ISRCTN64888465 https://doi.org/10.1186/ISRCTN64888465

Study on the effectiveness of a low histamine diet and diamino oxidase enzyme supplementation in patients with histamine intolerance

Submission date 25/07/2022	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 06/09/2022	**Overall study status** Ongoing	
Last Edited 04/07/2025	**Condition category** Other	

Plain English summary of protocol

Background and study aims
Histamine intolerance is due to an inability to metabolize histamine from the diet, mainly due to reduced activity of the enzyme diamine oxidase (DAO) in the intestine, which causes an increase in the blood concentration of this amine and the appearance of clinical symptoms such as abdominal pain, diarrhea, vomiting, constipation, skin problems (urticaria, dermatitis or pruritus), respiratory problems (sneezing, rhinitis, nasal congestion and asthma), cardiovascular problems and/or headache. Many patients with this disorder often have more than one of these symptoms at a time. The aim is to study the effectiveness of the low-histamine diet and/or DAO enzyme supplementation in the treatment of symptoms associated with histamine intolerance due to DAO deficiency.

Who can participate?
Adults over 18 years of age with two or more symptoms associated with histamine intolerance (headache, dermatological, respiratory, and digestive) and altered plasma DAO enzyme activity and/or have any of the genetic variants of DAO deficiency

What does the study involve?
Participants are randomly divided into eight treatment groups:
1. Placebo group: participants will receive a gastro-resistant mini tablet (placebo) (three times /day, 20 minutes before each meal) and follow a Mediterranean style diet.
2. Diet group: participants will receive a gastro-resistant mini tablet (placebo) three times/day (20 minutes before each meal) and will follow a low histamine diet.
3. Pig DAO supplement + Mediterranean diet: participants will receive a gastro-resistant mini tablet with the animal DAO enzyme (4.2 mg) three times/day (20 minutes before each meal) and will follow a Mediterranean style diet.
4. Pig DAO supplement + low histamine diet: participants will receive a gastro-resistant mini tablet with the animal DAO enzyme (4.2 mg) three times/day (20 minutes before each meal) and will follow a low histamine diet.

5. Vegetable DAO supplement + Mediterranean diet: participants will receive a gastro-resistant mini tablet with the vegetable DAO enzyme (4.2mg) three times/day (20 minutes before each meal) and will follow a Mediterranean style diet.
6. Vegetable DAO supplement + low histamine diet: participants will receive a gastro-resistant mini tablet with the vegetable DAO enzyme (4.2 mg) three times/day (20 minutes before each meal) and will follow a low histamine diet.
7. High dose of vegetable DAO supplement + Mediterranean diet: participants will receive a gastro-resistant mini tablet with the high-dose vegetable DAO enzyme (8.4 mg) three times/day (20 minutes before each meal) and will follow a Mediterranean style diet.
8. High dose of vegetable DAO supplement + low histamine diet: participants will receive a gastro-resistant mini tablet with the high dose DAO enzyme (8.4 mg) three times/day (20 minutes before each meal) and will follow a diet low in histamine.
The maximum duration of the intervention will be 3 months from the beginning until the end. The researchers will check whether or not the activity of the DAO enzyme is altered, and a blood sample will be taken to perform a genetic study. After signing the general consent of the study, participants will have a total of four visits (V1, V2, V3 and V4). At the V1 visit (at baseline) participants will be given an information collection notebook and assigned to one of the two groups: DAO or placebo. They will also receive dietary recommendations that may include:
1. Low histamine diet (DAO-DIET group and DIET group)
2. Standardized Mediterranean-style diet (PLACEBO group and DAO group)
In addition, at baseline, the following information will be collected: symptom assessment and quality of life questionnaires, dietary questionnaire (weekly registration). Blood, urine, and feces samples will be also collected.
At the remaining visits (V2, V3 and V4) the researchers will collect the same information as in the V1 visit although the determination of the DAO activity and microbiota will only be carried out in V1 and V4. Before all of these visits participants must fast, with a minimum fasting time of 10 hours.

What are the possible benefits and risks of participating?
Participation will allow the researchers to evaluate:
1. The effect of diet and DAO supplementation in the treatment of symptoms associated with histamine intolerance
2. The validity of urinary determination of histamine metabolites as a marker of histamine intolerance
3. The role that the gut microbiota may have in histamine intolerance.
4. The validity of single nucleotide polymorphisms (SNPs) as genetic markers of histamine intolerance due to DAO deficiency
In addition, the study can help participants to better understand their state of health, although it is also possible that they may not get any direct benefit from participating. In any case, participants will contribute to a better understanding of the effect of a food supplement on the improvement of the symptoms of histamine intolerance.
The study does not pose any risk to the participants' health since the amount of blood extracted will be slightly higher than the amount extracted when performing a complete analysis. The removal of the blood sample can cause a burning sensation at the point where the needle is inserted into the skin and can cause a small bruise that disappears within a few days. More rarely it can cause brief dizziness.

Where is the study run from?
Hospital Clínic de Barcelona (Spain)

When is the study starting and how long is it expected to run for?
June 2022 to June 2027

Who is funding the study?
DR Healthcare España, S.L.U (Spain)

Who is the main contact?
1. Dr Ramon Estruch Riba, restruch@clinic.cat
2. Dra. M. Carmen Vidal Carou, mcvidal@ub.edu

Study website
https://www.clinicbarcelona.org/idibaps

Contact information

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
DAO/311776

Study information

Scientific Title
Low histamine diet and diamino oxidase enzyme supplementation

Acronym
DAO

Study objectives
The effectiveness of a low-histamine diet and diamino oxidase (DAO) supplements has been demonstrated in small clinical studies published in recent years, most of them reporting favourable results in terms of improvement or total remission of symptoms. However, these dietary studies have certain limitations, mainly in involving a small group of patients and/or a short intervention period. Therefore, current dietary management strategies for histamine intolerance still require more controlled, randomized, double-blind, and more ambitious, well-designed clinical trials to definitively confirm their effectiveness.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/07/2022, Institutional Review Board of the Hospital Clinic of Barcelona (Hospital Clínic De Barcelona, Villarroel, 170 – 08036 Barcelona, Spain; +34 (0)93 227 54 00; CEIC@clinic.cat), ref: HCB/2022/0437

Study design
Prospective single-centre double-blind randomized placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Home

Study type(s)
Quality of life

Participant information sheet
Not applicable

Health condition(s) or problem(s) studied
Symptoms associated with histamine intolerance due to DAO deficiency

Interventions
A total of 400 patients divided into eight treatment groups (50 individuals per group) will be assigned randomly using a computer-generated random number table:
1. PLACEBO GROUP: 50 participants will receive a gastro-resistant mini tablet (placebo) (three times/day, 20 minutes before each meal) and follow a Mediterranean-style diet.
2. DIET GROUP: 50 participants will receive a gastro-resistant mini tablet (placebo) three times /day (20 min before each meal) and will follow a low histamine diet.
3. PIG DAO SUPPLEMENT + MEDITERRANEAN DIET: 50 participants will receive a gastro-resistant mini tablet with the animal DAO enzyme (4.2 mg) three times/day (20 min before each meal) and will follow a Mediterranean-style diet.
4. PIG DAO SUPPLEMENT + LOW HISTAMINE DIET: 50 participants will receive a gastro-resistant mini tablet with the animal DAO enzyme (4.2 mg) three times/day (20 min before each meal) and will follow a low histamine diet.
5. VEGETABLE DAO SUPPLEMENT + MEDITERRANEAN DIET: 50 participants will receive a gastro-resistant mini tablet with the vegetable DAO enzyme (4.2 mg) three times/day (20 min before each meal) and will follow a Mediterranean-style diet.
6. VEGETABLE DAO SUPPLEMENT + LOW HISTAMINE DIET: 50 participants will receive a gastro-resistant mini tablet with the vegetable DAO enzyme (4.2 mg) three times/day (20 min before each meal) and will follow a low histamine diet.
7. HIGH DOSE OF VEGETABLE DAO SUPPLEMENT + MEDITERRANEAN DIET: 50 participants will receive a gastro-resistant mini tablet with the high-dose vegetable DAO enzyme (8.4 mg) three times/day (20 min before each meal) and will follow a Mediterranean-style diet.
8. HIGH DOSE OF VEGETABLE DAO SUPPLEMENT + LOW HISTAMINE DIET: 50 participants will receive a gastro-resistant mini tablet with the high-dose DAO enzyme (8.4 mg) three times/day (20 min before each meal) and will follow a diet low in histamine.

The interventions will last for a period of 3 months, after which they will be re-evaluated by the medical team to assess the degree of effectiveness of the administered intervention.

The combination of these groups will allow:
1. The comparison of the PLACEBO and DAO groups will allow the researchers to determine the effect of DAO supplementation on the reduction of symptoms.
2. The comparison of the PLACEBO and DIET groups will allow the researchers to determine the effect of diet on the reduction of symptoms.
3. The comparison of the DAO and DAO-DIET groups will allow the researchers to determine the synergistic effect between diet and DAO supplementation.
4. The comparison of the DAO and DIET groups will allow the researchers to determine the effect of the two treatments separately.
5. The comparison of the PIG DAO and VEGETABLE DAO groups will allow the researchers to determine which of the two types of DAO is more effective.
6. The comparison of the groups DAO VEGETAL and DAO VEGETAL IN HIGH DOSE will allow the researchers to determine which of the two doses is more effective.

Intervention Type
Mixed

Primary outcome measure
1. Plasma DAO enzyme activity measured using radioimmune assay (REA-HIT test) at the recruitment visit and 3 months
2. SNP-type variants associated with reduced levels of DAO activity measured using multiplex PCR at recruitment visit
3. Symptoms and quality of life measured using validated questionnaires at baseline, 1, 2 and 3 months:
3.1. Gastrointestinal symptoms (Criteris Roma IV, Bristol Stool Scale, Gastrointestinal Quality of Life Index [GIQLI])
3.2. Headaches (quality of life questionnaire: Migraine Disability Assessment [MIDAS] and Headache Impact Test [HIT-6] scale)
3.3. Respiratory symptoms (SNTO-22 or PNIF, Quality of Life Questionnaire for patients with rhinoconjunctivitis [RQLQ])
3.4. Dermatological symptoms (Index SCORing Atopic Dermatitis [SCORAD], Itch Severity Scale [ISS], Quality of Life Questionnaire Dermatology Life Quality Index [DLQI]/Quality of Life Index for Atopic Dermatitis [QoLIAD])
3.5. Quality of life (SF-36)
4. Effectiveness of the low histamine diet assessed using weekly record at baseline, 1, 2 and 3 months
5. Low-histamine diet assessed using a 151-item consumption frequency questionnaire (FFQ) at baseline and 3 months

Secondary outcome measures
1. Metabolomic markers in urine (histamine, methylhistamine, imidazole acetic acid, methyl-imidazole acetic acid) measured using ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) (untargeted) at baseline, 1, 2 and 3 months
2. Intestinal microbiota assessed using mass sequencing of bacterial 16S rRNA genes, v3-v4 regions at baseline and 3 months
3. Biochemical parameters of the study:
3.1. Serum tryptase levels (marker that measures the total level of tryptase released by mast cells into circulation) determined by immunoassay using the UniCAP Thermofisher method (which includes alpha and beta-tryptase) at baseline, 1, 2 and 3 months
3.2. Eosinophils, basophils, TSH, copper, zinc measured using the standardized methods of the CORE laboratory of the Hospital Clínic of Barcelona at baseline, 1, 2 and 3 months
4. Safety study parameters: blood count, blood biochemistry (glycemia, HbA1c, kidney and liver function, ionogram, lipid profile, nutritional assessment, C-reactive protein and interleukin 6) and urine (basic examination) – proteinuria and sediment) measured using the standardized methods of the CORE laboratory of the Hospital Clínic of Barcelona at baseline, 1, 2 and 3 months

Overall study start date
08/06/2022

Completion date
07/06/2027

Eligibility

Key inclusion criteria
1. Adults over 18 years of age
2. Recent history of two or more symptoms associated with histamine intolerance (headache, dermatological, respiratory, and digestive)
3. Present altered plasma DAO enzyme activity and/or have any of the genetic variants of DAO deficiency:
3.1. SNP-type variants associated with reduced levels of DAO activity (oral mucosal smear or blood)
3.2. rs10156191
3.3. rs1049742
3.4. rs1049793
3.5. rs2052129
4. Not having started dietary treatment (low histamine diet/DAO enzyme supplementation) before starting the study

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
400

Key exclusion criteria
1. Food and/or environmental allergies
2. Have taken pharmacological treatment with antibiotics or probiotic supplements in the last month before the start of the study
3. Being pregnant

Date of first enrolment
19/09/2022

Date of final enrolment
07/03/2027

Locations

Countries of recruitment
Spain

Study participating centre

Hospital Clínic of Barcelona
C/Villarroel 170
Barcelona
Spain
08036

Study participating centre
Campus de l'Alimentació de la Universitat de Barcelona
Avda. Prat de la Riba, 171 (Santa Coloma de Gramenet)
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Sponsor information

Organisation
DR Healthcare España, S.L.U

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Sponsor type
Industry

Funder(s)

Funder type
Industry

Funder Name
DR Healthcare España, S.L.U

Results and Publications

Publication and dissemination plan
Following the completion of the study, the results are expected to be published whether they are positive or negative. When one of the parties wishes to use the partial or final results, in part or in full, to disseminate and/or publish them as an article, conference etc, they must request the consent of the other party in writing. They must communicate the authorization or express their disagreement or reservation in writing within a maximum period of 20 calendar days. After this period without an answer, the authorization for the dissemination of the results will be understood.

Intention to publish date
01/11/2023

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Ramon Estruch (restruch@clinic.cat) and Dr Mari Carmen Vidal (mcvidal@ub.edu). There are restrictions on the availability of data due to the signed consent agreements around data sharing, which only allow access to external researchers for studies following the project's purposes. Requestors wishing to access the DAO trial data used in this study can make a request to restruch@clinic.cat and mcvidal@ub.edu.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 3		26/07/2022	No	Yes
Protocol file	version 3		26/07/2022	No	No