

Diamine oxidase enzyme: a novel biomarker in respiratory allergy

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Background: Well-known allergy tests are used to evaluate and diagnose allergic diseases. The aim of this study was to assess the role of serum level diamine oxidase (DAO) enzyme as a diagnostic marker in respiratory allergy.

Methods: This case-control study included 40 patients with respiratory allergies (atopic asthma and allergic rhinitis) as well as 40 age- and sex-matched controls. A detailed past medical history of allergy was collected from each participant including family history of allergy. Physical examination, pulmonary function test (PFT) and measurement of serum levels of total immunoglobulin E (IgE) and DAO were performed. Skin-prick test and specific IgE to common aeroallergens were also carried out.

Results: DAO levels were higher in patients than controls. There was a positive correlation between severity of disease and DAO. No significant association was found

between DAO level and age, type of respiratory allergy, duration of disease, PFT, eosinophilia, and total IgE. DAO had a high negative predictive value (94.7%) and high sensitivity (97.5%).

Conclusion: DAO may be helpful in the assessment of severity and in ruling out respiratory allergy. © 2019 ARS-AAOA, LLC.

Key Words:

diamine oxidase; DAO; bronchial asthma; allergic rhinitis; skin-prick test; total IgE; specific IgE; allergy tests

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Respiratory allergy is growing significantly. Estimations worldwide reveal that 5% to 12% of the population are asthmatic, whereas 20% have allergic rhinitis, which is the leading cause of decreased individual productivity. One study showed that around 45% of patients had not yet been diagnosed and that respiratory allergies were underdetermined.¹ Accurate screening and early diagnosis are crucial in the management of respiratory allergy.

Mast cells are the main contributor of a typical allergic inflammatory reaction. These cells are activated by exposure to allergens, which, in turn, results in the release of many mediators including histamine, leukotrienes, and specific cytokines.² Histamine is the main biomarker of the

degranulation of a mast cell and is of utmost importance in allergic diseases.³ Histamine is the result of decarboxylation of the amino acid L-histidine by the enzyme histidine decarboxylase (HDC), which is only detected in active histamine-secreting cells. HDC is synthesized only when histamine is needed and quickly degrades when a sufficient amount of histamine is produced. Alternatively, histamine N-methyltransferase (HNMT) and diamine oxidase (DAO) are continuously produced and, therefore, are the most important regulators of histamine catabolism.^{4,5}

Diagnosis of respiratory allergies, immunoglobulin E (IgE)-mediated in particular, depends mainly on traditional tests such as the skin-prick test, intradermal skin test, and specific IgE. Some cellular tests appeared later and proved to be useful. These tests mainly assess the activity of blood cells in vitro.⁶

The enzyme-affinity-gold method was then discovered based on the affinity of DAO for its substrate (histamine) and localization of histamine intracellularly in mast cells. Following this successful process, a similar technique was applied, aiming to localize histamine in basophils.⁷

In 2015, Shamji et al.⁸ found intracellular DAO measurement to be accurate in assessing histamine function and a useful biomarker for allergen immunotherapy.

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TABLE 1. Demographic distribution of the study population*

Variable	Groups		Test value	p
	Cases	Control		
Age (years)			-0.76	0.44
Range	18–56	18–56		
Mean $\pm$ SD	33.5 $\pm$ 12.0	35.5 $\pm$ 11.3		
Duration of disease (years)				
Range	1–30	–		
Mean $\pm$ SD	7.9 $\pm$ 5.5	–		
Gender, n (%)			0.48	0.48
Male	13 (32.5)	16 (40.0)		
Female	27 (67.5)	24 (60.0)		
Diagnosis, n (%)				
Atopic bronchial asthma	17 (42.5)	–		
Allergic rhinitis	23 (57.5)	–		

*Values of $p > 0.05$ insignificant; $p \leq 0.05$ significant; $p \leq 0.001$ highly significant.

This study aimed to assess the serum-level DAO enzyme as a diagnostic biomarker in atopic bronchial asthma and allergic rhinitis.

Patients and methods

This case-control study included 40 patients with respiratory allergies (atopic asthma and allergic rhinitis). Inclusion criteria included patients above 18 years of age that were diagnosed as atopic asthma or allergic rhinitis. Cases were stratified according to severity. Diagnosis of asthma was made according to the Global Initiative for Asthma guidelines (GINA).⁹ Severity of asthma was assessed according to the National Heart, Lung, and Blood Institute guidelines, by means of the severity of symptoms and a pulmonary function test.¹⁰ Allergic rhinitis diagnosis was made according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines.¹¹ Diagnostic criteria of allergic rhinitis include a positive history of nasal itch, sneezing, rhinorrhea, seasonality, and positive signs of nasal shiners, pale mucosa, polyps, and postnasal drip. Measures of severity include symptoms, sleep disorders, impact on daily life/activity, and duration/frequency of symptoms. Symptoms, sleep disorders, and impact on daily life/activity were described as mild and moderate/severe. Duration/frequency of symptoms were described as intermittent (< 4 days/week or < 4 weeks) or persistent (≥ 4 days/week or ≥ 4 weeks).

Patients were recruited from the Allergy and Clinical Immunology Outpatient Clinic of Ain Shams University Hospital. Forty age- and sex-matched healthy individuals were included as a control group. Individuals were excluded from the study if they were taking antihistamines, systemic

glucocorticosteroids (oral or injection), or drugs affecting the activity of DAO for the past 2 weeks (such as aminophylline, clavulanic acid, metoclopramide, verapamil, or heparin). Additionally, patients with a 2-week intake history of foods containing histamine such as fermented foods, beverages, processed meat and seafood, or patients with any other medical disorders (eg, hepatic or renal disease) were excluded from this study. The Research Ethics Committee of Ain Shams University approved the study and an informed consent was obtained from all participants.

A detailed past medical history of allergy was collected from each participant including family history of allergy. A physical examination, pulmonary function test (PFT), and skin-prick test to common aeroallergens were performed in the clinic. Furthermore, total serum IgE, specific IgE to common aeroallergens, and the serum level of DAO were performed using enzyme-linked immunosorbent assay (ELISA).

Assessment of pulmonary functions

Spirometry was performed at the Pulmonary Functions Laboratory at Ain Shams University Hospital, using the FlowmateV Plus spirometer (Spirometrics, Gray, ME). Tests were completed while the patient was in the sitting position. The tests followed the criteria and standards of the European Respiratory Society (ERS) and the American Thoracic Society (ATS).¹² Evidence of variation in lung function or documentation of increased forced expiratory volume in 1 second (FEV1) greater than 12% during the bronchodilator reversibility test is diagnostic for asthma.⁹

Skin-prick test

Antihistamines were discontinued for 2 weeks prior to testing. Ruling out acute illness was mandatory before performing the test.¹³

The skin was punctured using a calibrated lancet (1 mm) held vertically while introducing a drop of diluted purified allergen. Allergen extracts included *Alternaria alternata*, *Aspergillus niger*, *Candida albicans*, birch pollen, cat and dog epithelia, *Dermatophagoides pteronyssinus*, *Dermatophagoides farina*, cockroach, and latex. A drop of histamine (10 mg/mL) and saline solution were used as a positive and negative control, respectively. The maximum or mean diameter of the wheal to various allergens was read at 15 minutes. A wheal of 3 mm or more in diameter was considered positive, indicating sensitization to the allergen.¹⁴

Laboratory investigations

Five milliliters (5 mL) of venous blood was drawn by venipuncture from patients and controls, and collected into a gel Vacutainer tube (Becton Dickinson, Oxford, UK). It was left to clot and then centrifuged at 1500g for 15 minutes at 4°C. The serum yielded was used for estimation of total IgE levels by ELISA, detection of specific IgE by enzyme allergosorbent test (EAST), and detection of DAO by ELISA, as detailed in the next 3 paragraphs.

TABLE 2. Laboratory results of the study population

Variable	Groups		Test value	p
	Cases	Control		
Diamine oxidase (ng/mL)			2.61	0.009*
Range	11.7–323.9	8–295		
Median (IQR)	42.1 (30.5)	14.7 (91.1)		
Total IgE (IU/mL)			6.82	<0.001**
Range	0.6–1866	5–56		
Median (IQR)	308.00 (715.6)	19.00 (18.7)		
CBC, n (%)			2.05	0.152
Normal	38 (95.0)	40 (100.0)		
Eosinophilia	2 (5.0)	0 (0.0)		
PFT, n (%)			5.33	0.149
Normal	35 (87.5)	40 (100.0)		
Mild obstructive pattern	3 (7.5)	0 (0.0)		
Moderate obstructive pattern	1 (2.5)	0 (0.0)		
Mixed obstructive restrictive	1 (2.5)	0 (0.0)		
Skin-prick test, n (%)			61.28	<0.001**
Negative	2 (5.0)	37 (92.5)		
Positive	38 (95.0)	3 (7.5)		
Specific IgE, n (%)			72.38	<0.001**
Negative	2 (5.0)	40 (100.0)		
Positive	38 (95.0)	0 (0.0)		

*Significant ($p < 0.05$).**Highly significant ($p < 0.001$).

CBC = complete blood count; IgE = immunoglobulin E; IQR = interquartile range; PFT = pulmonary function test.

Estimation of total IgE levels (IU/mL) was done using an ELISA kit supplied by R-Biopharm and performed according to the manufacturer's instructions (RIDASCREEN; R-Biopharm, Darmstadt, Germany; Catalog number: A0141). This procedure has a sensitivity of 1 IU/mL. The normal level of total IgE in adults is less than 100 IU/mL.

Detection of specific IgE (IU/mL) was by EAST supplied by R-Biopharm (Catalog number: A0040), specific for *Alternaria alternata*, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Aspergillus niger*, birch pollen, cat and dog epithelia, cockroaches, latex, and *Candida albicans*. Specific IgE levels ≥ 0.35 IU/mL were considered positive.

DAO concentration (ng/mL) was evaluated using a DAO sandwich ELISA kit according to the manufacturer's instructions (SunRed Biological Technology, Shanghai, China; Catalog number: 201-12-0777). Sera or recombinant human DAO were added to plates coated with a polyclonal antibody against DAO and incubated at 37°C for 1 hour for the standards. Optical density was determined at 450 nm using a Stat Fax 2100 microplate reader

(Awareness Technology, Inc., Palm City, FL). The lower end of sensitivity of the assay was 1 ng/mL and the upper limit was 600 ng/mL. Samples with readings over the upper limit were diluted until their absorbance readings fell within the linear range of the assay. Repeated freeze-thaw cycles of standards, detection reagents, samples, and assay diluents were avoided.

Statistical analysis

Analysis of data was performed using the SPSS program, version 20 (IBM Corp., Armonk, NY). Data was expressed as mean $\pm$ standard deviation (SD) for parametric data and as median and interquartile range (IQR) for nonparametric data, respectively. Categorized data was expressed as number and percentage. For the parametric data, Student *t* test was used to compare the means of 2 groups. Nonparametric data was analyzed using the Mann-Whitney *U* and Kruskal-Wallis tests to compare 2 and 3 groups, respectively. Chi-square test was used to compare categorical data. To assess the strength of the relationship between

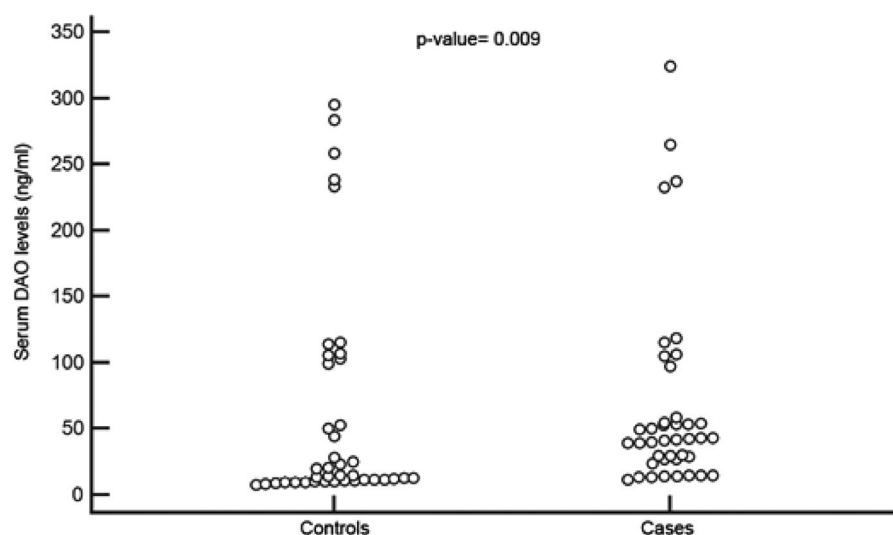


FIGURE 1. DAO level in cases and control group. DAO = diamine oxidase.

serum DAO levels and the other variables, Spearman's correlation coefficient test was performed. The receiver operating characteristic (ROC) curve analysis was used to evaluate cutoff points of laboratory data to differentiate between asthmatic and allergic rhinitis patients and controls. Values for which the sum of sensitivity and specificity reached the maximum were used as cutoffs. All *p* values are 2-sided. A *p* value of <0.05 was considered statistically significant.

Results

Forty patients with respiratory allergy (atopic asthma and allergic rhinitis) along with age- and sex-matched controls were enrolled in this study. Demographic and clinical characteristics of both groups are shown in Table 1. Age ranged between 18 and 56 years. The duration of disease in study patients ranged from 1 to 30 years. The study included

more females overall in both groups with a percentage of 67.5% in patients and 60% in the control group. No statistically significant differences were found between both groups with respect to age and sex.

Laboratory results are shown in Table 2. Serum absolute eosinophilia appeared in 5% of patients with no statistically significant difference between the cases and controls. Eosinophilia refers to an absolute eosinophil count in the peripheral blood of $\geq 0.5 \times 10^9/L$, which is considered abnormal in most laboratories.¹⁵ Total IgE was significantly higher in patients with a median total IgE of 308.00 IU/mL vs a median IgE of 19 IU/mL in the control group (*p* < 0.001). Specific IgE was significantly higher in patients as compared to the control group (*p* < 0.001). According to the PFT results, 35 patients were of normal pattern, 3 were of mild obstructive pattern, and 2 were of moderate obstructive pattern with no statistically significant difference between them. The skin-prick test was positive in 95% of

TABLE 3. DAO levels in different classes of respiratory allergy classified according to severity

Diagnosis	Classification	DAO (ng/mL)		Test value	<i>p</i>
		<i>n</i>	Median		
Atopic bronchial asthma	Intermittent	3	13.9	11.22	0.004*
	Persistent mild	7	28.8		
	Persistent moderate	7	54.4		
Allergic rhinitis	Intermittent	2	12.6	17.22	<0.001**
	Persistent mild	8	28.3		
	Persistent moderate	9	52.9		
	Persistent severe	4	250.7		

*Significant (*p* < 0.05).

**Highly significant (*p* < 0.001).

DAO = diamine oxidase.

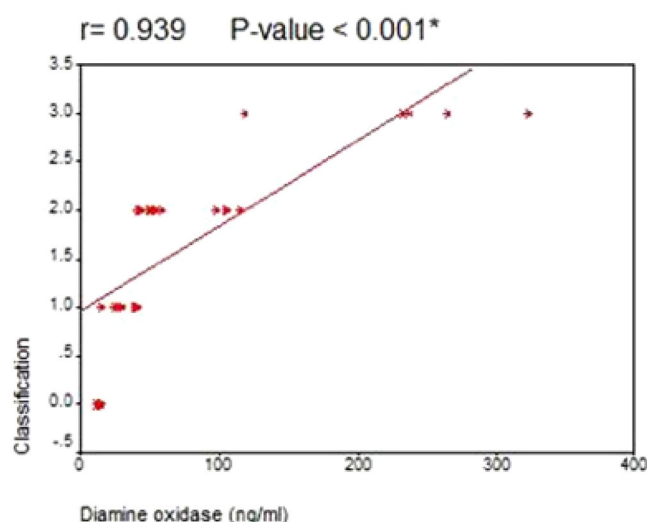


FIGURE 2. Correlation between serum DAO level and severity of disease. DAO = diamine oxidase.

cases and 7.5% of controls with a highly significant difference ($p < 0.001$).

DAO level was significantly higher in patients than controls with a median of 42.10 in patients vs 14.70 in controls ($p < 0.05$; Fig. 1).

No significant association was found between DAO levels and age, type of respiratory allergy, duration of disease, PFT, eosinophilia, or total IgE. Furthermore, no significant difference was found between DAO levels and number or type of allergens positive in either the specific IgE or the skin-prick test.

Table 3 illustrates the level of DAO in different classes of respiratory allergy stratified according to severity. Among the 23 patients who were diagnosed with allergic rhinitis, 2 patients were classified as intermittent moderate, 8 as persistent mild, 9 as persistent moderate, and 4 as persistent severe. DAO showed a high statistically significant difference between the classes of allergic rhinitis ($p < 0.001$). Among the 17 patients diagnosed with atopic asthma, 3 patients had intermittent symptoms, 7 had persistent moderate symptoms, and 7 had persistent mild symptoms. DAO showed a statistical difference between the classes of severity of bronchial asthma ($p < 0.05$).

There was no correlation between DAO and age, total IgE, or duration of the disease. There was, however, a positive correlation between severity of disease and DAO (Fig. 2).

As seen in the ROC curve results, the DAO cutoff level was 13.3 ng/mL, which was higher than normal. The DAO

test has a sensitivity of 97.50% and specificity of 45%. The positive predictive value (PPV), negative predictive value (NPV), and accuracy of this test are 63.9%, 94.7%, and 67%, respectively (Table 4, Fig. 3).

Discussion

Worldwide, respiratory allergies have inflated significantly resulting in serious negative impact on social and personal lives. Yet these diseases have not gained proper attention and are unfortunately underestimated and neglected. Moreover, the real dilemma is that the general population has yet to receive proper awareness and education of these diseases.^{16,17}

Bronchial asthma and allergic rhinitis have frequently been termed the “1 airway disease.” This is because they may coexist in the same patient and either condition may lead to the other. Therefore, more respect is owed to the complexity of risk factors and diagnosis of this disorder.^{18,19}

Diagnosis of respiratory allergy depends mainly on well-known classical methods such as the skin-prick test, intradermal skin test, and measurement of serum total and specific IgE. In addition, complete blood count (CBC), PFT, provocation tests, and imaging modalities aid in diagnosis.

This study aimed to evaluate the DAO enzyme as a diagnostic marker of respiratory allergy. We hypothesized that its level in serum can be used as a new marker in respiratory allergy diagnosis. Although some studies measured DAO intracellularly,^{7,8} this study measured the serum level of DAO.

DAO is a secretory protein that is responsible for histamine breakdown (mainly extracellularly) and functions to end an allergic event. DAO is present in minimal amounts in the circulation and is abundant in organs such as the kidneys, placenta, and ascending colon. DAO is especially high in the small intestine because its baseline levels increase markedly with a mature intestinal mucosa. Furthermore, multiple factors affect DAO levels including certain drugs and foods.⁵

Few studies investigated serum DAO in respiratory allergy. The first study was performed in 1996 by Toyoshima et al.²⁰ and illustrated the DAO activity in asthmatic children. Alternatively, many studies were done to evaluate DAO in patients with histamine intolerance (HI).^{21–23}

Aside from allergic airway diseases, a study evaluated the postmortem values of DAO and histamine in fatal anaphylaxis. Although high levels of histamine were

TABLE 4. ROC curve for diamine oxidase (ng/mL) between cases and controls

Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	Youden's index
>13.3 ng/mL	97.5	45.0	63.9	94.7	0.67	0.42

AUC = area under ROC curve; NPV = negative predictive value; PPV = positive predictive value; ROC = receiver operating characteristic.

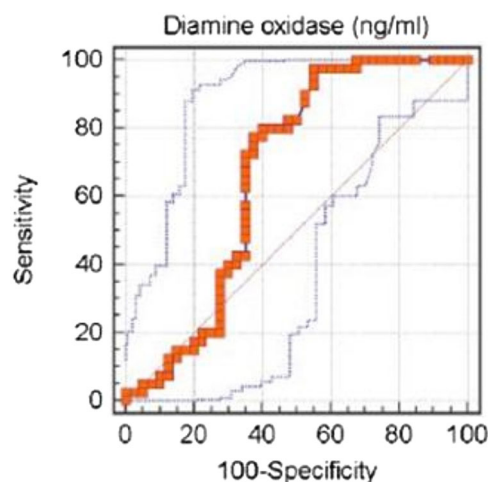


FIGURE 3. Sensitivity and specificity of serum diamine oxidase.

detected and aided in diagnosing anaphylaxis, DAO did not show considerable change in its level and therefore did not prove to be helpful.²⁴ Another recent study demonstrated that DAO was increasingly released in anaphylaxis in an amount enough to degrade histamine, but DAO activity was dampened.²⁵ DAO was also evaluated in a study on chronic urticaria patients; the study found that levels of DAO changed according to fish-eating habits and levels of specific IgE. After fish intake, low levels of DAO were detected during the urticaria exacerbation. The researchers tied this low level to the relative enteric deficiency of DAO.²⁶

In this present study, DAO level was higher in patients with atopic asthma and allergic rhinitis (median 42.10) than controls (median 14.70), with a cutoff level of 13.3 ng/mL. This observation may be explained as a result of high histamine activity.

The sensitivity and specificity of the test was 97.5% and 45%, respectively. The PPV was 63.9% while the NPV was 94.7%. Accuracy of the test, calculated as the ratio of the true positive to the true negative, was 67%.

Total IgE is a poor test because numerous factors affect its level, and therefore, can seldom be used in diagnosis of allergic disease. Although normal values of total IgE cannot exclude the presence of allergic disease, high values of total IgE also cannot prove incidence of allergy.²⁷ High levels of circulating IgE can be found in various diseases, including infections, primary immunodeficiency, inflammatory diseases, hyper-IgE syndrome, and malignancies.²⁸ Although IgE measurement is helpful in screening for respiratory allergies, other diagnostic tools are mandatory for complete evaluation.²⁷ On the other hand, the present study found that the DAO test had a high sensitivity and negative predictive values, and therefore, may be a promising test to rule out the presence of allergic disease.

As for the skin test, its accuracy exceeds 85% in terms of sensitivity and specificity regardless of extracts used, whether standardized or commercial.²⁹ Skin-prick testing

is the preferred method as it is a simple, quick, and sensitive test. In addition, false negatives rarely occur, and a negative skin-prick test may doubt the presence of IgE-mediated allergy.³⁰ Unfortunately, there are some drawbacks to skin-prick testing. Age is 1 of the factors that affect reactions. Infants and older adults seem to have less reactivity. In addition, various skin conditions, including pigmentation and certain skin lesions, interfere with the results of skin-prick tests. Furthermore, patients using long-term corticosteroids and those with chronic diseases, such as renal failure and diabetes, alter skin sensitivity.³¹ The skills and experience of personnel in performing the test along with the quality control also affect the reliability, accuracy, and interpretation of the skin-prick test.³²

Similarly, many factors were found to affect the specific IgE level. These factors include age, type of inhaled allergen, total IgE, and the season of the year. This may explain why many studies revealed a wide sensitivity range of 60% to 95% and specificity of 30% to 95%.³³ Interestingly, Asha'ari et al.³⁴ compared the serum specific IgE test with skin-prick test and concluded that the specific IgE had a higher sensitivity but lower specificity for the allergens tested. Additionally, specific IgE may provide false positive results due to the presence of nonspecific antibody binding activity, which is inconsistent with clinical findings.²⁸

In this study, DAO was compared with several variables including age, gender, duration of the disease, type of respiratory allergy, and allergens in skin-prick test and specific IgE. There was no correlation between any of these variables and the serum level of DAO. Serum DAO positively correlated with severity of respiratory allergies. DAO was statistically significant in atopic asthma and was highly significant in patients with allergic rhinitis.

Toyoshima et al.²⁰ studied the relationship between DAO and severity of asthma. They found that DAO activity in the non-attack phase of mildly asthmatic children was within the normal range and was higher in the non-attack phase of moderately or severely asthmatic children. Additionally, the study postulated that DAO activity was higher than normal during acute asthmatic attacks and much higher in severe attacks compared to mild ones.²⁰ Two explanations were proposed detailing the reason behind the increase of DAO during asthmatic attacks. One explanation is that the DAO activity in activated eosinophils, and possibly neutrophils, increases significantly in acute asthma attacks. The second explanation is that the heparin released from bronchial mucosal mast cells stimulates DAO release from the small intestine.³⁵

Meza-Velázquez et al.³⁶ studied the relationship between DAO and severity of allergic rhinitis. They focused on the possible association between 2 functional single-nucleotide polymorphisms (SNPs) in DAO with the severity of allergic rhinitis and the number of allergic diseases. Patients possessing the mutant allele developed more allergic diseases and were at higher risk for severe rhinitis despite low IgE levels.³⁶ Also Khalifa et al.³⁷ evaluated the relationship between polymorphisms of the same gene and development of

allergic asthma. They found that this polymorphism may be involved in the pathophysiology of asthma but not severity. García-Martín et al.³⁸ also revealed that patients carrying mutated DAO genes tended to have more manifestations of asthma though they showed lower IgE levels.

Alternatively, no correlation was present between skin-prick test, specific IgE, and severity of disease. This shows that neither of these allergy tests are as suited to evaluate severity of disease.³⁹

DAO appears to be a promising, simple, in vitro method that can be used to rule out allergy when skin-prick test cannot be performed or results of specific IgE tests are doubtful. Furthermore, determining severity of cases may aid in proper treatment. Further cohort studies are recommended to assess DAO before and after therapy. Comparison of atopic and non-atopic asthma groups would be beneficial.

Studying intracellular DAO expression on exposure to allergen would help identify its exact mechanism.

Conclusion

In conclusion, this study showed the importance of DAO testing in allergy patients. DAO levels were higher in atopic asthma and allergic rhinitis patients compared to controls. DAO had a high sensitivity and negative predictive value. There was a positive correlation between severity of diseases and DAO. No association was found between DAO level and age, type of respiratory allergy, duration of disease, PFT, eosinophilia, and total IgE. DAO may prove useful in the assessment of severity and ruling out respiratory allergy. Large-scale studies may be helpful to better understand the relationship between DAO and allergy. ☞

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