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Predictive Value of the Serum Diamine Oxidase Level in the Diagnosis of Seasonal Allergic Rhinitis

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ABSTRACT

Background: Allergic rhinitis (AR) is characterized by the increased sensitivity of the nasal mucosa to allergens and has a significant impact on life quality. There is promising evidence that biomarkers can help in the diagnosis, treatment, and follow-up of patients with AR. Diamine oxidase (DAO) is one of the enzymes responsible for the breakdown of histamine, the primary mediator of allergies.

Objective: To investigate the significance of DAO as a useful biomarker for diagnosis and the severity of AR.

Methods: In this case-control study, 24 patients and 24 healthy controls were recruited and their serum DAO levels, total IgE levels (using ELISA), blood eosinophil count, and percentage (using complete blood cell count) were measured. The sino-nasal outcomes test-22 (SNOT-22) questionnaire was used to assess the severity of symptoms in patients. The Receiver Operating Characteristic (ROC) analysis was used to assess the predictive power of DAO level for the diagnosis of AR. The relationship between DAO and disease severity, as well as other AR-related clinical factors, were also investigated.

Results: DAO levels were lower in AR patients compared with the controls. The DAO level did not significantly correlate with the severity of AR according to the Allergic Rhinitis and its Impact on Asthma (ARIA) score, though it was lower in patients with persistent or moderate to severe symptoms. The total IgE, eosinophil percentage, and SNOT-22 score all had an inverse relationship with DAO. Moreover, DAO was significantly associated with the diagnosis of AR, with an Area under the ROC Curve (AUC) of 0.771, a sensitivity of 75%, and a specificity of 62.5%.

Conclusion: DAO might be a valuable biomarker in the diagnosis of allergic rhinitis.

Keywords: Allergic Rhinitis, Diamine Oxidase, Eosinophil, Total IgE

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INTRODUCTION

Allergic rhinitis (AR) is one of the most common types of rhinitis, characterized by allergic inflammation of the mucous membranes of the upper respiratory tract, particularly the nasal mucosa, in response to irritants and environmental allergens. Rhinitis is classified into two broad categories: allergic and non-allergic, which can be distinguished mostly by their clinical and paraclinical manifestations. Allergic rhinitis is classified as seasonal or permanent. Seasonal rhinitis is most prevalent in the spring, summer, and early autumn, and is caused by an allergic reaction to pollen from flowers, grass, trees, and weeds, as opposed to the more common permanent rhinitis. It is less severe than seasonal allergies and is caused by allergens in people's living environment, such as dust and fungi [1, 2].

Worldwide, allergic rhinitis is the most frequent allergic illness. This allergy condition ranks sixth in terms of prevalence in the United States, affecting approximately 20% of the population. Males and females are equally affected by this condition [3]. According to several studies, the prevalence of this condition in Iran is between 10% and 15% [4]. It is critical to note that the prevalence of rhinitis, like other allergies, is increasing dramatically worldwide. In the United States, the disease is predicted to cost $ 5 billion annually in terms of direct costs and $ 4 billion in terms of indirect costs (including absenteeism from work and school), and if left untreated, the disease can be accompanied by asthma, sinusitis, and middle ear infection and inflammation [5-7].

Allergic rhinitis is a type I hypersensitivity reaction caused by an increased sensitivity of the nasal mucosa to allergens by IgE receptors. Mast cells and basophils significantly contribute to allergic inflammation by secreting inflammatory mediators such as leukotriene, histamine, and cytokines in response to allergens. Histamine, the primary biomarker generated by mast cells and basophils, plays a significant role in the development of allergic disorders [8]. As a result of the development of an antibody-antigen complex on the surface of mast cells and basophils, histamine-containing granules are released into the bloodstream, increasing capillary permeability and causing allergy symptoms such as red eyes, itching, nasal congestion, and runny nose [9].

There are two main enzymes, known as N-Methyl Transferase (primarily inside the cells, breaking endogenous histamine) and diamine oxidase (DAO) (mainly outside the cells, breaking exogenous histamine from foods or other sources), which catabolize histamine and reduce its concentration after the release [10, 11]. When these enzymes are impaired, an accumulation of unprocessed histamines causes and exacerbates allergic symptoms. A deficiency of diamine oxidase or failure in histamine reduction is one of the primary causes of histamine intolerance, and histamine imbalance, which could result in unpleasant symptoms identical to allergic disorders [11-13].

There is an encouraging evidence for the use of DAO biomarkers to aid in the diagnosis, treatment, and follow-up of AR patients [14, 15]. The assessment of DAO is accurate, affordable, quick, and without the need for a highly-trained health-care provider [16]. Therefore, in this study, we examined the utility of DAO as a new biomarker for the diagnosis, treatment, and follow-up of patients with seasonal allergic rhinitis by comparing the serum DAO levels among patients with seasonal allergic rhinitis and the healthy individuals.

MATERIALS AND METHODS

This case-control study aimed to determine the serum level of diamine oxidase as a diagnostic marker in patients with seasonal allergic rhinitis. Adult patients with seasonal allergic rhinitis, referred to a tertiary university hospital from December 2020 to February 2021, were

recruited using a consecutive sampling. Diagnosis for all the patients was made by an otolaryngologist using clinical findings, patient history, and paraclinical findings and imaging. The 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 [17, 18]. Also, the age-sex-matched healthy controls without allergic rhinitis or any other allergic diseases were recruited and referred to the ENT clinic for other reasons. Pregnant women, lactating mothers, patients with immunosuppression, patients with a history of vasomotor rhinitis or bacterial sinusitis, patients with a history of nasal or sinus tumors or trauma, or any other surgical intervention were excluded. Moreover, patients were strictly screened for allergic conditions; patients with a two-week history of taking food containing histamine (such as chocolates, tomatoes, nuts, fermented foods, beverages, processed meat, and seafood) or patients who used antihistamine or glucocorticoids drugs or any other drugs affecting the DAO level (such as aminophylline, clavulanic acid, metoclopramide, verapamil, or heparin) [11, 19] in last two weeks were excluded from the study.

After entering the study, the patients and the healthy controls were fully informed of the study process and aims, and then written informed consent was obtained from them. The Ethical Committee of Isfahan University of Medical Sciences approved the study (IR.MUI.MED.REC.1399.514). According to a pre-designed checklist, demographic information of the patients, including age, sex, duration of illness, and family history of allergies were collected. The patients were also divided into Intermittent / Persistent and Mild / Moderate-Severe (based on symptoms, sleep disorders, and impact on daily life/ activity) according to ARIA classification [20]. Duration/frequency of symptoms was described as intermittent (<4 days/week or <4 weeks) or persistent (≥4 days/week or ≥4 weeks). The Persian version of the SNOT22 questionnaire was also completed for the patients [21]. A symptom-based rhinosinusitis outcome measurement includes 22 items, and each item is given a score from 0 to 5 and the final score is the sum of the scores given to all items. The lower scores for this questionnaire indicate a higher life quality for patients [22]. Next, five milliliters of blood samples were drawn by venipuncture from patients to determine the serum level of DAO, the number of eosinophil cells, and the total IgE level. All the participants had to be on empty stomachs for at least 8 hrs. before the blood collection. After counting the blood cells, serum was isolated from the blood samples and the total IgE and human DAO levels were measured by enzyme-linked immunosorbent assay (ELISA). The concentration of DAO (ng/mL) was determined according to the manufacturer's instructions using a DAO sandwich ELISA kit (Bioassay technology laboratory, Shanghai, China; Catalog number: E0776Hu). The normal range for this kit was higher than 50 ng/ml in serum samples. For the standards, the serum samples were added to plates coated with a polyclonal antibody against DAO and incubated for 1 hr. at 37 °C. After washing, the optical density was measured at 450 nm. The assay had a detection range of 1 to 400 ng/mL and a sensitivity of 0.53 ng/mL. The samples with absorbance readings greater than the upper limit were diluted until they fell within the assay's linear range.

Statistical Analysis

The mean and standard deviation were used to describe quantitative variables. Count and relative frequency were used to describe categorical variables. The Shapiro-Wilk test was used to measure the normality of the data. As the data do not follow the normal distribution, the median and range were used to describe the quantitative data. The Mann-Whitney U test was used to compare the mean between the two groups. A univariate linear regression test was used to measure the data correlation. The Chi-square test was used to

analyze Binary data. Logistic regression was used to evaluate the association of variables with the AR diagnosis. The receiver operating characteristic (ROC) curve analysis was used to evaluate the cutoff points of laboratory data to differentiate between AR and the healthy controls. Values for which the multiplication of sensitivity and specificity reached the maximum were used as cutoffs. IBM SPSS software version 24 was used to analyze data. In all the experiments, P<0.05 was considered significant.

RESULTS

In this case-control study, we recruited 48 patients, including 24 patients with allergic rhinitis and 24 healthy controls. The demographic and clinical information of participants are presented in Table 1. The mean age of participants was 31.48 and 31.5 across the patients and the healthy controls, respectively. Most of the patients were female (54.17%) and reported having a family history of allergy (60.87%). There was no statistical difference regarding age and gender between the two groups. The mean duration of having AR symptoms among patients was 4.65 (6.04) years. Among the patients, according to the ARIA severity scoring, four of them described their disease as mild intermittent, twelve as moderate to severe to intermittent and eight of them described the severity of their disease as moderate to severe to persistent. The level of DAO is significantly lower in AR patients than in the controls (P=0.001). The total IgE level, the relative frequency of eosinophils, and SNOT score were all higher in patients compared with the healthy individuals. The Median SNOT score in the population was 22, while this value was 6.5 for the healthy controls and 50 for the patients with allergic rhinitis. (Table 1)

Next, we assessed the association of DAO with different clinical variables. As shown in Table 2, the length of the disease in patients, the total IgE level, percentage of eosinophils in the blood, and SNOT score (life quality) were inversely associated with the DAO levels. In other words, we had lower amounts of DAO in patients with longer periods of symptoms, higher levels of the total IgE, eosinophils, and higher SNOT-22 scores. Also, we assessed the association of DAO levels with the severity of AR according to ARIA scoring.

Table 1. Comparison of demographic and clinical characteristics of patients with allergic rhinitis and the healthy controls

Variable	Healthy group	AR group	Total	P
Age (Year)	31.48 (9.87)	31.5 (12.2)	31.49 (10.94)	0.617[b]
Gender (Male)	7 (29.17)	11 (45.83)	18 (37.5)	0.233[a]
Family Hx of allergy (Yes)	1 (4.55)	14 (60.87)	15 (33.3)	<0.001[a, ***]
DAO (ng/ml)	58.25 (52.81)	26.51 (11.29)	42.38 (41.04)	0.001[b, ***]
Total IgE (IU/mL)	69.78 (55.19)	235.19 (214.23)	152.49 (175.89)	0.027[b, *]
Eosinophil (%)	2.21 (1.73)	4.73 (3.39)	3.47 (2.95)	0.032[b, *]
SNOT score	11.6 (15.91)	43.3 (21.58)	28.56 (24.79)	<0.001[b, ***]

DAO: Diamine oxidase; SNOT: Sino-nasal outcome test; AR: Allergic rhinitis; [a]The Pearson chi-square; [bThe] Mann-Whitney U test; *P≤0.05; **P≤0.01; ***P≤0.001

Table 2. The association of DAO with clinical characteristics of allergic rhinitis

Variable	B (95%CI)	P
Disease length	-1.596 (-3.149 to -0.044)	0.044*
Total IgE	-0.074 (-0.140 to -0.008)	0.028*
Eosinophil (%)	-4.317 (-8.242 to -0.392)	0.032*
SNOT	-0.312 (-0.719 – 0.095)	0.129

DAO: Dependent; SNOT: Sino-nasal outcome test; *Significant at P<0.05

Table 3. Association of different factors with AR diagnosis and their predictive power

Variable	B	Standardized B	P	AUC	P	Best cut-off	OR
Family Hx of allergy (Ref=No)	3.486	32.667	0.002**	0.782	0.001***	-	
DAO level	-0.069	0.934	0.01**	0.771	0.001***	32.5	3.545
Total IgE	0.008	1.008	0.01**	0.686	0.027*	112	15.4
Eosinophil (%)	0.340	1.405	0.006**	0.680	0.033*	4.5	11
SNOT	0.080	1.084	0.001***	0.873	<0.001***	24	42.75

DAO: Diamine oxidase; SNOT: Sino-nasal outcome test; AUC: Area under the ROC curve; OR: Odds ratio; *P≤0.05; **P≤0.01; ***P≤0.001

The DAO level was lower in moderate to severe forms of AR compared with the mild form (the mean (SD): 25.71 (11.86) ng/ml vs 30.77 (2.97) ng/ml); however, the difference was not significant (the Mann-Whitney P=0.262). Similarly, the level of DAO was lower in patients with persistent symptoms compared with the patients with intermittent symptoms (the mean (SD): 23.07 (12.14) ng/ml vs 28.11 (10.63) ng/ml), however, this difference was not significant either (the Mann-Whitney P=0.255). (Table 2)

Finally, we assessed the predictive power of each factor in the prediction of AR. AS shown in Table 3, the family history of allergy, DAO level, the total serum IgE, the relative frequency of blood eosinophils, and SNOT score statistically associated with the incidence of AR. Among them, DAO negatively associated with having AR, while the others had a direct association with the outcome. The best cutoff value of DAO for diagnosing AR was 32.5 ng/ml, which yields a sensitivity of 75% and specificity of 62.5%. The patients with lower than 32.5 ng/ml of DAO were 3.545-fold more likely to have AR (Table 3).

DISCUSSION

The association between the level of DAO and diagnosis and severity of AR was sought in this study. Although the DAO level measured by ELISA, was lower in patients with persistent symptoms (compared with ones with intermittent symptoms) and in patients with moderate to severe symptoms (compared with mild symptoms), these associations were not significant. We also evaluated the correlation between the DAO level with other AR-related clinical factors i.e., the total IgE, eosinophilia, and SNOT-22 score which reflects the severity of AR-related symptoms. There was an inverse correlation between these factors with DAO. Likewise, the significant ability of positive family history of allergy, the total IgE levels, and relative frequency of blood eosinophil in the prediction of AR, the DAO also significantly associated with the diagnosis of AR with a considerable AUC of 0.771. Patients with lower than 32.5 ng/ml of DAO had a 3.545-fold more chance to be diagnosed with AR.

It is noteworthy to mention that, there were two cutoff points with relatively good performance. One of them (32.5 ng/ml) had higher sensitivity (75%) and lower specificity (62.5%) and the other one (42) had lower sensitivity (45.8%) and higher specificity (95.8%). Based on the common pathophysiology of allergic disease and the common role of DAO in metabolizing histamines, we think that the cutoff with higher sensitivity would be more helpful in diagnosing AR, complementary to clinical diagnosis based on the symptoms. However, drawing a strong conclusion and accurate cutoff need larger sample sizes.

AR is one of the world's most common diseases. AR prevalence has been estimated to range between 2% and 25% in children and 1% to more than 40% in adults [23]. One study found that nearly 45 percent of patients lacked a diagnosis and that respiratory allergies were underdiagnosed [24]. Histamine always has

been a prominent component of allergic reactions and the underlying mechanisms are becoming better understood. Histamine is the major biomarker of mast cell degranulation and plays an important role in allergic diseases [25]. Histamine is produced by the enzyme L-histidine decarboxylase. Histamine degradation, on the other hand, is thought to be regulated by two enzymes: histamine N-methyltransferase, which inactivates histamine, and diamine oxidase, which scavenges extracellular histamine following mediator release [26].

Histamine intolerance (HIT) is thought to result from a mismatch between histamine intake and catabolism [27]. Histamine overload can occur as a result of histamine-rich meals, excessive alcohol consumption, and/or inducers of endogenous histamine release. Also, insufficient levels or any inherited or acquired impairment in DAO's catabolic function, as the principal extracellular enzyme involved in histamine catabolism in the digestive system, may play a role in the pathophysiology of HIT [10, 27]. This association between the enzyme and extracellular histamine levels may contribute to the pathogenesis of allergy diseases and therefore chronic AR. Numerous investigations have examined DAO intracellularly or in serum [14, 28], and a few have examined the relationship between AR and DAO deficit [14, 29, 30]. Some have hypothesized that DAO levels in this sample of patients could be used as an allergy biomarker [14].

In this study we found that DAO level was lower in more severe types of disease or its persistent type, however, these differences were not significant. Likewise, another study, assessing the DAO activity in allergic patients demonstrated lower enzyme activity in patients with moderate to severe AR [15]. It seems logical that lower levels of DAO or any other conditions contributing to the dysfunction of this enzyme lead to the accumulation of histamine and therefore the development of AR symptoms [29, 30]. In this way, the level of DAO could be a useful biomarker for AR, which the results of our study confirm. There was another study that evaluated the predictive power of DAO in diagnosing atopic bronchial asthma and allergic rhinitis [14]. There was a considerable difference between this study and other existing papers. Although they found significant predictability for DAO, their suggested cutoff was 13.32 with AUC=0.67. Moreover, the authors of this study reported lower levels of DAO in the healthy controls than in the patients with respiratory allergies. A few biases in the selection of patients that was also noted in that paper would be responsible for this difference and necessitate caution in the interpretation of the data.

Although the case-control study could not make out the causative relationship, we tried to assess several different clinical features of allergy that had shown a valid relationship with AR. The limited specificity and complexity of symptoms likely contribute to the difficulty in determining and identifying histamine intolerance symptoms [10, 31]. Therefore, various questionaries were developed to assess the cumulative symptoms of the patients more reliably. SNOT-22 and ARIA scale were some examples of them [20, 22]. These scorings were shown to be highly representative of the severity of symptoms and their associated life quality. As expected, similar to other studies, we found a significant relationship between the SNOT score and AR in this study [21, 32]. Also, we found a significant inverse relationship between the DAO level and the score of SNOT-22. However, the existing data is not consistent. A study reported that DAO activity level was lower in patients with AR, however, they did not find a significant correlation between DAO activity with the score of the ESPRINT-15 questionnaire [15]. Another study found a linear relationship between AR severity with blood DAO levels [14]. It seems different scales for symptoms assessment and also different measurements of DAO (concentration vs activity) could result in this difference, as also debated by

several other papers [13, 14, 33-35].

The total IgE levels and eosinophil counts previously were shown to be highly correlated with the diagnosis of allergic disorders. Similar to other studies, in this study, we found a great association between the total IgE levels and the percentage of eosinophils in blood with the diagnosis of AR. The normal level of the total IgE in adults was determined to be between <100 or <140 IU/mL in different studies [14, 36, 37], likewise in this study, considering the best-found cutoff, patients with the total IgE of higher than 112 IU/mL had about 15 times higher chance to have AR. Similarly, higher blood eosinophil levels directly correlated with the diagnosis of AR, which is corroborated by other studies [37, 38].

We investigated the association of DAO levels with the total IgE and eosinophil counts and found an inverse significant correlation between DAO levels with the level of the total IgE and the percentage of eosinophils in peripheral blood. However, in a study by Refaat et al., assessing only 23 patients with AR with no control group, there was no significant correlation between DAO level with the total IgE level and eosinophilia. Other studies also demonstrated that although the total IgE level gets higher in patients with allergic disorders, there are allergic patients with normal levels of the IgE and also normal healthy individuals with high levels of the total IgE, therefore, controlled studies with a large sample size would be needed to draws a more reliable conclusion. The situation is the same about the duration of the disease, for which we found a direct association with DAO level [39-41].

A major limitation to this study was its limitation to fully draw causative relationships between DAO and AR, given the retrospective case-control design. Also, the lack of assessment of the specific IgE immunoglobulins which could be more helpful in diagnosing AR was another limitation to this study. The patients were selected from the referred patients to a tertiary hospital which could confound its ability to generalize the results to the entire population. A major strength of the study is considering the control group besides the patients with AR. Although, given the inconsistent reported results, larger studies would be needed to reach a reliable conclusion. Also, supposing the role of DAO in the development of AR, a prospective interventional study could assess the role of DAO supplements in the reduction of AR symptoms. The role of serial assessment of DAO levels, as a biomarker for monitoring the course of the disease, especially after diet avoidance (low-histamine diet) or using anti-allergic drugs could be investigated in future studies.

CONCLUSION

In conclusion, this study showed that DAO might prove to be a useful biomarker in the diagnosis of allergic rhinitis. DAO levels were lower in AR patients compared with the controls and DAO had a considerable predictive value for diagnosing AR. There was a negative correlation between DAO level and duration of disease, the total IgE, and blood eosinophils. Future studies may be helpful to better understand the relationship between DAO and allergic rhinitis.

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