin condition was even more evident, with a reduction of 38 symptomatic subjects between the start and end of the study, equating to 64.41% fewer affected.

Finally, the subjective perception of energy and fatigue showed the greatest change: of the 97 participants initially affected by persistent tiredness or fatigue, only 27 were still with symptoms after two months, showing an absolute improvement of 70 cases and a proportional reduction of -72.16%.

Table 6. Evolutionary results observed after two months of intervention with DAO, comparing the situation of the participants at the beginning (P1) and at the end of the study (P3) (Part 3).

Symptoms	P1	P3	P3-P1	Difference
Has the appearance of muscle or joint pain decreased?	64	36	-28	-43.75%
Has the frequency or intensity of migraines or headaches improved?	112	78	-34	-30.36%
Did digestive problems (diarrhea, constipation, bloating) improve?	104	55	-49	-47.12%
Did the skin condition improve?	59	21	-38	-64.41%
Do you feel more energetic or less fatigued?	97	27	-70	-72.16%

These results show that DAO supplementation, together with dietary recommendations, allowed a clinically relevant decrease in the prevalence of the main symptoms linked to histamine intolerance in this cohort, with a greater impact on fatigue, digestive symptoms and skin improvement. The consistency of the reduction in all the parameters evaluated supports the usefulness of the proposed approach and underlines the potential efficacy of the treatment in real-life conditions.

Table 7 presents key indicators on the impact of the intervention on complementary aspects of histamine intolerance management. First, it is noteworthy that 92 subjects (55.76% of the total evaluated) reported having reduced the need for headache medication after the DAO supplementation period. This suggests an indirect positive effect of treatment on the management of migraine and headache episodes, by reducing the use of common analgesic or anti-migraine drugs.

On the other hand, the adherence of dietary measures is evidenced with 54 participants (32.73%) who declared that they

had followed a diet low in histamine in addition to supplementation. This dietary modification is part of the standard approach to histamine intolerance and may have contributed, at least in part, to the symptomatic improvement observed in some subjects. Consequently, the results should be interpreted as the joint effect of DAO supplementation under real-world practice conditions, where dietary recommendations and spontaneous changes in diet are routine interventions. The study was not specifically designed or sized to formally compare subjects who did or did not follow a low-histamine diet, so it is not possible to isolate the relative impact of each therapeutic component; Future controlled studies that stratification by dietary guideline will be necessary to clarify this aspect.

Finally, the table shows that 88 people (53.33%) experienced a clear decrease in symptoms after the consumption of histamine-rich foods, which reflects the potential of combined

intervention (supplementation and dietary adaptation) to sig-

nificantly modify food tolerance and the appearance of clinical symptoms in this group.

Table 7. Evolutionary results observed after two months of intervention with DAO, comparing the situation of participants who responded at baseline (P1) and at the end of the study (P3) (Part 3).

Other parameters	P3	
Have you reduced the need for headache medication?	92	55.76%
Have you followed a low-histamine diet in addition to DAO supplementation?	54	32.73%
Have symptoms decreased after consumption of histamine-rich foods?	88	53.33%

Taken together, these results highlight the usefulness of DAO supplementation and complementary dietary strategies in reducing medication, improving digestive tolerance, and symptomatic control of patients with suspected histamine intolerance.

5.4. Discussion

The present observational study on the use and follow-up of diamine oxidase (DAO) supplementation in people with symptoms compatible with histamine intolerance offers a comprehensive and realistic view of the problem and the possibilities of intervention in daily life. The characterization of the sample, both in terms of distribution by sex and age range and symptom burden, confirms the representativeness of the group studied and reinforces the applicability of the findings to adult populations with clinical suspicion of histamine intolerance, aligning with the trend observed in the literature where a female and adult profile predominates.

One of the main contributions of this work is the confirmation, in real practice, of the high prevalence of neurological symptoms (migraines, headaches), digestive symptoms and fatigue among those who report histamine intolerance, as well as the notable frequency of reactions to foods rich in this mediator, being sausages, cheeses, processed fish and, to a lesser extent, alcohol and fermented foods, the main triggers. This multi-system pattern highlights the importance of systematically and structured assessment of the different symptom domains and dietary habits, in order to design personalized strategies and not only focused on a specific symptom or system.

The results after the intervention with NaturDAO for two months, either as a single intervention or combined with a low-histamine diet, are clinically remarkable. A significant – and in some cases very striking – reduction is observed in both the frequency of cardinal symptoms and the use of medication, especially in fatigue, digestive symptoms and skin manifestations, as well as a subjective improvement in general state and food tolerance. The reduction in the number of participants requiring headache drugs and those who present symptoms after histamine-rich foods, together with the voluntary adoption

of specific dietary recommendations, highlights the value of the multifactorial approach and the importance of food education to optimize outcomes.

One aspect to highlight is the coherence and robustness of the symptomatic reduction observed in all the parameters evaluated. The systematization of the questionnaire and individualized monitoring contribute to mitigate some typical biases of observational studies, such as information or confusion, although they do not completely eliminate the limitations inherent in real-life studies: absence of a control group, self-administration of the questionnaire and possible biases in memory or selection of participants.

5.5. Conclusions

In summary, this study describes observed improvements in the symptomatology associated with histamine intolerance in adults by supplementation with NaturDAO, within the framework of real-world evidence. The results highlight the value of standardized diagnostic tools and suggest the possible usefulness of combining dietary approaches with supplements in personalized strategies.

Abbreviations

DAO Diamine Oxidase
HIT Histamine Intolerance

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Author Contributions

Javier Moran: Conceptualization, Formal Analysis, Methodology, Supervision, Writing – original draft

Gerard Moles: Data curation, Funding acquisition, Inves-

tigation, Project administration, Resources, Software, Validation, Visualization, Writing – review & editing

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Data Availability Statement

The data supporting the outcome of this research work has been reported in this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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Biography



Javier Moran is a professor of Food & Regulatory Innovation at Catholic University of Murcia (UCAM). He is also a visiting professor at several universities (USIL, ISALUD, IFFE). He has participated in multiple international research collaboration projects in recent years. He currently serves on the Editorial Boards of numerous publications and has been invited as a Keynote Speaker, Technical Committee Member, Session Chair, and Judge at international conferences.

Research Field

Javier Moran: Food innovation, Food regulation, Functional foods, Nutraceuticals.