

# Histamine Intolerance: Clinical Characterization and Determination of Serum Diamine Oxidase (Dao) in a Series of Cases and Controls

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## Research

**Keywords:** Histamine intolerance (HIT), headache , dysmenorrhea, diamine oxidase (DAO)

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# Abstract

**Introduction.** Histamine intolerance (HIT) is a pathology with an estimated prevalence of 1% in which there is an imbalance between the intake of histamine via the digestive tract and the body's ability to degrade it. This results in an excessive accumulation of histamine that determines the appearance of gastrointestinal, skin, respiratory and neurological symptoms. The enzyme responsible for degrading histamine in the extracellular space is diamine oxidase (DAO); therefore, HIT is caused due to a deficit in the concentration and/or in the activity of this enzyme. Because histamine is the main mediator of the classic symptoms of IgE-mediated allergic reactions, it is difficult to differentiate a true allergy from HIT since it has basically the same clinical manifestations.

**Objectives.** The objective of this study was to perform a clinical characterization of patients with HIT and to determine the usefulness of quantifying serum DAO concentration in the diagnosis of HIT.

**Method:** Twenty-two patients over the age of 18 with a history of histamine intolerance were recruited, in whom IgE-mediated food allergy was ruled out, and 22 healthy patients. Both groups were surveyed and serum DAO concentration was determined.

**Results:** Middle-aged women predominated in the population with HIT. They described a wide variety of symptoms, with a dominance of abdominal pain, bloating, diarrhea, flushing, urticaria, itching, headache and dysmenorrhea. When comparing the average serum DAO concentration in the population with HIT (10.686 U/ml) with the average obtained in the control population (20.664 U/ml), there was a significant difference ( $p < 0.003$ ).

**Conclusion.** The determination of serum DAO concentration is a useful tool for the diagnosis of HIT.

## Introduction

Histamine is a biogenic amine that can be synthesized by *L-histidine decarboxylase* (HDC) from histidine amino acid and it is also synthesized by mast cells, basophils, platelets, histaminergic neurons and enterochromophins, where it is stored in intracellular vesicles and released after stimulation.<sup>1</sup>

Histamine exerts its effects by binding to four receptors (H1R, H2R, H3R and H4R) in certain cells of different tissues, generating smooth muscle contraction, vasodilatation, increased vascular permeability, mucus production, tachycardia, blood pressure changes, arrhythmias, gastric acid secretion and stimulation of nociceptive nerve fibers.<sup>2</sup>

Histamine can be metabolized in two ways: by oxidative deamination mediated by *diamine oxidase* (DAO) in the extracellular medium or by methylation mediated by *histamine-N-methyltransferase* (HNMT) in the intracellular space.<sup>3</sup>

Histamine can also be introduced to the body from exogenous sources, through the intake of certain types of foods with high concentrations of histamine.<sup>4</sup>

Different fermenting bacteria are able to decarboxylate histidine, forming histamine. The two key factors for histamine accumulation in food are the presence of bacteria with decarboxylase activity and the availability of the reaction's substrates. Thus, foods that are most likely to contain histamine are those with a high protein load and those fermented foods and beverages in which lactic acid bacteria are involved.<sup>5</sup>

Many foods have been considered capable of inducing the release of histamine from tissue mast cells, even if these contain low concentrations of histamine. In vitro studies of patients with a history of pseudoallergic reactions with food have shown massive degranulation of duodenal mast cells in the presence of certain histamine-releasing substances. However, clinical studies using oral provocation tests are required to support this hypothesis.<sup>6</sup> Figure 1.

Histamine intolerance (HIT) is a pathology in which there is an imbalance between the intake of histamine through the digestive tract and the ability of the body to degrade it. This results in an excessive accumulation of histamine that determines the appearance of symptoms when it binds to its respective receptors. It is estimated that the prevalence of HIT is approximately 1% of the population, with a predominance of middle-aged women. However, it is very likely that the prevalence is underestimated due to the wide variety of symptoms that are often misinterpreted by physicians and patients.<sup>7</sup>

DAO is continuously being secreted into the intestinal lumen, so that under normal conditions histamine from food and generated by bacteria in the intestine is satisfactorily degraded by it.<sup>8</sup> Thus, HIT may be a condition secondary to a quantitative deficit of DAO or a functional deficit of DAO.<sup>9</sup>

The quantitative deficit of DAO may be due to genetic defects—intestinal pathologies that damage enterocytes—that result in a decrease in DAO production; while the functional deficit may be due to the DAO inhibition by other biogenic amines, alcohol or drugs. A decrease in DAO activity has also been observed in patients with chronic kidney disease, viral hepatitis, cirrhosis, and chronic urticaria.<sup>10</sup>

Genetic polymorphisms influence both the expression and the function of DAO, but alone are not sufficient to generate HIT. The presence of environmental factors such as the use of concomitant DAO-inhibiting drugs is of paramount importance. Thus, HIT is caused by the sum of genetic and environmental factors.<sup>11</sup> The functional deficit of DAO can also be secondary to the deficit of its co-factors: vitamin B6, vitamin C, copper and zinc, being a reversible cause of HIT.<sup>12</sup>

Because histamine is the main mediator of the classic symptoms of IgE-mediated allergic reactions, it is difficult to differentiate a true allergy from HIT since it has basically the same clinical manifestations. An important key is that unlike the IgE-mediated reactions in which even small amounts of antigen trigger

the onset of symptoms, in HIT the accumulation of high concentrations of eaten histamine plays a fundamental role in the onset and severity of symptoms.<sup>13</sup>

The diagnosis of this pathology is complex because of the diversity of histamine-mediated symptoms and the lack of a reliable biomarker to date. Faced with a suspicion of HIT, the diagnostic algorithm should begin by recording a diary of symptoms associated with food intake. Potential food allergies should then be excluded through skin test or specific IgE determination for food allergens and a hidden systemic mastocytosis by measuring basal serum tryptase levels. Finally, the clinical response to the introduction of a histamine-free diet is essential in the diagnostic process.<sup>14-15</sup> Figure 2.

A double-blind, placebo-controlled histamine provocation has been proposed for the definitive diagnosis of HIT, in addition to the determination of plasma histamine concentration and the objectivation of clinical parameters. Other diagnostic methods include the measurement of DAO's intestinal activity, the analysis of its genetic polymorphisms in order to determine a possible genetic predisposition to HIT, and the measurement of DAO concentration and activity in peripheral blood. The latter are low-cost, easy-access, non-invasive tests.<sup>16-17</sup>

**OBJECTIVE:** Describe the clinical characteristics of patients with HIT, apply an ELISA assay to determine serum DAO concentration, and analyze the proportion of patients with a diagnosis of HIT with a deficit of this enzyme in comparison with healthy individuals.

## Method

A study of cases and controls was carried out. The study was approved by the Ethics Committee of the Clinical Hospital of the University of Chile, and all participants signed an informed consent. The group of cases included people over 18 years of age with a history of histamine intolerance, in whom an IgE-mediated food allergy had been ruled out by means of skin test and/or specific IgE. The control group included people over the age of 18 without a history of histamine intolerance and no kinship with the individuals under study. All persons diagnosed with food allergy or diseases associated with immune system disorders such as cancer and autoimmunity, chronic liver failure, and kidney failure, suffering severe burns or undergoing chemotherapy, as well as pregnant women, were excluded.

A survey was applied to all participants in the study to define the clinical characteristics of histamine intolerance in the case group and the same survey was applied to control individuals to rule out exclusion criteria.

A commercial DAO ELISA K8500 kit from Immunodiagnostik Germany was used to determine DAO concentration in the serum of patients and controls. The kit contains an anti-DAO antibody, a secondary antibody conjugated with streptavidin peroxidase and uses tetramethylbenzidine (TMB) as substrate. The yellow chromogen generated is read with a spectrophotometer at a wavelength of 450 nm. As a reference

range, levels < 3 U/ml have a high probability of HIT; levels of 3-10 U/ml, a probable HIT and levels > 10 U/ml a low probability of HIT.

A descriptive analysis was made with the information collected from the survey. The ROC curve was used to analyze the discriminative capacity of the ELISA kit to determine the quantitative DAO and Student's unpaired t-test was used to analyze whether the differences between the averages of the serum DAO concentration between the case population and the control population was significant, considering a 95% confidence interval.

## Results

Twenty-two HIT cases and 22 controls were recruited. In the group of cases there was a marked predominance of female population. The group was made up of 20 women and only 2 men. It was decided to recruit more women than men for the control group in order to match populations, this group consisting of 14 women and 8 men. The median age in the case group was 41 years (21-62 years) and in the control group 34 (24-59). It is worth noting that all of the cases in the case population had some comorbidity, with a predominance of high blood pressure, insulin resistance, chronic urticaria, allergic rhinoconjunctivitis, thyroid pathology and rosacea. While other studies excluded patients with gastrointestinal pathologies and bariatric surgery, this study decided to include them because they would be more likely to be intolerant to histamine. Individuals without comorbidity were selected for the control group.

When asked about the predominant symptoms in patients with histamine intolerance, abdominal pain, bloating, diarrhea, flushing, urticaria, itching, headache and dysmenorrhea predominated, occurring in at least 50% of the case population. Figure 3.

Most of the patients (14) described that symptoms appear within the first hour after eating histamine-rich foods, however 7 of them report the onset of symptoms several hours after eating and only one patient within minutes of eating. The majority of them (15) described that symptoms persist for several hours, but never more than a day. Of these, only 9 patients were able to accurately state the duration of the symptoms and the average duration of them was 4.8 hours. Only 6 patients reported a duration of symptoms of more than one day and 2 patients reported a duration of only minutes.

Among the foods and beverages mentioned by patients as triggering symptoms were wine, fish, shellfish, chocolate, cheese, tomato or tomato sauce and nuts. Among the fish there was a clear predominance of canned fish such as tuna.

When determining the serum DAO concentration in the case population, we found that 1 patient had a DAO level of  $\leq$  3 U/ml, 13 patients had levels between 3-10 U/ml and 8 of them had levels  $\leq$  10 U/ml. When determining the serum DAO concentration in the control population only 2 individuals had DAO levels of  $\leq$  10 U/ml and the rest (20) all had levels of  $\leq$  10 U/ml. When comparing the average serum DAO

concentration in the population with HIT (10.686 U/ml) with the average obtained in the control population (20.664 U/ml), there was a significant difference ( $p \leq 0.003$ ). Figure 4.

A ROC Curve was performed to analyze the specificity and sensitivity of the ELISA test. The curve shows that the sensitivity of the ELISA kit that quantifies the serum DAO concentration for the diagnosis of HIT is 0.63 and the specificity 0.9. It is therefore a good diagnostic test, which is able to rule out true negatives. Figure 5.

## Discussion

This study is the first one to recruit and describe a population with a clinical diagnosis of HIT in Chile. The studied population is notably dominated by middle-aged female patients, a finding compatible with that reported in the international literature. It is worth noting that all the patients recruited had some comorbidity that made the use of drugs necessary, regardless of the fact that these drugs were not on the list of drugs that interfere with DAO activity. This raises questions about the possibility that other commonly used drugs, which have not yet been reported in the literature, may interfere with DAO activity or with some of its co-factors.

When inquiring about the clinical presentation of HIT, the range of symptoms reported by these patients was quite broad, with a clear predominance of abdominal pain, bloating, diarrhea, flushing, urticaria, itching, headache, and dysmenorrhea. With regard to the timing of the symptoms, most patients reported the onset of symptoms within the first hour after eating and a duration of no more than 24 hours. This information allows us to define in which population we can suspect a HIT diagnosis.

With respect to foods that trigger HIT symptoms, wine, fish, shellfish, cheese, tomato, chocolate and nuts stand out, with the first five of these foods classically described as rich in histamine and the last two as histamine-releasing foods.

When measuring serum DAO concentrations, among the 22 patients with a clinical diagnosis of HIT, 1 had a high probability of HIT, 13 were likely to have histamine intolerance and 8 of them had a low probability of HIT, while in the control population only 2 patients had a likely histamine intolerance and the remaining 20 had a low probability of HIT.

It was very interesting to find that the determination of serum DAO concentration with the Immunodiagnostik ELISA Kit K8500, with the cut-off level proposed by the manufacturer of  $\geq 10$  U/ml for likely HIT, is a useful tool to discriminate between people with and without HIT, which shows its high specificity.

A study previously conducted by Kacik et al. in a pediatric population in which 26 children with IgE-mediated food allergy and 8 children with HIT were recruited, found that those with food allergy had an average serum DAO concentration of  $83.01 \pm 6.73$  IU/ml, while those with HIT had an average serum DAO concentration significantly lower of  $46.4 \pm 7.19$  IU/ml ( $p = 0.0016$ ).<sup>18</sup>

The most effective treatment for HIT is limiting the intake of histamine-rich foods. Monitoring the diet is difficult because the histamine content of foods is not specified. In addition, it is important to restrict the consumption of substances that directly stimulate the endogenous release of histamine or inhibit DAO activity.<sup>19</sup>

In general, a diet based on fresh food and the exclusion of processed, preserved or very elaborate foods is recommended. HIT is transitory in many patients, who may return to a normal diet within a few months. For more severe cases, the use of antiH1 and antiH2 is recommended. It is currently possible to replace DAO with an oral dietary supplement.<sup>16</sup> The administration of zinc, copper, vitamin C and vitamin B6, all DAO co-factors, may be administered to improve DAO's function.<sup>20</sup>

## Conclusion

HIT is a pathology that is prevalent in the general population, with a marked predominance of middle-aged females. It is underdiagnosed in part due to a lack of knowledge of the disease and because to date the diagnosis is eminently clinical. In Chile, this study is a pioneer in recruiting patients with HIT, describing their clinical characteristics and analyzing serum DAO concentration.

The population studied generally showed clinical manifestations within the first hour after intake of histamine-rich or histamine-releasing foods and the symptoms lasted no longer than 24 hours. The most common symptoms were gastrointestinal, skin and central nervous system disorders.

An accurate diagnosis is essential for the treatment of HIT consisting of guiding an appropriate restriction diet and making the pharmacological interventions necessary in each case. The quantitative determination of DAO using an ELISA kit proved to be a useful tool for discriminating between populations with and without DHA, which shows its high specificity.

## Declarations

Ethics approval and consent to participate

Previously to the study all the patients signed an informed consent approved for the Ethical Committee of the Hospital Clinico Universidad de Chile

## Consent for publication

We obtained a written informed consent of the patients for publication of this study.

### Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author, Dr. Pablo Ferrer Campos (E-mail:pferrer40@gmail.com).

## Declarations of Interest/Disclosures

The authors declare that they have no competing interests

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This work did not have funding.

### Author's contributions

Dr Teresa Peralta, she designed the project, recruited the patients and revised the manuscript.

Camila Beltrán-Ortiz, Biochemist, she carried out the experiments of this work and revised the manuscript.

Verónica Ramos, Biochemist, she carried out the experiments of this work and revised the manuscript.

Magdalena Durán, *Medical Technologist*, she carried out the experiments of this work and revised the manuscript.

Dr Maria A Guzmán, she designed the project, recruited the patients and revised the manuscript.

Dr Carla Bastias, she designed the project, recruited the patients and revised the manuscript.

Pablo Ferrer, Biochemist and Dr, PhD, he designed the experiments revised all the results and carried out the final critical review of the manuscript.

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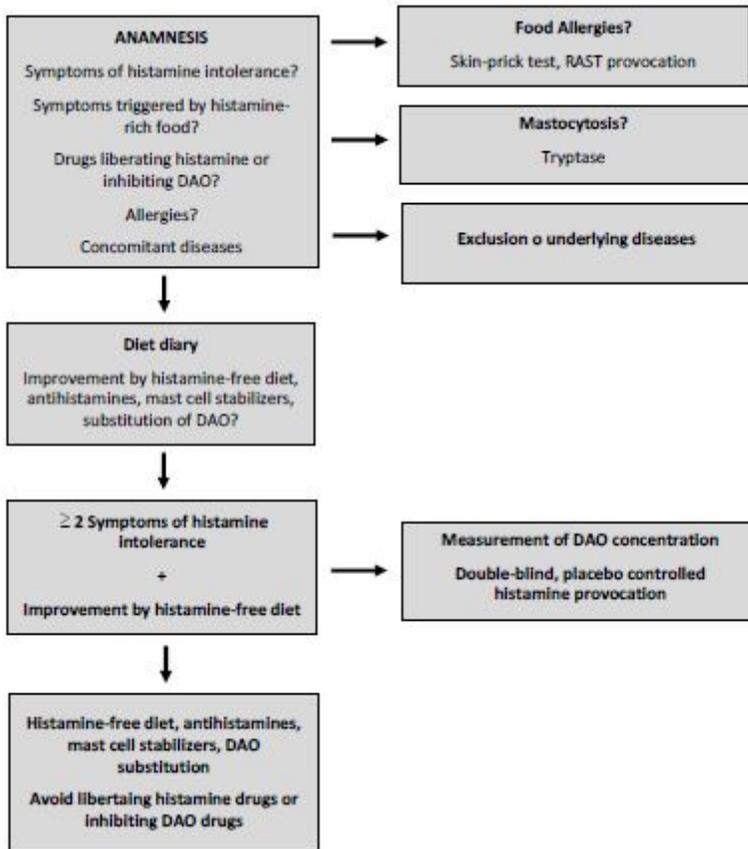
## Figures

<b>Foods rich in histamine</b>
Tomato, eggplant, spinach, fish, chicken, and any meat stored. Fermented food: cheese, cheese, sausages, sauerkraut, wine, beer, champagne.
<b>Histamine liberators</b>
Pineapple, banana, citrus, strawberries, nuts, papaya, tomato, legumes, dressings, cocoa, fish, pork, egg white Additives: dyes, preservatives, stabilizers, flavorings, etc
<b>Bacteria and yeasts that promote the formation of histamine</b>
Bread, sourdough, beer
<b>Substances decreasing DAO activity in food</b>
Alcohol
<b>Substances decreasing DAO activity in drugs</b>
Antiarrhythmics: verapamil, propafenone Antibiotics: cefuroxime, cefotiam, acidum clavulanicum, doxycyclinum, isoniazid Painkillers: metamizole Psychiatric medication: amitriptyline, diazepam, inhibitors MAO—1, haloperidol Antiemetics: metoclopramide Antihistamines: cimetidine Antihypertensive drugs: dihydralazine Antimalarials: chloroquin Bronchodilators: aminophylline, theophylline Diuretics: furosemide Mucolytics: N-acetylcysteine, ambroxol Muscle relaxant: alcuronium, pancuronium
<b>Histamine liberators in drugs</b>
Painkillers: morphine, pethidine, codeine, metamizole Antiflogistics: acetylsalicylic acid Antibiotics: chloroquin, pentamidine Anti-hypotensives: dobutamine Antihypertensive drugs: verapamil, alprenolol Antitussives: codeine Cytostatics: cyclophosphamide Diuretics: Amilorid Iodine-containing contrast medium Local anaesthetics: mesocaine, procaine, marcaine, prilocaine Anaesthetics: barbiturates, thiopental
<b>Pyridoxine (vitamin B6) inactivating drugs</b>
Antihypertensive drugs: Hydralazine Antibiotics: Isoniazid Hormonal contraception containing estrogens
<b>Allergic reactions</b>
IgE-mediated histamine release from mast cells
<b>Infections, Trauma, Shock</b>

Adapted from E. Kovacova-Hanuszkova et al. Histamine, histamine intoxication and intolerance. Allergol Immunopathol (Madr). 2015.

Figure 1

Sources of histamine and possible causes of the increase of plasma its concentration.



**Figure 2**

Diagnostic Algorithm for the diagnosis of HIT. Adapted from Maintz L, Novak N. Histamine and histamine intolerance. Am J Clin Nutr 2007; 85.

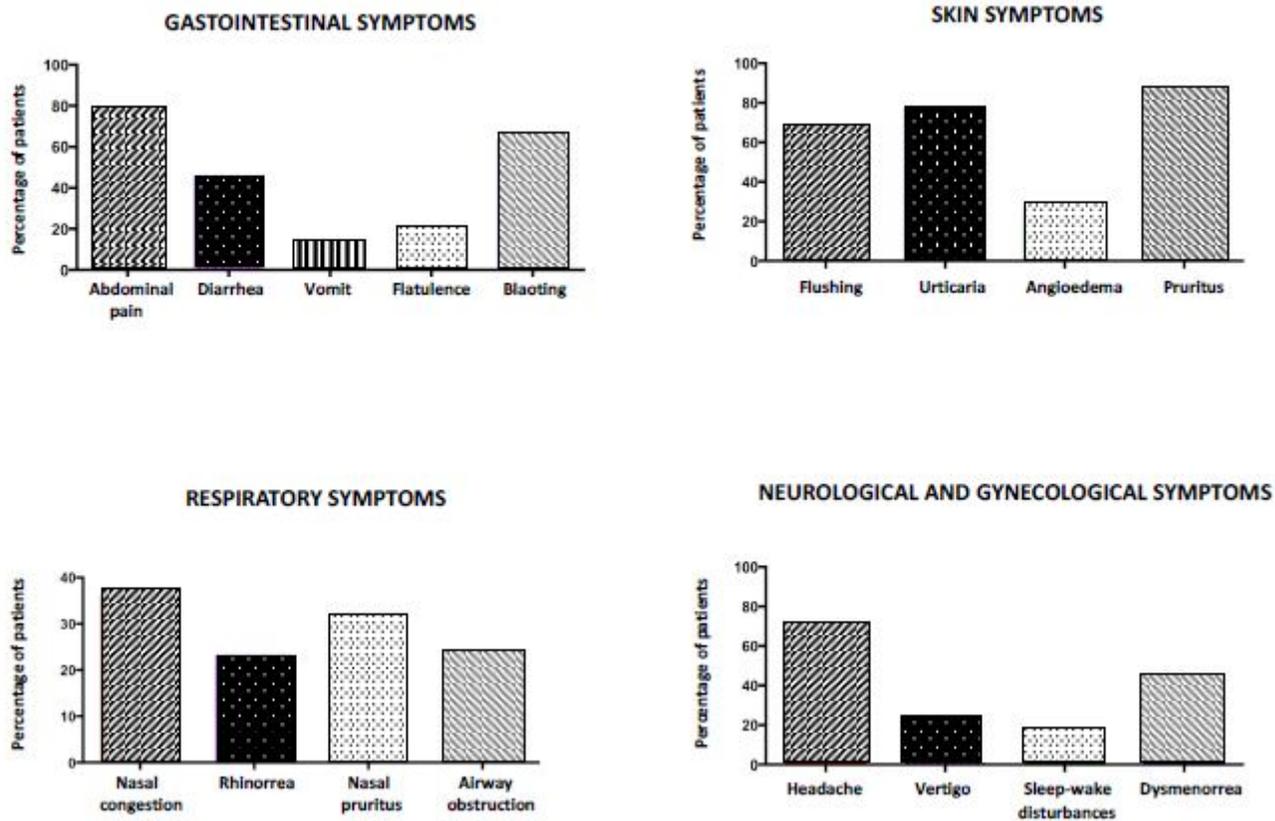


Figure 3

Prevalence of gynecological and neurological symptoms in patients with histamine intolerance.

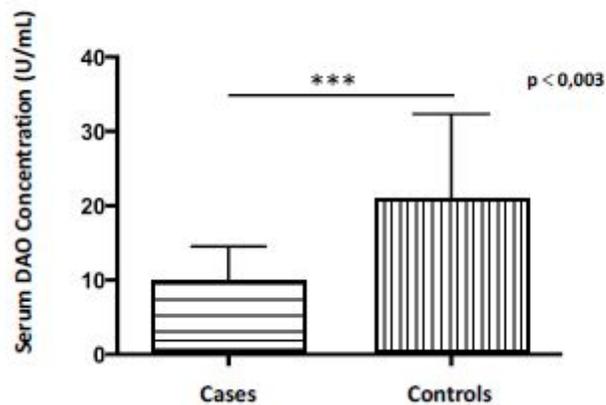
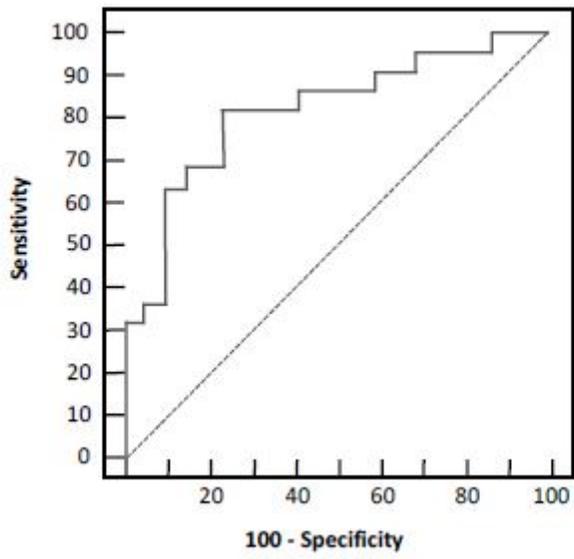


Figure 4

Average serum DAO concentration determination in populations studied.



**Figure 5**

ROC curve for the ELISA kit for quantitative DAO determination.