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Review

Advances in the Clinical Application of Histamine and Diamine Oxidase (DAO) Activity: A Review

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Abstract: The serum level of diamine oxidase (DAO) reflects the integrity and maturation of the small intestinal mucosa. This measure is important in diagnosing various diseases, including chronic urticaria tachyphylaxis, multiple organ dysfunction syndrome, preterm abortion, and migraine. This review aimed to summarize the findings of previous studies on the changes in DAO levels in diverse diseases and the application of this enzyme in the clinical setting, as well as the roles of this enzyme under physiological and pathological conditions. The advances in the mechanism and clinical application of DAO presented in this review will contribute to a better understanding of this enzyme and open up new and broader perspectives for future basic research and clinical applications.

Keywords: histamine; diamine oxidase; molecular mechanisms; clinical application

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1. Introduction

Diamine oxidase (DAO) is a secretory protein located in the cytoplasm of human and mammalian upper intestinal mucosa chromaffin cells and is responsible for catabolizing histamine (mainly extracellular) to stop allergic reactions [1]. DAO level is extremely low in peripheral blood; this enzyme is mainly distributed in the intestine and abundant in the kidney, placenta, and other organs [2]. With the maturation of the intestinal mucosa, baseline levels of DAO increase significantly, particularly in the small intestine. Various factors, including drugs and food, influence DAO levels [3].

DAO level in peripheral blood is comparatively stable, whereas the level in the intestinal mucosa decreases during ischemia, hypoxia, or nutritional dysfunction of the intestinal luminal tissues, consequently decreasing DAO level in the blood. DAO level reflects intestinal damage and repair. Specifically, plasma DAO levels can be used to monitor the function of the small intestinal mucosal barrier under noninvasive conditions. Thus, this measure has gained increasing clinical attention in recent years in the diagnosis of gastrointestinal diseases, histamine intolerance (HIT), migraine, and abnormal pregnancy and the prognosis of tumors.

Histamine is mainly produced by mast cells, platelets, basophils, histaminergic neurons, and enterochromatin cells, where it is stored in vesicles and released in response to stimulation. It is synthesized from the amino acid histidine by pyridoxal phosphate-containing L-histidine decarboxylase (HDC) and functions by binding to four receptors on target cells in various tissues. It causes smooth muscle cell contraction, vasodilation, increased vascular permeability and mucus secretion, tachycardia, arrhythmias, altered blood pressure, stimulated gastric acid secretion, and nociceptive nerve fibers [3].

Histamine is primarily metabolized in two ways: oxidative deamination by DAO and cyclomethylation by histamine-N-methyltransferase (HNMT). Histamine localization

determines whether it is catabolized by DAO or HNMT. DAO is stored in peripheral tissues, such as the kidney, colon, placenta, and thymus; it is responsible for scavenging extracellular histamine after the release of mediators and is secreted into the circulation when stimulated [4]. DAO can also catabolize other polyamines, such as putrescine and spermidine. By contrast, HNMT is a cell membrane protein that can only transform histamine into the intracellular space (containing mast cells and histaminergic neurons).

In recent decades, serum DAO has gained considerable interest from researchers because of its role in diagnosing various diseases. However, past research on DAO has mostly focused on fundamental experiments and there is a lack of publications discussing the latest developments in the application of DAO in clinical practice. This review aims to elucidate the differential expression of DAO in diverse diseases (Table 1) and the application of this enzyme in the clinical setting.

2. The Role of DAO Activity in the Monitoring of Diverse Diseases

2.1. Role of DAO in Detecting Various Gastrointestinal Diseases

Several human and animal experiments have confirmed that plasma DAO level is a key marker for assessing the function of the intestinal mucosal barrier [5]. The crucial role of DAO level in monitoring intestinal mucosal damage has also been validated in various clinical scenarios [6–9]. Injury to the intestinal mucosal barrier increases epithelial cell permeability, which consequently triggers an inflammatory response that is closely associated with inflammatory bowel diseases, especially Crohn's disease [10,11]. Elevated plasma DAO level indicates the repair of intestinal damage, and it can be used as a sensitive and precise marker in monitoring Crohn's disease activity [12,13]. DAO is a useful molecular parameter for the early and accurate diagnosis and identification of small bowel obstruction. Clinically, an increase in serum DAO level (twice the basal level) may be a useful marker to diagnose simple to strangulated intestinal obstruction. An animal study showed that serum DAO level significantly increases in simple intestinal obstruction but progressively decreases in strangulated intestinal obstruction [14]. This result can be attributed to reduced blood flow caused by strangulated intestinal obstruction. Additionally, an increasing number of animal experiments have demonstrated the value of DAO in the early diagnosis of acute mesenteric ischemia and superior mesenteric artery occlusion [15,16]. Another study specified that DAO = 29.81 U/L can be used as an early diagnostic criterion for diagnosing superior mesenteric artery occlusion [17]; however, this criterion is insufficient for clinical diagnosis, and extensive clinical studies in humans are needed.

2.2. DAO and Migraine

Migraine is a common neurological disorder and the third most common disorder, affecting up to 1 billion people worldwide [18,19]. HIT arises from a deficiency of DAO, and headache is one of the most documented of the several multifaceted symptoms associated with HIT. In a single clinical study [20], 198 volunteers were divided into migraine and control groups, and DAO level was measured using ELISA. The mean DAO level was significantly lower in patients with migraine than in the healthy volunteers. Moreover, DAO deficiency was more prevalent in patients with migraine (87%) than in healthy volunteers. Another RCT by Joan et al. [21] verified that 1 month of oral DAO enzyme supplementation reduces pain duration by 1.4 h in patients with episodic migraine; however, this treatment exerts no significant effect on migraine attack frequency or pain intensity.

Regarding the mechanisms underlying the association between DAO and migraine, a recent genetic study of 22 genome-wide association studies found that 38 genes are susceptibility loci for migraine [22]. Another study reported that the frequency of mutations caused by C2029G DAO single-nucleotide polymorphisms (SNPs) is significantly higher in patients with migraine than in healthy controls and that the C314T mutant allele of HNMT and the C2029G polymorphism of DAO interact to increase the risk and impact of migraine [23]. Another study examining alleles and the frequency of their allelic variants

in patients with migraine found that the *DAO* SNP rs10156191 is associated with reduced DAO activity and is related to the risk of migraine onset, particularly in women [24]. These results suggest that the risk of migraine is associated with the SNP rs10156191 and sex.

However, a recent study exploring the relationship between serum DAO and histamine levels and three polymorphisms in the *DAO* gene (rs10156191, rs1049742, and rs1049793) found similar frequencies of *DAO* genes and allelic variants in patients with migraine and controls [25]. Surprisingly, serum DAO levels were significantly higher in the patients with migraine than in the controls. The opposite conclusion may stem from differences in the methods used to measure DAO level, whether age- and sex-matched subgroups were used, and variations in the inclusion criteria.

2.3. DAO in Pregnancy Monitoring

DAO can be generated in large quantities by the placenta and is thought to be a paracrine signal during endometrial shedding and embryonic implantation [26], serving as a metabolic barrier against the excessive passage of active histamine from the placenta into the maternal or fetal circulation [27]. The balance between histamine and its degrading enzyme DAO plays an essential role in pregnancy [28]. Serum DAO activity has significant sex differences, with females showing greater fluctuations in serum DAO levels than males [29]. Hamada et al. [30] found that serum DAO levels vary with the menstrual cycle, with markedly lower plasma DAO levels in the follicular phase than in the luteal phase. DAO is synthesized by placental and trophoblast cells, explaining the high plasma DAO level during pregnancy [31]. The maternal plasma DAO level exponentially increases during the first 20 weeks of pregnancy by up to even 1000 times the pre-gestational level [28], which consequently decreases plasma and urinary histamine levels in the maternal circulation. In abnormal pregnancies, compared to normal pregnancies, the maternal plasma DAO level ceases to rise and the circulating histamine level increases, which significantly increases the risk of threatened abortion, pre-eclampsia, and spontaneous abortion [31–33]. Moreover, this level drops to pre-pregnancy values within 10–15 days after delivery [34]. Low DAO levels can also be used as a diagnostic tool for trophoblastic diseases. In pregnant females with trophoblastic diseases, such as choriocarcinoma and hydatid mole, DAO levels remain low despite high titers of human chorionic gonadotropin. In molar pregnancies, DAO levels are equal to those in normal pregnancies in early gestation but decline after 15 weeks of gestation. In addition, a sharp drop in the DAO curve is a sign of fetal distress or intrauterine death [27].

2.4. DAO as a Predictor of the Gastrointestinal (GI) Tract Toxicity of Drugs

In rats, the DAO level in blood significantly correlates with the level in small intestinal mucosal villi and with the severity of intestinal toxicity caused by anticancer drugs such as 5-fluorouracil (FT) [35]. Tsutomu et al. [36] measured serum DAO levels in 20 patients with gastric cancer during adjuvant chemotherapy with oral FT anticancer drugs and found that antitumor drug treatment decreased DAO levels and health status positively correlated with DAO levels in these patients. A recent prospective cohort study involving 50 patients with esophageal cancer treated with docetaxel + cisplatin + 5-FT reported that plasma DAO level reflects the ability of the intestine to absorb amino acids and thus can be used as an indicator of the efficacy of chemotherapy in patients with esophageal cancer [37]. Serum DAO activity decreases gradually over the course of anticancer drug treatment, and the percentage decrease in DAO activity correlates closely with the severity of gastrointestinal toxicity [38]. This result indicates that plasma DAO levels can be used to monitor and evaluate the GI toxicity response to chemotherapy in patients with cancer [38,39]. Colchicine increases gut permeability, alters the intestinal microbiota, exacerbates flora displacement, and inhibits inflammatory response in mice, which may increase toxic load in the mouse intestine. Thus, the serum levels of DAO and lipopolysaccharide are increased [40]. Plasma DAO level is an important measure in conducting drug/food therapy studies of anticancer drug-induced

gastrointestinal toxicity and monitoring intestinal integrity and related complications in gastric, esophageal, liver, colorectal, breast, head, and neck cancers [41–46].

Table 1. Serum DAO in different diseases.

Disease	Origin	Change of Serum DAO *	Comments	Refs.
gastrointestinal diseases	rats, mice, humans	increased	More clinical studies are needed to support the diagnostic value of DAO.	[12,15–17]
migraine	humans	decreased/increased	Oral DAO supplementation might be a new therapy for migraines.	[18–21]
pregnancy	humans	increased	Serum DAO has a role in pregnancy confirmation and screening for trophoblast diseases.	[23,25,26]
gastrointestinal tract toxicity	humans, rats, mice	decreased/increased	The precision of DAO levels reflecting toxicity needs further study.	[28–31]
liver disease	humans	increased	DAO might be a potential biomarker in patients with liver and intestinal dysfunction.	[32,33,35]
histamine intolerance	humans	increased	The role of DAO in the diagnosis of histamine intolerance and its treatment has been clarified.	[38–41]

* DAO expressed differently in a variety of diseases, suggesting the respective direction of future research.

2.5. DAO in Hepatitis and Post-Hepatitis Cirrhosis

Plasma DAO level has also been associated with the development and prognosis of many liver disorders, such as hepatitis, cirrhosis, and orthotopic liver transplantation. Li et al. [47] conducted a 1-month follow-up study of 106 patients newly diagnosed with acute-on-chronic hepatitis B liver failure (ACHBLF) and found that plasma DAO level reflects the severity of ACHBLF and is an independent risk factor for 1-month mortality. Furthermore, DAO level is more sensitive than the conventional model for end-stage liver disease, with a plasma DAO level of 15.2 ng/mL as the cut-off point. As for patients with hepatitis B virus-associated decompensated cirrhosis, plasma DAO levels > 19.7 ng/mL have been associated with high 6-month readmission rates [48]. Considering the connection between DAO level and intestinal mucosal condition, a previous study measured serum DAO and endotoxin levels in patients with liver cirrhosis and found that DAO level is significantly higher in patients with liver cirrhosis than in healthy individuals [49]. This result suggests that DAO level is a sensitive marker for the early diagnosis of gut failure in liver cirrhosis.

Recent studies on serum DAO levels have extended their focus to liver transplantation. The only curative procedure for patients with end-stage liver disease is orthotopic liver transplantation (OLT). To assess the role of histamine and plasma DAO in OLT, an RCT of 22 liver transplant patients and 22 healthy adults as controls found that the baseline levels of histamine and plasma DAO were markedly elevated in patients undergoing OLT; however, the concentration of histamine decreased and DAO increased significantly during OLT [50]. This result can be attributed to the intraoperative use of norepinephrine. As mentioned in these studies, serum DAO mainly reflects the function of the intestine rather than the liver.

2.6. DAO and HIT

HIT is a disturbance in histamine homeostasis caused by reduced intestinal degradation of histamine due to DAO deficiency [51]. DAO deficiency may be a major cause of HIT, in which alterations in histamine homeostasis lead to a decrease in intestinal degradation and a subsequent increase in plasma [52]. DAO deficiency may be congenitally caused by genetic mutations in DAO genes or alterations in protein coding resulting in decreased DAO levels; it may also be acquired from lesions that reduce DAO secretion, particularly

in inflammatory or degenerative bowel diseases [53]. The multifaceted clinical symptoms associated with HIT include headache, gastrointestinal disturbances (such as abdominal pain, diarrhea, and flatulence), urticaria, pruritus, nausea and sneezing, runny nose, cardiac arrhythmias, hypotension, and muscle pain [21].

HIT is a disease characterized by a disequilibrium between accumulated histamine and histamine degradability. The degradation of histamine in the intestine decreases with reduced DAO activity, resulting in the accumulation of histamine in the blood plasma and adverse reactions [54,55], which mainly originate in the gut [56]. Impaired histamine degradation due to reduced DAO activity and subsequent histamine overload may lead to symptoms similar to those of allergic reactions [3]. In patients with HIT, ingestion of histamine-rich foods, alcohol, or drugs that either release histamine or block DAO may induce diarrhea, headache, respiratory allergies (e.g., atopic asthma and allergic rhinitis) [57], hypotension, cardiac arrhythmias, urticaria [58], pruritus, flushing, and other conditions. This finding indicates that serum DAO level is valuable in the diagnosis of HIT [59], and symptom severity is associated with DAO deficiency.

A recent questionnaire follow-up study of 133 outpatients with HIT (serum DAO values < 10 U/mL) with onset symptoms (primarily gastrointestinal, cardiovascular, respiratory, and skin complaints) was conducted to explore the onset of non-specific GI and extraintestinal symptoms arising from the distribution of the four histamine receptors in different organs and tissues of the body. Results of this study showed that patients with HIT predominantly had gastrointestinal manifestations, with abdominal distention being the most common symptom (92%), followed by cardiovascular symptoms and, finally, respiratory and skin complaints [3,60–62]. Another study showed that in patients with low DAO levels (<40 HDU/mL), the clinical symptoms typical of HIT disappear, and serum DAO levels significantly increase after the introduction of a histamine-free diet [63]. Similar effects can be exerted by oral DAO supplementation in patients with HIT [64]. Cucca et al. found that patients with DAO values of 3–10 U/mL exhibit the most complicated clinical presentation but also respond best to treatment with a low-histamine diet and/or DAO supplementation [65]. The prevailing consensus is that incorporating a histamine-reduced diet and/or oral microbial DAO capsules into a targeted dietary intervention can help alleviate HIT-related symptoms [66,67]. HIT has been a hot research topic for almost a decade, but evidence-based, double-blind, placebo-controlled, and crossover in vivo studies are still necessary to understand the effects of oral DAO supplementation and provide a basis for further investigations on HIT.

3. Effect of Food/Drugs on DAO Determination

Histamine-induced food intolerance used to be defined as an intolerance to red wine and the symptoms of allergy after ingestion of histamine-rich foods, which is not IgE-mediated. These symptoms are milder and less persistent, with a deficiency of diamine oxidase leading to a reduction in histamine degradation that results in excessive accumulation of histamine [68], thus explaining the alleviation of HIT symptoms after a histamine-free diet or antihistamines [69].

A decrease in intestinal mucosal DAO activity was found in patients with food allergy [70]. Foods that are known to contain histamine include milk, eggs, tuna, sauerkraut, cheese, nuts, seafood, fresh fruits, and vegetables associated with pollen, all of which are common allergens [68,71–73].

Xu et al. observed in a mouse model of induced inflammatory bowel disease that polysaccharides of Tremella fuciformis could restore intestinal microbiota and microbial metabolites and then significantly increase intestinal flora diversity, thereby reducing serum DAO activity; this suggests that Tremella fuciformis may serve as a food supplement to improve intestinal disease [74].

As mentioned before, serum DAO activity varies more in females, and serum DAO values vary with the menstrual cycle, peaking at the luteal phase [75]. Miyoshi et al. analyzed the relationship between DAO activity and dietary nutrient intake/energy ratio

through dietary surveys and measurement of serum DAO activity in 34 healthy Japanese women during the follicular and luteal phases and found that serum DAO activity was positively correlated with the intake of long-chain fatty acids, especially saturated and monounsaturated fatty acids; however, it was unrelated to consumption of medium and short-chain fatty acids, protein, carbohydrate lipids, and dietary fiber. Further studies found that serum DAO activity in the luteal phase was also positively correlated with dietary intake of phosphorus, calcium, magnesium, iron, zinc, and vitamin B_{12}, but not in the follicular phase [76]. Previous studies have found that elevated blood histamine levels during premenstrual syndrome can be alleviated by increasing serum DAO activity with oral magnesium or calcium [77]. This also reminds us of the need to consider the effects of gender, menstrual cycle, and nutrients when assessing serum DAO activity as a means of identifying various diseases.

Alcohol and drugs are also notable inhibitors of DAO. Sessa found that ethanol inhibited DAO activity while acetaldehyde stimulated DAO activity [78,79], and there are as many as 94 known inhibitors of DAO, such as dihydrazine, nafamostat, isoniazid, d-tubocurarine, pancuronium, clavulanic acid, promethazine, verapamil, metoclopramide, numerous antibiotics, etc. [68,80,81]. All of them induce allergic reactions by inhibiting DAO activity. The mechanism of inhibition is sometimes competitive, as with dihydralazine and pancuronium bromide, and sometimes non-competitive (e.g., pentazocine), which may be of particular importance for long-term treatment. It has also been shown that drugs such as Lianshu preparation, berberine, apocynin, and phosphatidylcholine can improve intestinal mucosal barrier damage and protect the integrity of the intestinal mucosa by enhancing the activity of DAO enzymes [82–85].

Histamine-induced food intolerance affects the quality of life of a large proportion of the population, and both DAO deficiency and/or histamine receptor upregulation can exacerbate the symptoms of histamine toxicity. Thus, effective measures must be taken to manage these patients.

4. Low-Histamine Diet/DAO Supplements

To address these clinical diseases and possible mechanisms, a variety of DAO supplements have been developed, and a low-histamine diet is recommended for symptomatic relief and prognostic improvement. Research has shown that treatment with a low-histamine diet only reduces symptoms in HIT patients, and there is no specific drug available to cure [86]. Commercially available dietary supplements, such as Daosin or products from DR Healthcare, are commonly used to provide exogenous porcine DAO to supplement endogenous DAO in the human small intestine through protein derived from porcine kidneys [87]. However, DAO extracted from porcine kidneys does not yield sufficient DAO activity for clinical application at present [66,88]. Dietary treatment of HIT (low-histamine diet and DAO supplementation) can ameliorate intestinal dysbiosis by reducing the relative abundance of histamine-secreting bacteria (i.e., Pseudomonas spp., Aspergillus spp., Aspergillus spp., and Lachnospira spp.) and increasing the bacterial flora associated with intestinal health, thereby improving the clinical symptoms of HIT [89,90].

Interestingly, a recent study has shown that the enzyme-linked UHPLC-FL (ultra-high performance liquid chromatography and fluorimetric) technique has the advantage of rapid, reliable, and highly specific detection of DAO activity in food matrices and could be used as a tool to validate foods with the potential to treat HIT and help in the discovery of more DAO dietary supplements [91].

5. Laboratory Methods for Quantitative Measurement of Serum DAO Concentrations

Given the role of DAO as a diagnostic marker in the identification of gastrointestinal disorders, migraine, pregnancy monitoring, the GI tract toxicity of drugs, hepatitis and post-hepatitis cirrhosis, HIT, and other diseases, a reliable and accurate method for quantification of DAO antigens is necessary.

Strictly speaking, the most direct and reliable method of diagnosing DAO activity should be an assay of intestinal mucosal DAO activity performed on colonic tissue sampled during a colonoscopy. However, intestinal DAO activity is inaccessible in terms of direct measurement and few studies have been conducted on this diagnostic method, with current studies mainly focusing on the methodological measurement of serum DAO activity and values. Previous studies have demonstrated that serum DAO activity is closely related to intestinal nucleic acid and protein synthesis and may reflect the severity of intestinal mucosal damage [92].

DAO activity has been assayed based on the detection of hydrogen peroxide, aldehyde, or dioxygen by spectrophotometric, titrimetric, manometric, fluorometric, polarographic, amperometric, biometric, and radiometric techniques [93–95]. Radioactive methods using a combination of isotope dilution and gas flow counting are the most reliable. However, isotope dilution is a more time-consuming and laborious method, while the liquid scintillation technique is more sensitive, simple, and fast for radioactive determination of DAO activity, making it suitable for large-scale sample measurements [96]; this method is thus referred to as the "gold" standard method for DAO activity determination. Schwelberger et al. prepared five monoclonal antibodies targeting human DAO by immunizing mice with in vitro-expressed fragments of human DAO protein and found that the detection of DAO was 100-fold more sensitive than the most sensitive enzyme assays currently available. Owing to the increased sensitivity of the new monoclonal antibody, DAO expression and cellular localization in various human tissues can be validated, and DAO can also be detected at sites where DAO enzymatic activity has not previously been clearly demonstrated, such as in urine [97].

A new ELISA quantification method described by Boehm et al. allows accurate measurement of DAO concentrations in various biological fluids, showing high agreement with radioactivity assays. Accurate and reliable ELISA assessment of DAO may be used to validate the role of DAO as a potential biomarker in various diseases [98]. Since enzyme activity can be abnormal in patients with normal DAO levels, it is suggested that a link between DAO concentration and activity be made for the clinical diagnosis of various diseases. Beltrán-Ortiz et al. constructed a method which simultaneously determines DAO serum concentrations using the immunodiagnostic DAO ELISA K8500 kit and the standard colorimetric method for determining serum DAO activity, and they found that it was more specific for HIT diagnosis; interestingly, the concurrent application of the two tests was effective in reducing false-positive and false-negative results in HIT patients [59].

However, the reference values for DAO levels in serum have not yet been established, and the measured DAO values and activity in serum do not correspond to those in the intestinal mucosa [99]. In some cases, serum DAO enzyme activity assays can also be considered as a supplementary test if intestinal mucosal DAO activity assays are not feasible.

DAO belongs to the group of copper amine-containing oxidases [100]. As a product of AOC1 gene encoding, DAO preferentially degrades histamine and various polyamines, such as putrescine or spermidine [101]. However, as the main enzyme for the extracellular degradation of histamine, whether DAO exists in the serum or plasma of non-pregnant healthy individuals is controversial. Schwelberger et al. found that purified plasma amine oxidase (PAO) from porcine plasma could efficiently convert histamine and N-methylhistamine, inactivating various amines in the circulation (including histamine); he thus concluded that DAO was not normally present in the bloodstream [102]. This group also failed to detect DAO in human serum through Western blotting in another trial, suggesting that the enzyme activity detected in plasma or serum may be mediated by vascular adhesion protein-1 (VAP-1, also known as PAO) rather than DAO [97]. This differs considerably to conclusions previously reported on the measurement of serum DAO activity, which may be related to the inability of monoclonal antibodies to detect DAO in blood, at least not in relevant quantities.

The main role of DAO is the degradation of extracellular histamine, which has been heavily studied in recent years. DAO catabolizes other polyamines, such as putrescine,

spermidine, and cadaverine, and cadaverine in particular may be a better selective substrate for DAO [103–105]. Meanwhile, other amines may act as competing substrates and interfere with the degradation of histamine by intestinal DAO [106]

6. Conclusions and Future Perspectives

DAO level measurements are useful for the early diagnosis of inflammatory bowel diseases, acute mesenteric ischemia, and other intestinal pathologies. DAO also plays an essential role in a wide range of clinical applications, including detecting various allergic diseases, liver diseases, and pregnancy-related diseases, and can also be used to evaluate the GI toxicity of anticancer drugs. Gender, menstrual cycle, and various foods or drugs that affect the determination of DAO levels pose problems for the reliability of the enzyme in diagnosing clinical disease. At the same time, this can provide novel ideas for the treatment of various diseases, such as HIT and histamine toxicity. Current studies on the use of a low-histamine diet/DAO supplementation mainly focus on HIT and are not widely available. In addition, analysis of blood DAO levels is challenging, and the high economic cost of DAO assays may be the reason why DAO activity assays are not yet widely accepted in daily clinical practice. Routine analysis has been limited to enzymatic assays, which are often less sensitive and impractical, and their specificity and operability still require further optimization.

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