

Is DAO in serum affected by food challenge with a histamine-rich meal?



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This case study examines the kinetics of the diamine oxidase levels after challenge with a histamine-rich meal in patients with histamine intolerance as an alternative diagnostic tool to conventional tests combined with the dietary intervention. (J Allergy Clin Immunol Global 2023;2:100097.)

Key words: Histamine hypersensitivity, diamine oxidase, DAO, kinetics, food challenge, histamine-rich meal

Histamine hypersensitivity (HIT) is characterized by an imbalance between accumulated histamine and histamine degradation attained mainly through the enzyme diamine oxidase (DAO).¹ Histamine is present in different foods and drinks and can elicit heterogeneous clinical symptoms when ingested, usually symptoms of the skin, gastrointestinal canal, the nervous, and cardiovascular system.¹ According to the European Food Safety Authority report, the foods containing high levels of histamine derive from fish products, matured sausages, cheese, and fermented fish products.²

Patients suspected of having HIT show no signs of IgE-mediated food allergy in allergy tests. The whole investigation is based on the relevant anamnesis for food hypersensitivity. Consequently, elimination of the suspect foods is necessary, and if a symptom-free period is successfully attained, the eliminated foods are reintroduced to evoke allergy symptoms again and thus establish the diagnosis. At the beginning of 2000s, measurement of DAO level in serum became available commercially and was deemed an additional diagnostic tool. Low levels of DAO in serum have been considered associated with a diagnosis of HIT,³ but the clinical relevance of a DAO test has been questioned owing to the multiple factors affecting the measurement.⁴

Because DAO is often used as a single value analysis when a patient is seeking medical help, it is impossible to know how and whether the DAO levels fluctuate. Furthermore, whether there are

Abbreviations used

DAO: Diamine oxidase

HIT: Histamine hypersensitivity

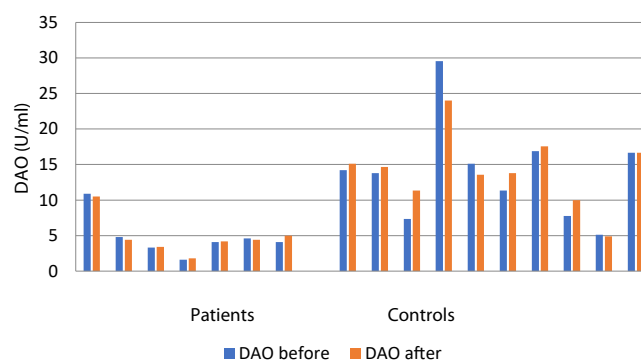


FIG 1. Fluctuation of the DAO levels before (blue column) and about 3 hours after (orange column) ingestion of a histamine-rich meal in both patients (P) and control subjects (C). No significant changes in the mean DAO levels could be noticed either between the 2 groups or before and after the ingestion of the histamine-rich meal.

any changes in DAO levels after ingestion of a histamine-rich meal is still unknown.⁵ One study determined the circadian profile of DAO levels in patients with HIT, with lower DAO levels present only in a small subgroup of patients with HIT.⁶

This clinical case report presents the determination of DAO levels and kinetics measured in serum before and up to 4 hours after challenge with a histamine-rich meal.

A total of 7 patients were referred to the allergology clinic of Sahlgrenska University Hospital in Gothenburg for investigation of suspected HIT. All 7 patients had been diagnosed as histamine intolerant owing to at least 2 self-reported typical symptoms only after intake of foods rich in biogenic amines. IgE-mediated food allergy was excluded. A symptom-free period followed exclusion of the histamine-rich food either when the patients avoided the food by themselves owing to symptoms or under dietician-guided elimination. After the symptom-free period, relapse of symptoms was confirmed when 1 or more of the foods rich in histamine was reintroduced according to the guidelines.⁴ Except for 2 patients who had controlled non-type 2 asthma, none of the patients who were recruited and underwent investigation at the clinic had any other diagnosis such as pollen allergy, irritable bowel disease, inflammatory bowel disease, or mast cell disease. None of the female patients was pregnant. A total of 10 healthy individuals were recruited as control subjects and underwent the same analysis and single meal challenge.

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TABLE I. Changes in DAO levels in all patients and controls before, during, and after challenge with histamine each meal

Study subject	Reported atopic disease	DAO level before meal (U/mL)	DAO level after meal (U/mL)	Change in DAO level after meal (1 = rise; 2 = reduction; 0 = no difference)	Any symptoms after meal (1 = yes; 2 = no)
Patient 1	Asthma	10.9	10.5	2	1
Patient 2	—	4.8	4.4	2	1
Patient 3	—	3.3	3.4	1	1
Patient 4	—	1.6	1.8	1	1
Patient 5	Asthma	4.1	4.2	1	2
Patient 6	—	4.6	4.4	2	1
Patient 7	—	4.1	5.0	1	1
Control 1	—	14.2	15.1	1	2
Control 2	—	13.8	14.7	1	2
Control 3	—	7.3	11.3	1	2
Control 4	—	29.6	24.0	2	1
Control 5	—	15.1	13.6	2	2
Control 6	—	11.3	13.8	1	2
Control 7	—	16.9	17.6	1	2
Control 8	—	7.8	10.0	1	2
Control 9	—	5.1	4.9	2	2
Control 10	—	16.7	16.7	0	2

Before the challenge, all subjects were instructed to eat an ordinary breakfast with a low histamine content. Shortly after breakfast, a first blood test to measure serum level of DAO was performed. All subjects were served a histamine-rich meal provided by the allergy dietician. The meal contained 75 g of tuna in mayonnaise, 50 g of cooked prawns, 1 egg, 15 g of cured ham, 15 g of smoked ham, 25 g of matured soft cheese, 20 g of matured hard cheese, and white bread; 15 g of dark chocolate and 1 small citrus fruit were served as dessert, with optional choice of coffee.²

After 3 to 4 hours, a new test to measure serum DAO level was performed. Symptoms of abdominal pain, skin symptoms, headache, or other optional symptoms were scored 0 to 3 by the subjects and registered in symptom diaries as used before.⁷ Symptoms were documented before the meal; 1, 2 and 3 hours directly after the meal; and the morning of the next day.

The levels of DAO activity in the samples were measured with a commercially available kit (DAO-REA Sciotec, HS 421-37; Tulln an der Donau, Austria) according to manufacturers' instructions.⁸

All participants in the study were aged 18 years or older and gave informed consent to participate in the study according to the guidelines of the local ethics review authority. The case study was approved by the ethics review authority in Gothenburg, Sweden (document no. T351-17).

Descriptive statistics are presented as min-max values and comparisons between groups with a chi-square test.

The median baseline DAO levels of the patients before the histamine-rich meal was 4.1 U/L compared with 14.0 U/L in the controls subjects, whereas after the histamine-rich meal, the median DAO levels were 4.4 U/L in the patients versus 14.2 U/L in the control subjects. Of the 7 subjects, 4 had increased DAO levels after the challenge meal, and in this respect, they did not differ from the control subjects, with 6 of the 10 controls having increased levels of DAO ($P > .05$) (Fig 1). Of the 7 patients, 6 reported typical symptoms after the meals versus 1 of the 10 controls ($P = .04$). Gastrointestinal symptoms after the meal were reported by 5 patients, headache was reported by 3, and skin symptoms were reported by 2. One control subject reported gastrointestinal symptoms after the meal. No significant differences in changes in serum DAO levels could be related to the reported symptoms (Table I).

For the first time, the kinetics of the DAO levels after the ingestion of a histamine-rich meal could be examined in this short case report study.

To our knowledge, this is the first case study to examine the kinetics of DAO levels, showing no significant changes in DAO levels for up to 4 hours after challenge with histamine-rich foods in patients with HIT despite the fact that they developed symptoms. Although the number of participants in this case study is small, the results signify that there are no available reliable diagnostic tools yet other than the typical anamnesis for histamine-rich food-related hypersensitivity in combination with exclusion of the IgE-mediated mechanism of food allergy and use of an elimination diet to establish the diagnosis of HIT. Further studies investigating the kinetics of DAO levels in patients with HIT in larger populations are needed to better understand the pathophysiology in these patients and acquire potentially improved alternative diagnostic tools for diagnosis of histamine hypersensitivity besides the current dietary interventions or food challenges.

PRACTICAL TIPS

DAO measurements were not useful as clinical tool to diagnose HIT in the study setting. There are still no available reliable diagnostic tools for HIT other than anamnesis for histamine-rich food-related hypersensitivity in combination with exclusion of the IgE-mediated mechanism of food allergy and use of an elimination diet to establish the diagnosis.

REFERENCES

- Maintz L, Novak N. Histamine and histamine intolerance. *Am J Clin Nutr* 2007;85:1185-96.
- European Food Safety Authority. Scientific opinion on risk based control of biogenic amine formation in fermented foods. *EFSA J* 2011;9:2393.
- Cucca V, Ramirez GA, Pignatti P, Asperti C, Russo M, Della-Torre E, et al. Basal serum diamine oxidase levels as a biomarker of histamine intolerance: a retrospective cohort study. *Nutrients* 2022;14:1513.
- Reese I, Ballmer-Weber B, Beyer K, Fuchs T, Kleine-Tebbe J, Klimek L, et al. German guideline for the management of adverse reactions to ingested histamine: guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the German Society for Pediatric Allergology and Environmental Medicine (GPA), the German Association of Allergologists (AeDA), and the Swiss Society for Allergology and Immunology (SGAI). *Allergo J Int* 2017;26:72-9.

5. Wantke F, Proud D, Siekierski E, Kagey-Sobotka A. Daily variations of serum diamine oxidase and the influence of H1 and H2 blockers: a critical approach to routine diamine oxidase assessment. *Inflamm Research* 1998;47:396-400.
6. Pinzer TC, Tietz E, Waldmann E, Schink M, Neurath MF, Zopf Y. Circadian profiling reveals higher histamine plasma levels and lower diamine oxidase serum activities in 24% of patients with suspected histamine intolerance compared to food allergy and controls. *Allergy* 2018;73:949-57.
7. van Odijk J, Peterson CG, Ahlstedt S, Bengtsson U, Borres MP, Hulthén L, et al. Measurements of eosinophil activation before and after food challenges in adults with food hypersensitivity. *Int Arch Allergy Immunol* 2006;140:334-41.
8. Sciotec. DAO-REA method analysis from Sciotec. Available at: <https://eaglebio.com/wp-content/uploads/2019/06/KR8220-Diaminooxidase-DAO-REA-H-Nuclid-ELISA-Assay-Kit.pdf>.