Migraine, a food-borne syndrome caused by DAO deficiency

Adriana Duelo
Degree in Nutrition and Dietetics. Health Science Faculty, Blanquerna. Universitat Ramon Llull. Barcelona, June 2012.

"To my father, without him I would not have started this project, he has always supported me; and to my mother, for her patience and support during all this time".

I. INTRODUCTION

Migraine affects 12-17% of the adult population in western countries, without much variation in other countries, more than 1 in 10 people. According to the latest PALM study from 2006 (Action Plan to Fight Migraine) published in Cephalalgia, a journal of the International Headache Society, over 3.5 million people in Spain have this condition.(1) Moreover, it is nowadays a very costly pathology to society: First, because of direct costs, particularly medical costs (diagnostic studies, consultations and pharmacological treatments); second, and just as significant, because of the economic losses it causes in the labour environment due to absenteeism from work and therefore reduced productivity.(2) In Spain, 20 million working days are lost every year for this reason, which involves an approximate cost of 2,000 million euro. At European level, this cost reaches 27,000 million euro every year. (3)

There are different known causes that can trigger migraine, but the importance of nutrition is not known or not taken into account by most of the healthcare professionals who study and treat this syndrome. For decades, the correlation between migraine and nutrition has been limited to the listing of alleged trigger foods based on patient surveys but without any scientific basis. This project attempts to go further and clarify the true origin of this correlation between nutrition and migraine. It has been proven that food itself is not the cause, but the patient's individual susceptibility depending on his/her body functionality. In other words, the purpose of this paper is to highlight the important and possibly prevailing correlation between nutrition and the triggering causes of migraine, but with a focus on the individual patient rather than food.

1.1. DEFINITION OF MIGRAINE

Migraine is a complex syndrome with relapsing and incapacitating episodes or attacks. It is suspected to be of genetic origin, but its etiopathogenesis seems to be unclear. There are many clinical, histochemical, electrophysiological, molecular and genetic approaches that make up a set of findings which are shedding light on the aforementioned etiopathogenesis.

Unilateral or throbbing headache associated with photophobia and phonophobia, nausea and vomiting is a major clinical sign of migraine.

It is a syndrome with multiple symptoms characterized by relapsing headache attacks with pulsating and throbbing pain, usually located in the sinus area; it occurs at certain intervals and there is no pain between intervals. Pain is generally located on one side, but the affected side can change from attack to attack (actually, the word "migraine" is derived from the Greek word "hemikrania", meaning "half-skull"). A migraine episode or attack is highly variable in severity, frequency and duration. For adult patients, its duration is 4-72 hours; when it exceeds 72 hours, it is regarded as migraine complications, normally due to

drug abuse. In children, an episode or attack may last less than 4 hours.

The common symptoms of a migraine episode, in addition to the pain, include: nausea, vomiting, diarrhoea, sensitivity to sounds (phonophobia), light (photophobia), odours (osmophobia) or movement, loss of appetite, dizziness, gastric distress and cold/hot sensation.

It is known that three out of four migraine patients are women, that is to say, women account for 75% of affected patients compared to 25% of men.

A migraine episode process usually progresses in a similar manner, including five phases that match certain vascular disorders that involve superficial temporal arteries and progress from a normal state to vasodilation and pain:

1. - Prodromal phase
Three or four hours before the onset of head pain or headache, patients begin to feel intolerance to light, increased thirst, excessive sleepiness and hypersensitivity to environmental noises. All of this, in combination, can produce a character disorder. At a vascular level, there is no artery involvement in this first phase.

2. - Vasoconstriction and aura phase
This phase usually lasts 1-2 hours before the onset of pain; it is characterized by diverse visual disturbances, dizziness and numbness of limbs. This sensation is actually caused by reduced blood flow and therefore oxygen after an arterial vasoconstriction. When symptoms in this phase become noticeable and severe, it is known as **aura phase**; however, only a small percentage of patients suffer it as such.

3. - Headache phase
The third phase is when head pain or **headache** starts; it corresponds to the arterial vasodilation phase. It is a very severe pain that lasts many hours, usually accompanied by pulsating pain. After the first hours of the onset of pain, nausea and vomiting occur.

4. - Resolution phase
The migraine patient tries to relieve the symptoms by falling asleep, but it is not always possible. It can be said that the resolution phase begins with sleep.

5. - Postdrome phase
After the migraine episode, patients present with asthenia, fatigue, weakness and depressive mood.

1.2. TYPES OF MIGRAINE

The definition and classification of migraine has always been difficult, either for the high variability of symptoms among its many patients or for the different episodes observed in the same patient. However, its origin begins to unravel with the support of new laboratory tests and other objective diagnostic markers. This diagnosis improvement shows the current need for optimizing the quality of life of migraine patients. It is an advancement that will benefit all industries that, for one reason or another, are in any way involved in the disease.

Nowadays, the current classification globally accepted by the medical community is that published by the International Headache Society (IHS); it identifies the different types basically based on one very specific symptom associated with the disease, aura. More specifically, the classification is made according to the trigger factor (origin) of the disease. [5]
- Migraine without aura: formerly known as common migraine. It is a condition in which the patient had five or more headache episodes with duration of 4-72 hours without treatment and with two of these qualities: unilateral, pulsating, moderate to severe intensity, worsening due to physical activity, nausea with or without vomiting, photophobia and phonophobia. It is characterized by the absence of focal neurological symptoms. It is more common than migraine with aura.
- Migraine with aura: formerly known as classic migraine. It includes the above-

mentioned qualities but it is also preceded by neurological symptoms in the cerebral cortex or the brainstem. In general, these symptoms develop gradually for 5-20 minutes and they persist 60 minutes at most; they are described above. For people who have migraine with aura, this is a warning sign before the development of headache and pain.

More than 40% of patients with migraine present with both episode types on an alternating basis. However, the occurrence of migraine without aura alone is more common (1 out of 3-4 cases of migraine involves aura). [6, 6.1]

1.3. "TRIGGER FACTORS"

There are many potential factors that are considered as migraine triggers; for this reason, not every patient should be treated similarly. It is influenced by physical, biological and psychological factors.

It is important to know the exact origin of the disease, the root cause as it can facilitate the treatment approach and improve the management of migraine by the patient and the healthcare professional and minimize the effects of this condition[7]; this is why the best migraine treatment starts with an accurate diagnosis.

The following factors are generally identified as triggers :[8]
- Nutrition: The importance of some specific foods has always been discussed in relation to the occurrence of migraine, but the true origin of this connection has never been sought so far; this is the objective of this project.
- Fasting: It has been proven that skipping meals can trigger a migraine, which is related to the previous factor.
- Sleep disorders: Especially due to a lack of sleeping routine because a person is getting either too much or too little sleep. Getting 7-8 hours of sleep and waking at the same time each morning can help prevent some episodes. In fact, there are people who suffer from migraine on holidays, because it is usual to spend more time in bed (commonly known as "weekend migraine").
- Lifestyle: People with migraine are usually very active, which means that certain habits are influenced by a busy lifestyle. A person with migraine should set up, as much as possible, a certain daily routine and avoid any disturbance.
- Stress: It clearly has a connection to the patient's personality; this does not mean that a migraine patient lives under special conditions, but a migraine patient has less tolerance for those situations considered to be stressful. This project will also address the correlation between this condition and a biological origin.
- Hormonal disorders: Three-quarters of migraine patients are women and hormonal disorders are a trigger factor for them. Changes in hormone levels during menstruation and ovulation can trigger migraine episodes. In the case of childhood migraine, the proportion of male and female patients is similar. There is always a balanced proportion of migraine patients during pregnancy and after menopause. The secondary objective of this project is to demystify this statement.
- Environmental factors: atmospheric changes that impact the weather or the temperature, differences in pressure (as during flights), prolonged exposure to fluorescent lights, computer screens, strong odours and high altitudes are other triggers that may be involved in the occurrence of migraine episodes.

Obviously, all these trigger factors can overlap at some point in the same patient. This is why it is important to know the scientific explanation of every possible cause of migraine.

1. 4. NUTRITION, ONE OF THE MAIN BUT UNKNOWN CAUSES

Already at the beginning of the 2nd century A.D., migraine was considered different from common headache; this theory would be described by Dr Areteo de Capadocia. This doctor did not believe in migraine or other diseases medical treatments; he

preferred to use his nutrition expertise to resolve these conditions. [9, 10]

Until well into the 20th century, no importance is given to this key migraine trigger factor. In fact, there are many who still don't believe it. The correlation between nutrition and migraine episodes occurrence has always been taken into account, but this correlation was remote, as it was based on descriptions provided by the patients according to their own experience. For this reason, there are lists of "migraine trigger foods" that had no scientific basis but were equally valid. Throughout all of this time, a balanced diet was recommended to avoid those foods that could trigger episodes at some point.

After establishing this clear correlation, it remains to be seen its real and ultimate origin. So, in order to find out the truth of this matter, a number of questions arise: Why the way in which foods can affect an individual changes from one person to another? What is the difference, since they are the same foods? Where is the problem? Could this difference be caused by the individual rather than the food? Why do we still consider food as the cause of the problem?

This is where genetic factors come in. About 70% of patients have a family history of headache. The risk of migraine in children is about 70% if both parents are affected, 45% if only one parent has migraine, 30% if a family member who is not a parent is affected, and 20% if there is no family history of headache. [10] It is clear that the individual is the answer to this correlation between nutrition and migraine; otherwise, some foods like chocolate (a common food mentioned by migraine patients) would affect all patients equally, and it does not.

The correlation between foods and individuals regarding the occurrence of migraine is currently being explored. It has been observed that histamine-rich foods or those involved in histamine metabolism can cause a number of disorders, including migraine. However, this only applies to people who have a deficient or reduced activity of diamine oxidase (DAO), one of the most important enzymes for histamine metabolism.

II. OBJECTIVES

2.1. Examine nutrition as one of the predominant trigger factors of migraine.
2.1.1. Understand the importance of histamine in the human body and its role related to nutrition factors causing migraine by observing its functions and metabolism.
2.1.2. Find justification for the role of histamine based on individuals with DAO enzyme deficiency.
2.1.3. Relate histamine to foods historically identified as migraine triggers through a case series of patients, as well as other amines and factors that promote the accumulation of histamine.
2.2. Plan a dietary treatment for the accumulation of histamine in patients with DAO deficiency and explain it based on real cases while assessing the outcomes.

III. METHODOLOGY

The research method used in this project consists mainly of an extensive bibliographic research through digital format, book articles and scientific studies.
However, in order to plan a dietetic treatment (one of the key points of this project); in addition to using the bibliography, the knowledge acquired in the academic field will be applied.

IV. RESULTS

4.1. HISTAMINE

Histamine is a molecule derived from an essential amino acid, histidine, and it is produced by decarboxylation through enzyme L-histidine decarboxylase.
Histamine is a biogenic amine, of the aromatic amines family, with physiologic

cell functions. Biologic amines are basic organic nitrogenous compounds of low molecular weight, and have in common the presence of an amino group and the biologic nature. Tyramine, β-phenethylamine, tryptamine and serotonin are included in the group of aromatic amines. (11)

4.1.1. Functions

Histamine has many physiological and patho-physiological functions: It takes part in the regulation of local blood circulation, in capillary permeability, contraction and relaxation of smooth muscles and blood vessels, secretion of hydrochloric acid in stomach, immediate hypersensitivity responses, allergic processes, inflammatory ones as part of the immune response to external pathogens, tissue healing, and its action has also been observed as neurotransmitter in the nervous system.(12,13,14)

Therefore, and taking into consideration its multiple roles, indispensable for the efficient functioning of many metabolic processes, it is not surprising that histamine appears to a higher or lower quantity in a great variety of food, both of animal and plant origin. This is the reason why it is important to know how to control the adverse effects that the accumulation of histamine may cause.

4.1.2. Location

Histamine is produced by all living beings, and it is a natural constituent of tissues, this data have been known since 1927 when Best, Dale, Dualery and Torpe discovered its presence in fresh samples of liver and lung.(15) Therefore, the main histamine source is the human body, i.e. endogenous histamine. Histamine is made from histidine, it is stored in mast cells (immune system cells) and basophils (granulated blood cells) and excreted through the bowel, being degraded when passing through the intestinal mucosa by diamine oxidase (also known as amoloride-binding protein or histaminase), located in this area. The second source is the derived from food. Obviously, the same molecule is involved, but with different functions.
One of the main functions of endogenous histamine is its intervention in the immune system, in allergic reactions. It is synthesized within mast cells and basophils of connective tissue and mucosa, then, it is deposited in its secretory granules ready to be expelled by exocytosis any time the known allergen contacts the sensitized must cell producing the allergic reaction.

Nevertheless, histamine location within the body is not specific, as there are four types of histamine receptors (H1, H2, H3 and H4) in different areas. Type H1 is located in smooth muscle cells membrane in vessels, bronchi and intestinal tract, in heart conduction tissue, in some secretory cells and in sensory nerve endings. H2 receptors are mainly located in parietal cells membrane in gastric mucosa, in smooth cells of vessels, in myocardial cells and sinus node, in basophils and in mast cells where H2 receptors act as autoreceptors. Despite H3 receptors' low-density, presence of this type has been detected in several tissues such as lung, stomach, bowel and pancreas tissues. CNS has the three receptors in histaminergic neurons. (16)

The second histamine source (food), may represent more problems, as its regulation depends on the person. If some alteration in its metabolism occurs and normal histamine concentrations in blood do not remain (50-70 mg/l), free circulation of this amine in high concentrations triggers undesirable effects, such as migraine.

4.1.3. Histamine origin in food

Biogenic amines, including histamine, are formed in food from amino acid precursors by the action of decarboxylase enzymes present in microorganisms. This event does not occur in natural or physiological amines, which are formed during metabolic processes of plants and animals.

In any case, the capacity and intensity to form one or more biogenic amines vary depending on the strain, and it is affected by

the conditions in which they develop.

The possibility of alternative biosynthetic routes and combined participation of different types of microorganisms and their possible interactions makes it more complicated to determine the exact responsibility of amine biogenesis in food. (11)

Therefore, for histamine to grow in food specific requirements are needed:

1. Growth of micro-organisms with decarboxylase activity.

2. Availability of amino acid precursors and cofactors.

3. Favourable environmental conditions for synthesis and decarboxylases activity (pH, Aw, Tª…) (17)

4.2. METABOLISM OF FOOD HISTAMINE

Foods are complex and consist of nutrients that require to be degraded from the moment they enter the oral cavity. Digestive organs carry out the digestion of food thanks to digestive enzymes that reach the intestinal tract through several digestive secretions (salivary, gastric, pancreatic, intestinal and biliary) obtaining the nutrients required for the proper functioning of the organism. (18)

Histamine, a molecule which is present in every food of animal and plant origin, should be metabolized in order to be eliminated by urine without problems. Note that exogenous histamine does not have a functional role within the organism, and for this reason, it is eliminated without using any property.

There are two known main routes of histamine metabolism in living beings, where Histamine N-methyltransferase (HMT) and diamine oxidase (DAO) are implicated.

4.2.1. Degradation by Histamine-N-metyltransferase (HMT or HNMT)

In this route, HMT inactivates histamine by methylation of the imidazole ring forming N-methylhistamine, which becomes N-methylimidazole acetaldehyde by Monoamine Oxidase (MAO) and finally enzyme aldehyde dehydrogenase (ALDH) converts it in N-methylimidazole acetic acid.

HMT is an enzyme that degrades histamine in the liver tissue, but it is also present in lower quantity in other tissues. Many studies establish a small relation of HMT in histamine metabolism in intestinal mucosa, as its activity is almost insignificant compared to DAO activity. (19) According to a study carried out by the University of Extremadura, HMT deficiency is not linked to the appearance of migraine either. (20)

It is a cytosolic protein and therefore, it can only convert histamine in the intracellular space of cells. This proves that its capacity to degrade histamine is lower than the diamine oxidase route, which has a role in inactivation and removal of extracellular histamine; and this confirms therefore that pathologies related to a high histamine concentration in blood, are associated with DAO deficiency and not with HMT. (21)

4.2.2. Degradation via diamine oxidase (DAO)

In this route histamine suffers an oxidative deamination by DAO. The products are imidazole acetic acid and at the end, its riboside. Both metabolites of histamine route, the imidazole acetic acid and the N-methylimadazole acetic acid (of HMT route) have low activity and are removed by urine.

DAO is the most important enzyme that degrades histamine; but it is only located in some tissues; specifically in intestinal mucosa, kidneys, placenta, thymus and seminal vesicles. DAO also has little participation, not always, in the liver tissue. It is mainly located in intestinal epithelium, where it absorbs histamine (endogenous histamine too) and where DAO degrades it controlling the pass into portal blood. DAO located in liver controls the pass of histamine towards systemic circulation and

when it is in the kidney, DAO degrades the reabsorbed histamine in the proximal tubule. (22)

As stated earlier, diamine oxidase is the main enzyme that degrades ingested histamine. Moreover, when DAO acts like a secretion protein, it can be responsible for waste collection after extracellular histamine is released and, therefore, tissues containing DAO are decisive in the systematic control of histamine bioavailability. (21)

Diamine Oxidase is involved in other processes such as regulation of cellular division or differentiation in rapid proliferation tissues (bone marrow and intestinal mucosa), and can act as neurotropic link.

In pregnant females, DAO activity is higher than in not pregnant, from 500 to 1000 times higher. Placenta produces additional DAO amounts as a fetus-protection measure, ensuring correct histamine degradation, and as a result, migraine disappears during pregnancy. (23)

4.2.3. Alteration in the metabolism of food histamine

DAO deficiency is an alteration in the metabolism of food histamine that appears when diamine oxidase (DAO) enzyme activity is low, in other words, when for some reason (see point 4.2.5) there is a significant deficiency in the functional activity of the main enzyme in the metabolism of histamine. The imbalance between ingested histamine and histamine released from the storage cells, and the capacity for histamine degradation, leads to histamine accumulation in plasma and the occurrence of adverse effects on health. (24)

Of these two routes, the most affected is the one that develops via DAO, mainly located in the intestinal mucosa. The other route, within the liver tissue, is less affected as DAO does not always act.

4.2.4. Differentiation of adverse effects

In healthy people, histamine taken with food is degraded quickly by diamine oxidase (DAO) enzyme, but people with low functional DAO activity have the risk of suffering from histamine intolerance or food histaminosis. (21)

A distinction must be made between histamine poisoning and histamine intolerance, as these terms represent two different concepts likely to cause confusion. Besides this, histamine accumulation could also occur as a result of an IgE allergic response or pseudo-allergic without IgE.

In short, all listed cases show an important accumulation of histamine in plasma that gives rise to many adverse effects. However, the most important process that should be explained in detail, in order to distinguish it from the other concepts, is histamine intolerance, since this is the only one related to diamine oxidase enzyme.

4.2.4.1. Histamine poisoning

This occurs due to an excessive ingestion of histamine. During the 50s, it was described as a cause of a food allergy, and even today there are incorrect diagnoses. Currently, this theory has been discarded for two reasons: mainly because the person was not affected in other occasions by the same food product; and secondly because there were outbreaks in which all affected persons who had consumed the food product with an excessively high histamine content, presented symptoms of histamine toxicity.(25)

Epidemiological data is numerous, but dispersed:

In the recent years, the reported cases of this kind of poisoning have increased. During 2003, 9 outbreaks were reported in Spain; by contrast, in 1994 only 6 cases were reported. Moreover, in Catalonia 2 outbreaks were reported between 1982 and 1990, whereas only 3 cases occurred in Barcelona in 2005. (17)

This poisoning is also known as scombroid poisoning or scombrotoxicosis, as this mainly appears due to the consumption of contaminated fish of the Scombridae and Scomberesocidae families, (25) such us tuna, bonito, sardines, fresh anchovy, mackerel

and horse mackerel.[26] It has not been observed free histamine in white fish.[27]
Histamine is formed by the action of the micro-organisms present in the fish muscles. When disturbed, the fish releases the histamine precursor, histidine, and the micro-organisms use this free amino acid to uncontrollably generate histamine. [26]

The two main causes of histamine poisoning are the unsanitary handling of this type of fish and the inadequate storage temperatures. The key for maintaining a low number of bacteria, and thus also of histamine, is to cool immediately after fish capture and maintain adequate temperatures during storage and handling. Some countries have created guide-lines stablishing the maximum histamine levels permitted in fish, but the fact that its concentration can vary from one contaminated of fish to another, make it difficult to lay down some regulatory limits useful for warning of the potential health hazards.[28]

Symptomatology may become substantial, but in most cases symptom pictures are not severe, as not all symptoms are always present, and remit in few hours. However, if histamine concentration reaches 500 ppm, poisoning symptoms may appear in sensitive individuals, and if concentration exceeds 1000 ppm, poisoning is almost assured in any consumer. [26] Taking this data into account, the FDA (Food and Drug Administration) has seen that the minimum toxicity level of histamine is 500 mg/kg in fish. But the limit was stablished at 50 mg/kg, as some parts of the fish have been found to contain higher concentrations than others, i.e. histamine is not evenly distributed.[29] For its part, the European Union has stablished a higher limit, 100mg/kg.
Obviously, this value is not useful for avoiding adverse effects in people with histamine intolerance, as in those cases lower limits should be applied. [17]
Some of the most typical symptoms of histamine poisoning are: hives, redness, nausea, vomiting, diarrhoea, hypertension and headache. [17] These are characteristic signs of food allergy and some of them of intolerance; this is why both concepts can be confused at first sight.

4.2.4.2. Histamine intolerance

Also known as food histaminosis, it occurs when the body has a low capacity to degrade histamine. Many studies carried out during the last 10 years have demonstrated that the factor causing this inability to synthesise food histamine, is the lack of diamine oxidase. A reduced activity of this enzyme, caused by different reasons which are described in the next section, results in histamine accumulation within the body triggering many adverse effects.

Unlike food allergy, the occurrence of symptoms or adverse effects is not linked to the intake of specific food; by contrast it can be related to a wide variety of food with different histamine contents. Symptoms can also occur even after the ingestion of products with low histamine levels. This imposed considerable difficulty when establishing a maximum tolerable dose; in fact, there is no clear consensus on this value.

Values that range from 50µg of histamine (in one serving of wine, 125ml, for example) to 60-75mg, prior pure histamine administration, have been listed as triggers of DAO deficiency symptoms.[17] [19,21,30,31,32,33,34]

Adverse effects caused by histamine accumulation	
Central Nervous System	Migraine, headaches, dizziness…
Cardiovascular System	Hypotension, hypertension and arrhythmia
Epithelium	Hives, oedema, atopic skin, eczema, rash…
Respiratory System	Nose congestion, sneezing, asthma...
Digestive System	Irritable bowel, Crohn disease, diarrhoea,

	stomach pain, nausea, vomiting…
Muscular System	Muscle pain, fibromyalgia
Bone System	Bone pain

Due to the wide variety of symptoms derived from DAO deficiency, which represent chronic pathologies with a high prevalence in population, immediate research and advances on its origin and possible treatments are required.

It is not necessary for all symptoms to manifest, although most patients with low functional DAO activity present other related symptoms, being migraine the prevalent one.[30] 20% of patients experience 1 or 2 of these associated symptoms, 41.3% of patients experience 3 or 4 of these symptoms and 33.8% present more than 5. Migraine is always de most highlighted syndrome when interviewing the patients due to its disabling character. [35]

The most frequent symptoms that normally come across with migraine are:

- Gastrointestinal disorders (constipation, flatulence or swollen feeling).
- Dry or atopic skin.
- Bone and/or muscle pain.
- Unjustified chronic fatigue.

The biological process of food histaminosis is different for each adverse effect, this is why it is necessary to explain how migraine appears, distinguishing it from the other effects.

As it has been said before, migraine is the most highlighted symptom of food histaminosis. This has been compared with a study carried out by the Nutrition and Bromatology Department of the Barcelona University in 2010, which reveals that 95% of patients with migraine have reduced DAO activity.[30] This concluding data reflects an important relation between migraine onset and DAO deficiency which is not relevant in other symptoms. This is one of the reasons why it is important to study the food-borne migraine.

In the metabolism of histamine, it should be degraded by DAO enzyme in order to become N-acetyl aldehyde imidazole; an accumulation of the amine is produced due to the lack of enzyme in the intestinal mucosa cells. Low enzyme activity causes the concentration of food histamine, which cannot be metabolized and a transepithelial permeation of exogenous histamine occurs. This way, histamine enters the bloodstream increasing its plasma concentration and once located in blood it spreads throughout the body, and to the superficial arteries. Histamine acts in this area causing inflammation followed by one of the most common effects, vasodilatation, and migraine process starts. The vasodilatation caused by histamine is linked to the side effects suffered in the Nervous and Cardiovascular Systems mainly, but also in the epithelium. [17, 24]

A recent study presented by the Colomina General Hospital, in Mexico, in January 2011, established the hypothesis of a causal connection between histamine accumulation and migraine onset. It explains a mechanism different from the enzymatic deficiency, but in both cases there is a genetic base. It is linked to histamine H3 receptor, which is the only one present in the Central Nervous System. They confirm that patients with migraine involved in the study, present an allelic variant of H3 receptor compared to the controls, and therefore the receptor is not able to carry out its main function (regulate histamine activity, as well as its synthesis and release mechanisms), resulting in histamine accumulation.[37]

4.2.5. DAO deficiency in patients with migraine

The main cause of the enzymatic dysfunction has a genetic origin.

Some people have or produce few diamine oxidase, this is the reason why until recently, migraine was believed to be hereditary, when in fact; the hereditary

factor is the deficiency of DAO. Moreover, drugs represent another factor that enables histamine decrease, and it is well known that people with migraine normally use drugs as a treatment.

Below 80 HDU/ml (Histamine Degrading Units), DAO activity is considered low. It has been proved that this value represents the minimum amount to ensure a correct histamine metabolism and to avoid adverse effects. Different reasons can cause a deficiency of this enzyme; they can accumulate intensifying the deficiency, and therefore, the symptoms.

4.2.5.1. Genetic factors

Clearly, genetics is one of the factors that causes DAO deficiency. This is why in the same family unit; several members may suffer from migraine.

The enzyme alteration together with the cause of the genetic deficiency, have not been properly studied yet, but it may be related to the genetic polymorphism of a DAO nucleotide. According to the National Centre for Biotechnology Information (NCBI) data, the gene encoding DAO is a polymorphic gene. The genetic sequence of DAO is found in a fragment located on chromosome 7 (7q34-q36) of the human genome and it consists of 5 exons and 4 introns. [38]

Many differences between the sequence of exons and introns of this gene, due to their genetic polymorphism, have been found. In total, there are 85 single nucleotide polymorphisms located and identified in the DAO human gene (17 in exons, of which 7 have substitution of amino acids).

Among all polymorphisms found in DAO sequence, it has been proved that only one of the 7 polymorphisms, (with reference rs1049793) located in the third exon, has relation with low DAO activity.

The discovery was the result of a study carried out in 134 white people, and showed that the individuals carrying this polymorphism, present lower DAO activity than controls with significant effect. Preliminary studies suggested that this polymorphism has an overall prevalence close to 0.30% (30% of mutated alleles).

Other studies on polymorphisms of the same type of substitution of amino acids do not show changes in DAO activity. This is the case, for example, of the polymorphism with reference rs4558339, changing from methionine to isoleucine amino acid; or rs35070995, changing from asparagine amino acid to histidine. In both examples, no further alterations occur in the properties of the enzyme, as amino acids were replaced by others of similar size and attributes.

In 2006, the University of Extremadura together with the Complutense University of Madrid carried out a cohort study to prove whether the polymorphism linked to low DAO activity affects the susceptibility and phenotypic expression of patients with ulcerative colitis (UC). The study involved a total of 490 individuals (229 with UC and 261 healthy volunteers). After 11 years of follow-up, it was confirmed that polymorphism rs1049793 coding for His645Asp, which is the altered protein of DAO enzyme, is related to the severity of UC. Mutation carriers were more vulnerable to suffer from UC and presented higher disease activity. [39]

After seeing the results of this study, in 2008, Complutense University of Madrid, wanted to find out if there exists a higher proportion of the mentioned genetic polymorphism (in the substitution of histidine by aspartic acid) in patients suffering from Crohn Disease (CD), an illness also affected by histamine accumulation in the body. Therefore, this new study would allow knowing if DAO may influence genetic susceptibility to CD and have repercussions on its phenotypic variables.

The epidemiological study involved a total of 212 CD patients and 261 healthy volunteers. Results did not show a clear relationship as there was no difference in the distribution of genotypes between CD patients and healthy controls, and there was

a minimum difference in the mutation between both groups. [19]

However, now it would be necessary to develop an epidemiological study following the same methodology than the previous ones in order to find out if there is a link between His645Asp polymorphism of DAO in patients with migraine.

4.2.5.2. Pharmacological factors

"Natural food products are complex mixtures comprising chemical substances, many of which have not a defined role in human nutrition yet. Most substances without known nutritional function which exist in products that we normally use do not seem to have harmful effects, or they may be present in such small amounts that they do not represent any danger to human health. Nevertheless, in some circumstances these substances may have damaging effects that must be taken into account. Some known substances found in fermented foods are not toxic in normal subjects, but they may be when the subject consuming the food is under treatment with certain drugs that are able to modify their metabolism within the organism."

Francisco GRANDE COVIÁN, 1981

There is a set of drugs involved in the deficiency or low activity of diamine oxidase enzyme. They block or inhibit enzymes involved in the metabolization of histamine, DAO in particular, or release endogenous histamine. This is a very significant risk, since over 90 drugs have been reported to be involved, many of them widely used. It has been estimated that 20% of the population use some of these drugs, increasing the risk of food histaminosis, that will trigger migraine, and of other symptoms or pathologies derived from histamine accumulation.

Moreover, in pathologies such as migraine, an effect of the consumption of these drugs may be the chronification of symptoms, as most drugs prescribed to palliate the effects of the illness are DAO inhibitors or endogenous histamine-releasing drugs. [40]

Some of the reported drugs are: analgesics, antidepressants, antirheumatics, antiarrhythmics, antihistamines and mucolytic, among others, being these last ones used especially in children.

See here below most representative drugs with inhibitory effect on the enzyme degrading histamine, DAO: [40, 41, 42]

Substance class	Active substance
Analgesics	Metamizole, aspirin (acetyl salicylic acid)
Antihistamics	Diphenhydramine, Cimetidine, Promethazine
Antiarrhythmics	Quinidine, Propafenone
Antiasthmatics	Theophylline
Antidepressants	Amitriptyline, tranylcypromine
Antihypertensives	Dihidralazine, Verapamil
Antirheumatics	Acemetacin
Antiseptics	Acriflavine
Antituberculosis	Isoniazid
Bronchiolitics	Aminophylline
Inotropic	Dobutamine
Diuretics	Amiloride, Furosemide
Expectorants	Ambroxol (Mucosán)
Mucolytics	Acetylcysteine (Fluimicil, Frenacil)
Antimalarials	Chloroquine
Antibiotics	Clavulanic acid, Isoniazid (Augmentine, Amoxiplus)
Antiemetics	Metaclopramide (Primperan)
Neuroleptics	Haloperidol
Prokinetics	Metaclopramide
Tranquillizers	Diazepan
Muscle relaxants	Pancuroni

See below most representative drugs with releasing effect of endogenous histamine: [40, 41, 42]

Substance class	Active substance
Analgesics	Acetyl salicylic acid, Meclofenamic acid, Mefenamic acid, Diclofenac,Indomethacin, Ketoprofen, Meperidine, Morphine of animal origin
Anesthetics	Thiopental, Prolocaine, Barbiturates
Antitussives	Codeine
Cytostatics	Cyclophosphamide

Expectorant	Ambroxol
Mucolytics	Acetylcysteine
Muscle relaxants	N-tubocurarine, Alcuronie
Anti-inflammatories	Naproxen

4.2.5.3. Pathological factors

DAO deficiency seems to be more prevalent in population with inflammatory bowel diseases. It has been mainly detected in patients with colon cancer.

It was observed in a study conducted in 1993 in Italy, an important DAO decrease in colon cancer patients. Levels of different amines such as putrescine, spermidine and spermine were investigated, together with their respective enzymes including DAO (also involved in putrescine metabolism). Results showed that DAO was the only component presenting a low activity that impedes degradation of this amine. (43)

Ulcerative colitis and Crohn disease, pathologies with DAO deficiency, are always monitored when developing any study related to endogenous histamine accumulation. When distributing patients in controls and patients with DAO deficiency, those subjects with inflammatory bowel diseases (such as UC, CD, irritable bowel and celiac disease) are usually excluded. These patients present higher permeability in the intestinal mucosa and low DAO activity which can interfere in the results. (44) This was the case of a study conducted in January by the Innsruck University that evaluated a new method for diagnosing histamine intolerance. (45)

DAO deficiency has also been demonstrated in postoperative bowel. Diamine oxidase is mainly located in the small bowel and if part of the mucosa decreases, so does the enzyme production area. (46)

In Crohn's disease patients, where DAO activity in the intestinal bowel is reduced by 50% regarding healthy population, a higher recurrence rate of the disease has been observed after surgery (mainly in those with low enzyme activity). Therefore, DAO is said to be a useful marker to foresee recurrence risks or complications in CD. (19)

4.2.6. Identifying DAO deficiency

After extensive search on the current methods available to detect DAO deficiency in human beings, only two methods have been found.

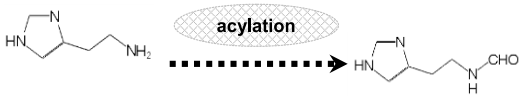
It should be noted that there exists bibliography from the 80s that contains investigations where the measurement of DAO in plasma was proposed as a method to determine the enzymatic deficiency. (47) It has been also found a study of the 90s conducted in rats where the enzyme level in the intestinal mucosa was measured through the expired CO_2, (48). In 2000, rats were used again to measure DAO in plasma (49), and in 2006 radio extraction assays using H3 receptor determined labelled putrescine-dihydrochloride as a substrate. (33)

The tests used nowadays, called D-HIT and DAO-REA, were created by an Austrian Laboratory in 2008, and have been implemented in many European laboratories. D-HIT test applies ELISA technique; using a sample, this test measures the amount of histamine that DAO enzyme is able to degrade, thus evaluating its activity. By contrast, DAO-REA compares biological histamine degradation with putrescine degradation. Find here below the description of D-HIT, as this test is not focused in putrescine metabolism but in histamine: (50)

1. PRINCIPLE OF THE ASSAY:
- 50 µl of patient's serum or plasma may be used as analyte.
- If using plasma, apply a correction factor when making the calculation.
- For first time, with D-HIT, activity of diamine oxidase is determined by degradation of histamine. All essays carried out by now, employed putrescine as a substrate for the enzyme; putrescine is another amine in which DAO is also involved but presents some differences.
- The result is given in HDU (histamine degrading units) per ml. 1 HDU corresponds to the activity of DAO that degrades 1 pmol/ml (0,11 ng/ml) of histamine.
- In the first step 50 µl of sample and 50 µl

of histamine-solution are pipetted in a micro well plate. During the incubation overnight histamine is degraded by DAO present in the sample.

- In the next step the remaining histamine is acetylated.



2. CONTENTS OF THE KIT

- Standard: 6 vials that contain diamine oxidase from porcine kidney, lyophilized. The real activity is stated on the label and in the QC-protocol.
- Control: A single vial that contains diamine oxidase from porcine kidney, lyophilized.
- Incubation Plate. (The wells contain lyophilised histamine).
- Antibody lyophilized
- ELISA-Plate, the wells are coated with acylated histamine.
- Assay Reagent 35 ml, ready to use.
- 4 lyophilized tubs of lyophilized acylation reagent.
- 5ml of acylation diluent (to dilute acylation reagent).
- Assay Buffer 30 ml, ready to use.
- Washing buffer concentrate 60 ml.
- Conjugate 13 ml, ready to use.
- Substrate 13 ml, ready to use.
- Saturated Solution 7 ml, ready to use.
- Instruction manual.
- 4 sealing tapes.
- Quality Control Protocol of the respective batches.
- Protocol sheet.

3. ADDITIONAL MATERIAL AND EQUIPMENT REQUIRED

- Precision pipettes in the range of 30 µl to 1000 µl
- Multichannel pipette
- Incubator 37°C
- ELISA-reader with filter 450 nm (optional reference 620 nm)
- Software for calculation of results

4. PERFORMANCE OF THE ASSAY

As the activity of DAO strongly depends on the actual physical status of the patient, and to avoid incorrect values, it is recommended to carry out the test 2 days after the presence of symptoms of histamine intolerance, i.e. 2 days after the migraine episode.

Freshly collected samples (of serum or plasma) must be cooled to 4°C during 48 hours. For prolonged storage samples must be frozen at –20°C.

After 48 hours, the samples are removed from the cooling zone and should be mixed well before assay performance to avoid erroneous results (lipemic or hemolytic samples). It is recommended that all reagents reach room temperature before use and also recommended duplicates for all determinations.

The steps used in this assay are described below:

Day 1

1. Take needed microtiter strips of **incubation plate** out of the foil pouch (wells may be different depending on the plate, but this fact does not affect test quality). Store the unused strips, sealed in plastic, into foil pouches at 4ºC together with the desiccant (this desiccant bag, with silicate gel beads, shall remain orange; otherwise the material should be discarded).
2. Dissolve **standard** in 0,5 ml of a**ssay reagent**; leave for 15 min at RT (18-26°C), and mix well (Vortex). *Store unused standard up to 3 days at 4°C, for prolonged storage freeze at -20°C. Do not thaw solution more than 2 times*.
3. Dissolve **controls** in 0,5 ml of **assay reagent**; leave for 15 min at RT (18-26°C), and mix well (Vortex). *Store unused control up to 3 days at 4°C, for prolonged storage freeze at -20°C. Do not thaw solution more than 2 times*.

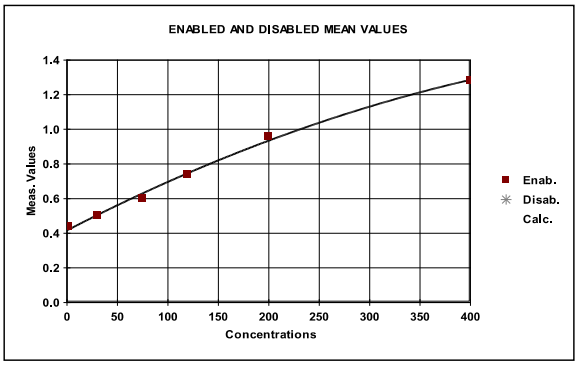
4. Mark in the protocol sheet the wells of the incubation plate used for standard samples.
5. Mix dissolved **incubation reagent** and add 50 µl into each well of incubation plate.
6. Incubate the strips at room temperature (18-26 ºC) during 30 minutes without covering.
7. After that, add each of 50 µl **standards**, **controls** and **samples** into respective wells of incubation plate.
8. Cover strips and incubate over night at 37°C, shake at 400 rpm.

Day 2

9. Dilute **washing buffer concentrate** with aqua deion (60 ml washing buffer concentrate plus 540 ml aqua deion.) *Diluted washing buffer is stable at 4°C until expiry date stated on the label*.
10. Reconstitute **antibody** in 20 ml of a**ssay buffer**. *Store unused antibody up to 3 days at 4°C, for prolonged storage freeze at -20°C*.
11. Reconstitute each **acylation reagent** by mixing it with 1ml of **acylation diluent**. Mixture can be used for 30 minutes.
11. Add 20 µl of the previous mixture to each **well of the incubation plate**.
12. Incubate strips for 30 minutes at 37 ºC (shaker at 400 rpm) without covering with sealing tape.
13. Add 150 µl of a**ssay reagent** to all wells.
14. Incubate strips again for 30 minutes at 37 ºC (shaker at 400 rpm).
15. Take needed microtiter strips of **ELISA plate**.
16. Transfer 30 µl of reaction mixture from incubation plate into respective wells of ELISA plate (use a multi-channel pipette).
17. Add 150µl of dissolved antibody into each well.
18. Cover strips and incubate for 45 min at 37°C on a shaker at 400 rpm.
19. Discard contents of wells and wash 4 times with 350 µl of diluted washing buffer (point 9).
20. Pipette 100 µl of substrate into all wells.
21. Cover and incubate the strips for 30 minutes at 37 ºC on a shaker.
22. Discard contents of wells and wash 4 times with 350 µl of diluted washing buffer (point 9).
23. Add 100 µl of substrate into all wells.
24. Incubate for 15 minutes at room temperature (18-26 ºC).
25. Add 50 µl of saturated solution into all wells.
26. Finally, read absorbance at 450 nm in an ELISA-Reader.

5. CALCULATION

Following the standard results, draw the standard curve. It is recommended to use a specialised program; otherwise, graph paper could be also used. Sample concentration can be observed in this standard curve.



The graphic shows a typical example of the calibration curve. *Results obtained from plasma samples shall be multiplied by the factor 1.25 to adjust matrix effects*.

6. RESULTS

Reference values:
DAO>80 HDU/ml: normal DAO activity
DAO 40-80 HDU/ml: reduced activity
DAO<40 HDU/ml: highly reduced activity

It is impossible to determine histamine intolerance in case of anaphylactic shock and during pregnancy. Also the intake of

alcohol and particular drugs may influence DAO value.

Standard range of results: between 2 and 400 HDU/ml (normally 20-100)
Sample volume: 50 µl serum or plasma
Duration: overnight and 150 minutes
Storage of the Kit: Reagents should be stored at 2 – 8ºC; the rest of the equipment could be stored at room temperature.

4.3. FOOD WHICH INTERFERES IN HISTAMINE METABOLISM

Several foods provoke histamine accumulation in the organism, but not all are necessarily rich in this amine.

Until now, the cause had been searched for in food as during years patients have linked several foods to migraine. Considering all the information disclosed until now, it can be concluded that the origin of this syndrome is in the individual itself, being food the access road of the component that leads to this accumulation.

In order to help histamine accumulation, food labelling has been proposed to indicate its presence, as it is done with those compounds related to food allergies. Only by providing proven existence of people (particularly sensitive) or situations (diseases or pharmacological treatments) that result in histaminosis, food industry will accept the challenge of obtaining low histamine foods, applying production technologies that directly indicate in which stages of the production process histamine is most likely to be formed.(52)

Besides histamine-rich foods, other factors causing histamine accumulation in the organism should be taken into account. Therefore, if histamine-rich foods were labelled, it would seem appropriate to clarify that food is not the only factor interfering in histamine metabolism.
These factors may be other biogenic amines that compete with histamine through the same metabolism routes, endogenous histamine releasing substances or even blocking enzyme diamine oxidase (DAO) components, such as acetyl aldehyde (ALDH) present in alcohol. Like histamine, biogenic amines could be modified applying technologies, but neither the methodology nor its costs have been described yet.
For this reason, it is recommended to follow a diet low in histamine, but not as a single preventative measure, since there are more obstacles to be taken into account. Several parameters should be modified, and this would make achieving a balanced diet difficult.

4.3.1. Histamine-rich foods

There are discrepancies on the criteria that helps consider a food rich in histamine or not.

Some authors suggest eliminating from diet those foods with concentrations higher than 20 mg/kg, while other authors are more demanding and consider low histamine foods those with quantities below 1mg/kg. (52) What is clear, however, is that the symptomatic dose is much lower in histaminosis than in toxicity, 15-20mg and 150mg respectively, since the tolerable dose in both cases is 100mg/kg. (53)

Traditionally, research on histamine contents had been focused on foods related to histamine poisoning episodes, such as oily fish, but this is a mistake since its mechanism of rising histamine levels is different. They are sporadic outbreaks which affect general population as a result of unsanitary food effects.

Even so, in Europe there are some initiatives (ALBA, Allergen databank; TNO Nutrition & Food Research) that seek to provide an exhaustive database about histamine contents in food, due to the decarboxylation of its amino acid precursor, histidine. The downside of this data is that it can vary greatly from one food to another. Histamine and other biogenic amines concentrations in food are highly variable within the same family and even among two samples of the same product. (52)

See below a table of histamine content in food:

Food product	Content (mg/kg)
Eggplant[54]	26
Avocado[54]	23
Alcoholic drinks (red , white and sparkling wine, bottled beer)[52]	nd – 13 nd – 21 nd – 6,3 nd – 2
Chards[52]	nd – 2
Cooked meat (ham)[52]	nd – 5
Champagne[54]	67
Fermented cabbage (sauerkraut)[54]	10 – 200
Spinach[52]	20 – 30
Wheat and rice flour[52]	nd – 5
Goat cheese[55]	nd – 87,1
Cured cheese[55]	nd – 162,1
Emmental cheese[54]	10 – 500
Fresh cheese[52]	nd – 5
Shredded cheese[55]	nd – 556,4
Packed shredded cheese[55]	nd – 1071
Roquefort cheese[54]	2000
Yogurt[52]	nd – 13
Legumes (lentils, chickpeas and beans)[52]	nd – 10
Raw milk[55]	nd – 389,9

nd: not detected.

Values are not properly coincident in any food among different sources, since histamine amount varies depending on the fermentation degree. For this reason, it is difficult to define a specific value for each food product. Taking into account the listed values, it is difficult to keep in our diet only those foods with a maximum content of 20mg/kg, since every product contains histamine.

In addition to this list, we find all those food products that, without being histamine-rich, influence too. In short, those foods that easily get damaged microbiologically, such as meat and fish or products and drinks produced by fermentation and maturation, are likely to present high histamine values. Although in lower concentrations, histamine has also been observed in food products containing blood or viscera, and in some vegetable products such as derived from soya. [52]

4.3.2. Foods rich in other biogenic amines

Biogenic amines are part of the body and catalyst products acting as hormones. All of them come from amino acids metabolism, and therefore, they can be found in every food with moderate or high levels of protein. Amines have a biological nature, hence the name, and present a physiological activity in animal, plants and microorganisms. [56]

Besides histamine, there are other biogenic amines not widely known among population because they do not have such a well-known paper as histamine in allergic processes. However, serotonin, also acts as a mediator in the immune response to allergens

Amines are classified into three groups :[11]

a) Aromatic amines: histamine, tyramine, b-phenethylamine, tryptamine and serotonin.
b) Aliphatic diamines: putrescine and cadaverine.
c) Aliphatic polyamines: agmatine, spermidine and spermine.

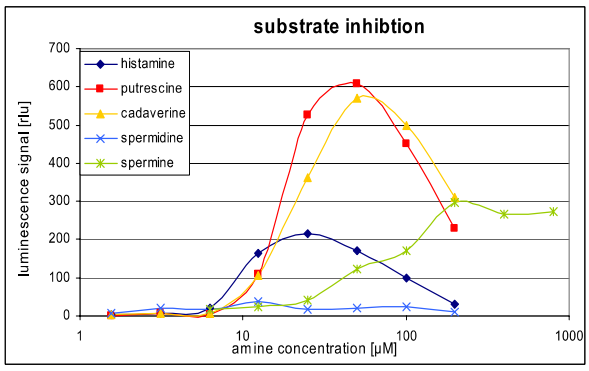
Studies on these amines started in the 60s as a result of the severe hypertensive crisis caused by the interaction between tyramine-rich foods and monoamine oxidase (MAO) inhibitor drugs, basically used as antidepressant [56]. Later on, it has been

observed that amines play a more important role in food intolerances.

Histamine, putrescine and cadaverine appear in higher concentrations in food due to microbiological contamination, by contrast, tyramine is linked to bacteria used in specific fermented products.[11] Moreover, the presence of these amines together with b-phenethylamine, tryptamine, serotonin and agmatine[57] may increase histamine adverse effects, as they compete for the same metabolic routes, at both intestinal and endogenous levels.[17] The Allergy Service of Vall d'Hebron Hospital supports it, and confirms that histamine, tyramine and phenethylamine are vasoactive amines that promote the onset of migraine.

Two studies already mentioned, one conducted by the Medical University of Lodz (Poland) in 2007 and the other by Innsbruck University (Austria) in 2011, also state that DAO is responsible for putrescine degradation. [44, 45]

The same occurs with cadaverine, neither of the two aliphatic diamines present a great biological activity, but they empower histamine intolerance, partially inhibiting DAO activity in histamine degradation process. [58]



Tyramine, derived from tyrosine, stimulates heart activity and blood pressure; which lead to migraine. [58] It has been always reported that tyramine interferes in histamine metabolism through monoamine oxidase route. There exists a lot of bibliography on the adverse effects of food tyramine as a result of an interaction with MAO drugs. However, other studies on DAO deficiency show a relation between histamine accumulation and the intake of tyramine-rich food.

The same occurs with serotonin, derived from tryptophan. Serotonin influences the respiratory rate and volume, the cardiovascular and digestive systems, stimulates the intestinal and stomach smooth muscles, takes part in the carbohydrates metabolism and it is also a neurotransmitter. [58]

In 1994, a team of the Chilean Fisheries Department presented a new indicator named "Bai index" that measures, especially in marine products, the level of some amines. It was observed that the levels of histamine, putrescine and cadaverine increase as product's decomposition progresses. By contrast, spermidine's concentration decreases. [56, 58] Currently, this indicator is called "Quality Index (QI)" and is used to determine fish hygienic conditions. [11]

$$QI = \frac{\text{histamine} + \text{putrescine} + \text{cadaverine}}{1 + \text{spermidine} + \text{supermini}}$$

In 2005, a Catalan group proposed another index that also measured tyramine, but excluding aliphatic polyamines as they do not affect. It was determined that values lower that 5 mg/kg correspond to a fresh product, between 5 and 20 mg/kg to an acceptable product, from 20 to 50 mg/kg to a poor quality product, and if the value is higher than 50 mg/kg the product is decomposed.

Apart from histamine-rich foods, in patients with low DAO activity the high intake of foods rich in other amines such as putrescine, cadaverine, b-phenylethylamine, tryptamine, serotonin, tyramine and agmatine can trigger DAO saturation, avoiding it to degrade ingested histamine properly.

The most competitive amines against histamine to be degraded by DAO are putrescine and cadaverine, since their degradation is quicker than histamine and

they capture the enzyme faster. Therefore, these two amines should be taken into account when planning a diet. (58.1)

Amines amount can be different in each type of food, as in the case of histamine. Depending on the higher or lower presence of biogenic amines, food with the same histamine amount, could trigger symptoms or not. (17) Nevertheless, for symptoms not to appear, specific amounts for amines are established, indicating the maximum tolerable level. However, these amounts only refer to toxicity since values relating the intake of foods rich in amines to DAO saturation have not been established yet, with all the consequences that the effects of food histaminosis will entail. It has only been found that the oral intake of 100-125 mg of tyramine can trigger migraine in susceptible patients, such as patients with DAO deficiency. (11) Toxicity effects may appear in 100-200 ppm of tyramine and 30 ppm of phenyletilamine. A total of 100-200 ppm of biogenic amines. However no conclusive studies have been developed by now. (11) *It has been shown that in the first day of storage, chicken already contains two amines, spermidine and spermine. 15 days later, the rest of amines appear. (58.2)

The fruits that contain higher level of biogenic amines that compete with histamine in order to be degraded by DAO are: Orange, tomato (mainly in sauces), banana, papaya, grapefruit and pineapple. (54)

According to the Biological Sciences' research team of the Institut d'Estudis Catalans, tyramine is found in the flesh of bananas in 7 ppm, and in lower concentrations in oranges, apples, pineapples, potatoes, tomatoes, and spinach. (11) However, orange, as it is one of the most common fruits in the Mediterranean diet, is more often associated with migraine than other fruits, despite having lower tyramine concentration.

Histamine is found in tomato and spinach, and serotonin in egg, banana and tomato. Beans contain dopa, which becomes dopamine within the body. (11)

Taking into account these foods rich in biogenic amines that can interfere in histamine metabolism by saturating DAO function, they can be classified into three groups:(11)

- Food with preformed amines: Food products containing blood or viscera, and some vegetables products (banana, orange, avocado, tomato, spinach, nuts). They are not linked to fermentation or deterioration processes.
- Food that easily deteriorates: Due to the own deterioration or to the rapid growth of microorganisms responsible for its degradation, such as meat and fish in particular.
- Fermented food: Such as non-distilled alcoholic drinks (wine, beer), meat derivatives (cold meat), cheese and vegetable products (fermented cabbage, soya sauce).

4.3.3. Endogenous histamine-releasing foods

This group consists of those foods which release endogenous histamine, i.e. histamine located in mast cells. Its presence causes symptoms similar to those of food allergy, but in this case it is not an immunologic mechanism.

Several foods with this characteristic have been described: alcohol (17), citrus fruits (54), strawberries (54), pineapple (54), kiwi (54), tomato sauce (54), seafood (54), chocolate (54), fish (54), mushrooms (54), pig (59), cereals (59) and egg white (59).

The mechanism that explains the release of endogenous histamine has not been found yet, only stress and several emotional factors have been noted.(44) However, there is an hypothesis that could be related to the high content of histidine (precursor to histamine) in certain foods (such as dairy products, meat, chicken, fish and other protein-rich foods).(60) It would not be strange to think that its accumulation may result in excess histamine, even within mast cell triggering a release not caused by immune factors.

The above mentioned foods, described as endogenous histamine-releasing foods, also contain other amines. Therefore, these foods can cause more severe symptoms than a product which is only rich in histamine. That is why a low-histamine diet would not be enough.

Some food additives such as glutamate, benzoate, several colorants (yellow E-102 and E-110, E-124, amarant E-123), sulphites and nitrites can release endogenous histamine. (54)

According to the Dermatology Department of the University of Bonn (Germany), the intake of endogenous histamine-releasing foods or drugs causes the same symptoms as the consumption of histamine-rich food; diarrhoea, migraine, asthma, hypotension, hives… They are all symptoms of food histaminosis or histamine intolerance. (21)

4.3.4. DAO-blocking foods

This last food group can empower plasma absorption and accumulation of histamine The most important is alcohol, mainly wine and spirits.(60.1) Its metabolizing system interacts with histamine's system, not because both are synthesized by DAO, but because their metabolite, the acetaldehyde (ALDH), competes with N-imidazole acetaldehyde or N-methylimidazole acetaldehyde (histamine metabolites) for the enzyme aldehyde dehydrogenase, both involved in alcohol and histamine degradation.(61) The consequence of this competition is that histamine metabolites build up inhibiting DAO and as a result, histamine levels increase in blood.

Alcohol is one of the most harmful products for people with DAO deficiency. It contains histamine, cadaverine and other amines, it releases endogenous histamine and has the property of blocking DAO, with the possibility of interfering in the metabolism of its own histamine and of the one found in ingested food.

Ethanol intake causes DAO activity reduction, even in healthy people without genetic DAO deficiency, and not only in people predisposed to low DAO levels.(62) Ethanol aggressively attacks DAO, so even with a normal level of DAO (activity higher than 80 HDU/ml) histamine saturation in blood occurs. This is perfectly reflected in the mechanism taking place in the hangover. Most people, even without having low DAO activity, present a typical picture of general discomfort (red eyes, occasional memory loss, vomiting, flatulence, vascular headache, intense thirst, abdominal pain, and even diarrhoea) that encompasses the set of symptoms, and these alcohol effects are due to the increased histamine in blood (61) and most of them coincide with migraine symptoms.

The Centre de Recerca del Metabolisme (CEREMET) of the University of Barcelona together with the Hospital Universitari Tries i Pujol (Can Ruti), are conducting a clinical trial which is focused on the relation between hangover symptoms and DAO activity, since it is believed that if the individual has high concentrations of diamine oxidase with high activity, will not develop hangover.

4.4. CURRENT MIGRAINE TREATMENTS

Migraine has always been treated pharmacologically. Neurologists, who are among the healthcare professionals who treat the highest number of migraine patients on a daily basis, have always considered pharmacological intervention as one major approach; in fact, they do not generally recommend a different approach. Fortunately, an important change is being gradually implemented taking into account nutrition and other non-pharmacological treatments.

Other treatments that are currently being implemented and supported by neurologists include neurostimulator implants and Botox injections in the sinus area. These measures are obviously very aggressive for the body as they can cause diverse symptoms and their efficiency has not been proven. Therefore, they should under no

circumstances be recommended.

Recent research from the last 10 years on the genetic origin of migraine have leaded professionals to choose other non-pharmacological treatment approaches; these treatments aim to resolve the issue at its source, using preventive treatments that include exclusion diets and/or diamine oxidase dietary supplements, as well as palliative care like sinus controlled pressure, acupuncture and more.

As explained above, most currently used drugs can block the DAO enzyme and, in conclusion, it does not make sense to recommend these drugs since they have only proven to cause a vicious circle that is difficult to break.

From the point of view of nutrition and dietetics, a very useful approach can be adopted in the scope of prevention because, as stated above, there are many foods involved that can promote the occurrence of symptoms in people with a genetic predisposition. However, exogenous DAO supplementation will have to be used in order to prevent nutritional deficiencies.

4.4.1. Pharmacological

There are two different pharmacological treatments for migraine. One is a symptomatic treatment for the occurrence of pain to improve symptoms (it will vary depending on whether it is mild/moderate or severe migraine); the other is a prophylactic or preventive treatment, used in patients who suffer more than 3 monthly episodes.

For mild to moderate episodes, analgesics or nonsteroidal anti-inflammatory drugs are used; with or without antiemetic purposes. These drugs aim to stop migraine and symptoms that go along with vascular headache and are present during the episode (nausea, vomiting, tingling, etc.). Simple analgesics are those that block pain and can be purchased in any drugstore without a prescription. Their components include acetylsalicylic acid [$C_6H_4(OCOCH_3)CO_2$], paracetamol [$C_8H_9NO_2$] and metamizole [$C_{13}H_{17}N_3O_4S$].[63] Among these three components, metamizole has been described as a DAO enzyme inhibitor and acetylsalicylic acid as an endogenous histamine liberator. Therefore, they should not be recommended for patients with DAO deficiency.

Anti-inflammatory drugs, as their name implies, can reduce inflammation in blood vessels. This group includes compounds like ibuprofen, naproxen or diclofenac. The latter two have been defined as an histamine liberator and a DAO enzyme inhibitor respectively. Furthermore, they have stomach side effects (gastritis and ulcers).[63] Therefore, they should also not be recommended.

Triptans are used for moderate to severe episodes. They act at presynaptic serotonin 5-HT receptors, located on the wall of the cerebral blood vessels, inhibiting the release of vasoactive and toxic peptides and thus preventing the development and spreading of neurogenic inflammation. They also prevent the vasodilatation in the extracerebral cranial arteries. However, attention should be drawn to the list of adverse reactions, including: sleepiness, dizziness, nausea, fatigue, sensation of heaviness in the limbs, paresthesia and throat and chest tightness. They are contraindicated in cases of severe kidney or liver failure, ischemic heart disease, peripheral vascular disease, stroke, high blood pressure and others.[7]

Major triptans include: Sumatriptan, Rizatriptan, Naratriptan, Zolmitriptan, Eletriptan, Almotriptan and Frovatriptan.[64] Ergotics are also available as a symptomatic treatment, but their use is not recommended as they can cause increased vomiting and nausea and lead to abuse and dependence.

The second type of treatment is called preventive therapy. It responds to the need to reduce the frequency and severity of episodes. This type of treatment consists of taking a drug that can prevent the occurrence of acute migraine attacks; this drug should be used for 3-6 months.

Examples: Sumial, Topamax, Tonopan, Triptisol (antidepressant) and antiepileptics, among others; according to Dr Jordi Pascual i Calvet, neurologist at Hospital del Mar, Barcelona. All these drugs are aggressive and, if the origin of migraine is correctly diagnosed, they are unnecessary.

Apart from these typical and known drugs for the treatment of migraine, since the importance of histamine accumulation is known, the use of antihistaminics for 14 days is recommended. [30] This is a completely counterproductive measure and it is not recommended. These drugs have proven to be DAO enzyme inhibitors and therefore they should not be recommended for patients with DAO deficiency.

4.4.2. Dietary

Once these explanations are known, the importance of exclusion diet therapies becomes clear: low levels of histamine, amines that compete for DAO, endogenous histamine-releasing foods and DAO inhibitors. There are also studies showing the efficacy of low-histamine diets. [21, 65]

Since there are so many proposed restrictions, it is necessary to assess and prioritise the use and avoidance of certain foods in order to prevent nutritional deficiencies. However, as it will be seen further on, this may be a difficult goal to achieve.

A one week diet is proposed so that all the possible combinations can be seen. Fictitious example: 50 years old menopausal woman, normal weight, with diagnosed DAO activity deficiency (below 45 HDU/mL for a more restrictive diet) and migraine symptoms, atopic dermatitis and irritable bowel (three prominent symptoms among these patients).

It seems to be a well-balanced diet with some points that need improvement, but there are many foods involved in the accumulation of histamine (most of them). It seems impossible to plan a diet without these foods, so only the essential ones are removed (histamine-rich, amine-releasing foods and foods with high levels of putrescine, cadaverine and alcohol). If everything is really removed, the result is a poor diet.

It has been decided to exclude or reduce those foods that have the greatest impact in one way or another, but most foods contain amines. This is the case of salted ham (one of the sausage products with the lowest levels of histamine), tomatoes, potatoes, cereals, champignon mushrooms, seafood or chocolate. There are also some foods like chard, olives or legumes that contain histamine, but it is only occasionally present and always in low concentrations, so their exclusion from the diet is not justified. [52]

It was also decided to exclude oranges because it is a very recurrent fruit in her diet and, even if it is not the fruit with the highest levels of histamine, in this case it is very important to take into account histamine accumulation in the body. The same applies to cow milk, because it is a daily use histamine-rich product and it can lead to problems in the long term.

Seafood contained in rice meals, for example, is allowed but it is important to observe how it is tolerated. The same occurs with chocolate; it is an occasional craving but it is required to be dairy-free chocolate, otherwise it would cause symptoms. The same applies to other food products, but it is difficult to know which one is best tolerated in the short term, since amines accumulation occur and most patients only feel some discomfort after a few days of eating that particular food. It does not have a short-term effect.

The professor of Nutrition and Bromatology at the University of Barcelona, M. Carmen Vidal Carou, explains that *it is extremely difficult to plan well-balanced diets with low histamine concentrations*. [65] Therefore, it is clear that this diet, which was planned taking into account every other factor that interfere with histamine metabolism and not only histamine-rich foods, gives rise to doubts about its quality. This is why it is

important to pay attention to essential nutrients.

Efforts have been made to avoid deficiencies by replacing removed foods with other similar foods. If citrus fruits are excluded and the intake level of tomatoes is reduced, a vitamin C deficiency can occur or it can be difficult to reach the recommended daily intake; to prevent this, it was proposed to add red bell pepper to salads, as this food has high levels of vitamin C. For this very reason, it is also highly recommended to avoid smoking because it contributes to oxidative stress.

This is also the case with omega-3, more specifically DHA, as the consumption of oily dish is not enough, linseed is proposed to be added to soy yogurts; as this will not be enough, DHA supplements are also required.

What should be done is to assess, once the diet is implemented, the evolution of the patient within 4 weeks and verify whether she still has the same number of episodes or she has improved[65] (if DAO inhibitor or endogenous histamine-releasing drugs are used, the results would change and could not be objectively interpreted).

After 4 weeks, if the patient has not improved, the diet would need to become more restrictive and, as it becomes more and more difficult to find food substitutes, another method should be used like diamine oxidase enzyme direct supplementation. This supplementation has been recommended in numerous studies. This would allow planning a near-normal diet that would exclude only those foods that cause most problems. As a consequence, the patient would feel better and better over time and she would finally stop their use and reserve them only for an occasional use when an acute episode occurs.

4.4.2.1. Dietary recommendations

Some recommendations are given to the patient along with the diet to facilitate the adherence to the instructions provided. These recommendations are specific for histamine intolerance:

- It is important to follow the diet guidelines to avoid an increased level of blood histamine and avoid the occurrence of migraine and other symptoms.
- A good solution is to consume soybean products as an alternative to dairy products.
- They also contain isoflavones, they improve menopause symptoms and they protect against cardiovascular pathologies, among others. If soy drink is not well tolerated, a different vegetable drink can be used instead, like rice or barley drink, as long as they are enriched with calcium.
- It is possible to replace morning orange juice with a different fruit, like pear or apple. It is possible to make, for example, pear and soy drink shakes as they are very tasty.
- For salads, it is recommended to substitute tomatoes with red bell pepper, as it contains a very high amount of vitamin C and it does not cause histamine accumulation.
- One daily coffee is beneficial for the vasoconstrictive effect of caffeine, so it is recommended.
- For light cooking: steaming, baking, microwave, greased paper, grilling. Avoid heavy cooking (sauces, etc.).
- Eat more whitefish and less oily fish (it is recommended to limit oily fish to 1-2 times weekly). Initially, seafood must be avoided (the amount contained in seafood rice is usually small).
- Eat chicken in moderation. There are other types of meat like ostrich, rabbit, horse or veal (lean parts only). Pork can be consumed, but pork sausage products are not recommended.
- To replace animal protein, in some cases it is possible to use rice with vegetables or vegetarian meat.
- If cereals or bread cause discomfort because of wheat, it should be replaced with another kind of cereal like barley, spelt or quinoa. It is also possible to eat rice or corn "pancakes".

- It is also important to avoid the consumption of alcohol, as it has a multiple effect: high content of histamine and other amines, DAO enzyme inhibitor and endogenous histamine liberator.
It is recommended to use a notebook for taking notes during the 4 weeks about the diet to be followed, state of pain, mood, etc. This will be a useful record to follow the progress.

4.4.2.2. Dietary recommendations

In addition to following a 4-week diet without or low in all factors involved in the accumulation of histamine in the body, and to the dietary recommendations, it is advisable to follow the nutritional guidelines in order to favour an increase of Diamine Oxidase activity through dietary supplements.

Since 1986, the correlation between a potential vitamin B6 deficiency and the lack of DAO activity has been discussed.

Vitamin B_6 is a cofactor for the enzyme, which allows the development of its activity. [66] In 2007, an article published by the Department of Dermatology at the University of Bonn (Germany) recommended taking a supplement of vitamin B6 in order to help migraine patients, since it can increase DAO activity. [21] Currently, it is advisable to give a supplement of 1mg/kg of this vitamin to patients with DAO deficiency. [30]

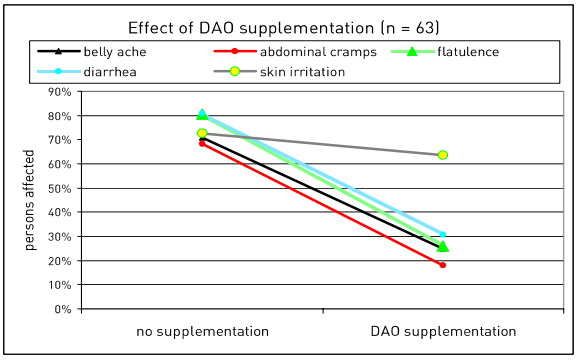
Along with B_6, vitamin B_{12} also acts as an activator and promotes DAO activity. It has been proven that the symptoms of migraine episodes may increase if the intestinal flora is altered by the use of anti-inflammatory drugs, irritant laxatives or antibiotics. As it is known, vitamin B_{12} is absorbed in the intestinal tract and, if the surface is damaged, the vasoactive and psychoactive effects of aromatic amines may cause the onset of migraine. [11]

Another related component is vitamin C. [21] In 1980, a study conducted in 400 patients at the Methodist Hospital in Brooklyn showed that patients whose levels of vitamin C were lower than 1mg/100ml had high levels of histamine in plasma. They concluded that vitamin C deficiency is one of the main causes of high levels of histamine. [67] Vitamin C acts as an antihistamine, destroying the histamine excess. On the basis of these results, plasma concentrations of histamine could decrease with the daily administration of 1 g of vitamin C, as it applies to other pathologies. Additionally, the consumption of vitamin C is recommended since this diet is poor in citrus fruits, which are rich in this vitamin, and the patient might not like peppers.

Another nutritional deficiency is omega-3 DHA (docosahexaenoic acid), found in oily fish. For this reason, it is recommended to take a supplement of minimum one capsule of 1,000 mg of DHA per day, since the recommended daily dose is around 300-400 mg. It is important that the supplement contains only DHA. [67.1]

Furthermore, some studies indicate the importance of copper and zinc in DAO activity. It has been shown that deficiencies of these minerals, which act as enzyme cofactors, may cause a decreased activity of the enzyme and, thus, it would be advisable to consume them as a dietary supplement. [30] Copper is linked to the Diamine Oxidase in oxidation and reduction reactions. [68] Therefore, a dietary supplement of these minerals may be effective, but the potential improvements in migraine patients have not yet been demonstrated by conclusive studies.

Lastly, the Diamine Oxidase enzyme itself is the most innovative dietary supplement and it is expected to reduce the accumulation of histamine in plasma. Even before it was produced, there was already a debate about the beneficial effects of the oral administration in patients with DAO deficiency.



Numerous studies refer to the exogenous administration of DAO as a treatment for food histaminosis —preventing thus the accumulation of food histamine in plasma or the competitiveness with other biogenic amines— since DAO level would enable the metabolization of other amines and it would also prevent a total blocking of the enzyme activity. [31, 69, 71, 72]

This dietary supplement was developed in 2007 by SCIOTEC, an Austrian laboratory mentioned previously in this paper.

A study was conducted in four Austrian medical centres together with the University of Vienna and the Medical University of Graz. This study included three groups: the first group was treated with a capsule of DAO and histamine, the second group with a capsule of DAO with tea, and the third one with placebo and histamine. The results concluded that the oral administration of one capsule of Diamine Oxidase per meal significantly reduced the symptoms of the first and the second group. [69, 70]

The preparation is obtained from the Diamine Oxidase enzyme produced in pig kidney. It seems that there is a high degree of homogeneity between human and swine DAO. This study indicates that DAO is easy to extract and, then, a method of purification with a high performance of the enzyme can be applied to it. Next, the enzyme is stabilized by precipitation at a temperature below 5°C. Additionally, the enzyme is introduced in small, 1mm diameter pellets, covered by a thin protective layer to ensure the enzyme does not become inactive once it gets into the acidic environment of the stomach. Finally, the pellets are introduced in the gelatine capsule, producing the dietary supplement ready to degrade the biogenic amines present in food.

After the capsule intake, it dissolves rapidly in the stomach and the pellets get to the small intestine, where the enzyme is released. [69]

It has been demonstrated that the enzyme degrades amines if they are in quantities equal to or less than 50µm. If the amount is higher, the enzyme is not able to degrade them. [69] This is one of the reasons why, if the patient decides to use this dietary supplement, it is necessary to follow the therapeutic diet or, at least, avoid the most dangerous food products.

Nutritional value for 100 g	
Energy value	342 Kcal / 1432 kJ
Proteins	20.1 g
Carbohydrates	63.1 g
Lipids	< 0.1 g
Protein extract with Diamine Oxidase	1.65 g (4.2 mg for each capsule)

A food supplement developed by a Catalan laboratory containing caffeine (because of its vasoconstrictor effect), vitamin B_6 and vitamin B_{12} has come out in the market.

After taking a look at the results in Austria and the prevalence observational study that was conducted in Barcelona in 2010, a double-blind study will be carried out by the General Hospital of Catalonia and the Nutrition and Bromatology Department at the University of Barcelona, where the effect of the exogenous administration of DAO in migraine patients will be directly addressed

4.4.3. Non-pharmacological palliative treatments

One of the techniques that has always been used and still is, and that can be performed

by the patient, is applying pressure to the temples (with the fingers or other methods). Nowadays, non-pharmacological new techniques are available. A study conducted by the Cagliari University Hospital (Italy) in 2009, showed that the prolonged compression of the superficial temporal arteries —the area where the greatest sensation of pain focuses— using a device, relieved the pain in a high percentage of migraine attacks. It was seen, from a group of 22 patients, that the number of migraine attacks decreased from 125 —during the month prior to the first use of the device— to 27, two months later.(73)

In 2008, the Spanish Association of Patients with Headache (AEPAC) already supported one of these new solutions to relieve the pain caused by vascular headache; it consisted of a plastic headband made by a Catalan laboratory. This device applies controlled pressure to the temples in order to produce a sense of relief from the very start, stopping the pain from vascular headache.(7) This headband was supported a year later by the Faculty of Medicine of the Autonomous University of Barcelona and the Vall d'Hebron University Hospital and is currently sold in pharmacies.(74)

4.5. RESULTS OF THE DIETARY TREATMENT IN REAL CASES

On the basis of the information obtained to elaborate this project, we have been able to put the theory into practice in patients diagnosed with DAO Deficiency that presented a variety of symptoms, most frequently migraine.

Below, there are three real cases of patients with DAO deficiency, a brief description of their habits, some changes we made and the results achieved. All three patients suffered from migraine and had other symptoms related to the accumulation of histamine — very frequent in this pathology.

Case nº1: Female – 37 years old – Symptoms: Migraine, dermatitis and feeling of swelling

During the dietary interview, we could perceive that she was not on a balanced diet and, most importantly, she was following a diet rich in histamine and other amines. In one single day, she had a high consumption of milk, citrus fruits and factory baked products. Therefore, the first dietary intervention was to replace these foods for other products, such as calcium rice drink (we considered soya drink but she also suffered from poor digestion), fruits with low levels of histamine, corn toasts and whole-grain crackers. Besides, we prescribed her the dietary supplement "Migrasin" for the weekends —she always had lunch with her family in restaurants, where the elaboration of food is often unknown—, on special occasions and celebrations, as well as for those days when she fancied a histamine-rich product that was listed as histamine or other amine-rich food.

After a month and a half, she came up for a second visit and the results were very good. She had not suffered any migraine episode —which was actually very unusual in their everyday life—, her skin had improved significantly and the feeling of swelling had disappeared. The only issue that remained was some flatulence, which disappeared after some specific recommendations.

Case nº2: Female – 36 years old – Symptoms: Migraine, muscle problems, feelings of swelling and dry skin

This profile is indeed similar to the last one, but it is common for this enzymatic deficiency. The first time she came to the examination room she was on a slimming diet which was not really balanced and based on some misconceptions. The consumption of amino-rich foods consisted on strawberry jam every morning, semi-cured cheese every mid-morning, orange juice before dinner and some oily fish per week. In this case, the patient did not want to establish a diet because she was on one; she preferred just some guidelines and recommendations she could apply by herself. We tried to make the diet more

balanced by filling empty slots during the day with foods with low content of histamine and other amines; we replaced other foods and recommended "Migrasin" when necessary as a complement and "Daosin" (caffeine-free product) together with some meals at dinner.

She felt better in less than a month. The migraine episodes decreased, they went from being almost daily to sporadic and of lower intensity. The skin hydration improved significantly and the feeling of swelling disappeared in a few days. She also experienced an improvement in the muscular load.

Case nº3: Male – 41 years old – Symptoms: Migraine and poor digestions

He had recently undergone a blood test to detect the functional deficiency of the Diamine Oxidase enzyme. The results showed that there was a very limited activity. Then he started to change his diet based on suggestions he found on the Internet. Still, migraine did not disappear and his digestions did not improve.

At the end, he came to the examination room. He still used to consume strawberries every day after lunch and he drank milk every morning. Both strawberries and milk are not especially rich in histamine, but their daily ingestion causes amine to accumulate and makes them impossible to degrade, which triggers symptomatology. We changed these two foods and some others and introduced a supplement of exogenous DAO.

He experienced a noticeable improvement in short time as well and now the migraine episodes belong to his past.

V. DISCUSSION

After considering all the objectives and opinions of some authors about this topic as well as the importance of migraine nowadays, we can sense that there is still a need for many validated scientific theories in both social and professional sectors in which migraine is present.

First, there are discrepancies among authors even in the definition of "migraine" itself. Different publications describe it as an illness, others as a syndrome. After studying what migraine really involves, it has been concluded that it should be considered a syndrome, as it is a group of symptoms, and not an illness that triggers a group of symptoms. Thus, each symptom should be considered independently in order to find out its origin.

Symptoms are perfectly recognizable and they are mainly gastrointestinal (nausea, vomits, irritable bowel syndrome...), epithelial (atopic dermatitis...) and cerebral (constriction and dilation of vessels that prevent oxygen from reaching the brain which produces photophobia, phonophobia, tingling in the limbs and, obviously headache, the most incapacitating symptom).

It is important to clarify the origin of these symptoms and some studies around the world have been focused on this. A possible origin of all those symptoms could be related to a deficiency of the Diamine Oxidase enzyme in the intestinal mucosa. The cause can be either genetic or, less likely, as a result of taking some drugs. So it is pointless to keep on stating that digestive symptomatology can arise from vascular headaches. That is not reasonable. However, it is logical to talk about a common origin: the accumulation of histamine in the plasma, which triggers the multiple issues that migraine can involve. Why, after this has been proved, we continue hearing the same speech?

The reason why at the beginning of this paper we have listed some possible factors that could cause migraine is because some external factors are still considered its main cause, despite the fact that many recent studies conclude that migraine could be mainly caused by genetic factors or the effect of some drugs.

Another important issue is the difficulty to find reliable lists of foods that contribute to increase histamine in the body. It is true that this point of view is very recent and that more analysis are required in order to confirm data, as they may vary depending on the source (taking into account that the samples are different). Due to the importance of this topic, it would be necessary to establish a final list including those foods. This way, foods could be labelled including the content of histamine or other important amines.

In short, we should aim to guarantee that food labels include every ingredient or substance present in the final product, including those identified as possible triggers of histamine intolerance. It would be helpful for consumers with DAO deficiency because they would be able to identify the ingredients to which they are sensitive.

Finally, after seeing the possible treatments, another issue arises. A reflexion should be made and food industry should set new objectives in this sense. It is clear that drug treatments are risky for patients suffering from migraine as they prevent them from healing or improving. For this reason, it would be necessary to take a step further and bring up new proposals. Some years ago, the food industry was already suggested to develop foods with low content of histamine and, if possible, of other amines as well. For now, this has not been implemented but it would be a great solution. The other option would be to consider developing functional products containing Diamine Oxidase enzyme which would help our body to better metabolize food. Patients could be on a diet based on low ingestions of foods causing histamine to accumulate in the plasma. However, this diet would not need to be totally strict, which will avoid nutritional deficiencies.

There are no known functional foods containing DAO, but some bibliography states that it could be added to any product like yoghurts, milk-based beverages, ice-creams, juices, soya drinks, other vegetal drinks, cereals... and it could be added, as powder, in microcapsules or nanocapsules (best option to avoid premature degradation in the stomach).

VI. CONCLUSION

At the end of this paper, all the initial questions have been answered. Our aim now is to continue researching, finding out and even suggesting new studies or publications that could somehow explain a decrease of migraine episodes caused by a deficiency of diamine oxidise enzyme due to a therapeutic diet. It would also be necessary, as recommended in one of the sections of this paper, to carry out an epidemiologic study in order to find out if it could be connected to the polymorphism of the amino acid His645Asp of the DAO enzyme in migraine patients.

The first objective, to go into detail about the food-related origin of migraine, has been achieved thanks to different proves that have been shown along this paper. Foods are the vehicle of components that trigger migraine symptoms. This point of view is new in many sectors, which still consider some foods as its cause. It has been proved that those foods, although they contain the main triggers, are not the main factors by themselves.

In order to get to know how these foods work inside our body, it was necessary to state what really causes the activation. One of the objectives here was to explain the role of histamine in the food-related migraine, studying its functions and metabolism. In addition, the role of histamine in migraine has been proved in patients showing a decreased activity of the DAO enzyme. The prevalence was higher in women, which demonstrates that, genetically, women have less DAO. This proves that the higher average of women suffering from migraine is not due to hormonal factors.

We tried to point to what happens in the body of this people and the situation is supposed to be clear. Later, histamine has been related to foods traditionally classified as migraine triggers due to patients' casuistry and pure biochemical research. Apart from that, all other components and factors contributing to the accumulation of histamine have been shown, which helps to get to know the whole process and not only a part.

Finally, we have suggested a dietetic treatment for those individuals suffering from migraine due to a DAO deficiency. We have seen that a strict diet with no trace of factors that could contribute to histamine accumulation is practically impossible because many foods are involved. We suggested, then, a diet with a low content of the most relevant foods and, at the same time and in order to avoid the appearance of any symptom, to introduce an exogenous dietetic supplement of DAO enzyme.

VII. BIBLIOGRAPHY

(1) STOVNER, L.J. [et al.] *The global burden of headache: a documentation of headache prevalence and disability Worldwide*. Cephalalgia, Vol 27. 2007.

(2) PÉREZ, D. *Impacto sociosanitario de las enfermedades neurológicas en España - La migraña*. [On-line]. Madrid: Fundación Española de Enfermedades Neurológicas, 2010. <http://www.feeneurologia.com/html2/index.php?option=com_content&view=article&id=118%3Aimpacto-sociosanitario-de-las-enfermedades-neurologicas-en-espana&catid=42%3Adocumentos-feen&Itemid=167&limitstart=8> [Accessed: 20 April 2011]

(3) *La migraña le cuesta a España dos mil millones de euros*. [On-line]. Madrid: elEconomista.es, 2011. <http://www.eleconomista.es/gestion-empresarial/noticias/2436170/09/10/La-migrana-le-cuesta-a-Espana-dos-mil-millones-de-euros.html> [Accessed: 22 April 2011]

(4) LOE, A. *Cefaleas*. [On-line]. Buenos Aires: Acupuntura Médica, 2011. <http://www.acupunturamedica.com/detalle.asp?indice=22 > [Accessed: 2 May 2011]

(5) DAHLEM, M. MIGRAINE AURA FUNDATION. *Migraine classification* [On-line]. Berlin: The International Headache Society, 2005. <http://www.migraine-aura.org/content/e25968/index_en.html> [Accessed: 29 December 2010]

(6) SHETH, K. *Migraña*. [On-line]. Baltimore: MedlinePlus, 2010. <http://www.nlm.nih.gov/medlineplus/spanish/ency/article/000709.htm> [Accessed: 22 April 2011]

(6.1) *Migraña con Aura*. [On-line]. Madrid: Sociedad Española de Neurología, 2005. <http://cefaleas.sen.es/publico/migran_con_aura.htm> [Accessed: 24 April 2011]

(7) *Factores desencadenantes*. [On-line]. Barcelona: DRHealthcare, 2007. <http://www.migracalm.net> [Accessed: 27 April 2011]

(8) *Migraine Triggers*. [On-line]. Berkeley: University of California. <http://docs.google.com/viewer?a=v&q=cache:rzoe5_nHrv8J:uhs.berkeley.edu/home/healthtopics/pdf/triggers.pdf+http://uhs.berkeley.edu/home/healthtopics/pdf/triggers.pdf&hl=ca&gl=es&pid=bl&srcid=ADGEESiSvJZu6Ueiyqnlv5_J72OARE7lrw7uXfShy5NmLcfk7bEoIIov5hqwcnpbHUZLJZBzsBwzhSmvmMlmkS69LKrumyB9oJrIOOCf6I9mRg_IAHOEtVYHhxVap9culWFhsL58cEus&sig=AHIEtbTjFmj7ahEcyz8O5KjwIBqS0tgAzw> [Accessed: 29 April 2011]

(9) *Médicos romanos del siglo I: Celso y Dioscórides*. [On-line] 2000. <http://www.cinicos.com/medicos.htm> [Accessed: 1 May 2011]

(10) *Migraña*. [On-line]. Madrid: Neurowikia (Sociedad Española de Neurología), 2011. <http://www.neurowikia.es/content/migrañ-0> [Accessed: 1 May 2011]

(11) MARINÉ FONT, A. *Les amines biògenes en els aliments: Història i recerca en el marc de les ciències de l'alimentació*. [Barcelona]: Institut d'Estudis Catalans, 2005. ISBN 84-7283-788-2

(12) *Histamina*. [On-line] Biopsicología.net, 2011. <http://www.biopsicologia.net/fichas/page_132.html> [Accessed: 3 May 2011]

(13) *Histamine Molecule*. [On-line]. London: Science Photo Library, 2010. <http://www.sciencephoto.com/images/imagePopUpDetails.html?pop=1&id=670032945

&pviewid=&country=56&search=amine&matchtype=EXACT>
[Accessed: 5 May 2011]

(14) Histamina. [On-line]. Ferato, 2010.

<http://www.ferato.com/wiki/index.php/Histamina> [Accessed: 5 May 2011]

(15) THORPE, W.V. *Vasodilator constituents of tissue extracts: Isolation of histamine from muscle*. Biochem J. (1928) ;22(1):94-101.

(16) PAZOS, A. *Mediadores celulares I. Histamina y 5-hidroxitriptamina*. Farmacología de la migraña.

(17) VIDAL CAROU, M.C. *Intolerancia a la histamina: Una nueva perspectiva para el viejo problema de la histamina i otras aminas biògenas en los alimentos*. 4ª reunión de la Sociedad Española de Seguridad Alimentaria, 2007.
<http://www.sesal.org/documents/Vidal-M-Carmen.pdf> [Accessed: 5 May 2011]

(18) GODALL i CASTELL, M. "Capítol 2: Digestió dels aliments". A: *Biologia Humana: Fonaments biològics per a Diplomatures de la Salut*. Barcelona: Biblioteca Universitària, 1996. P.297.
ISBN 84-7306-739-8.

(19) LOPEZ PALACIOS, N. *Estudio del polimorfismo genético de un solo nucleótido no sinónimo de la diamino oxidasa (refsnp id RS1049793) en la enfermedad de crohn*. [Madrid]: Universidad Complutense de Madrid, 2008.

(20) GARCIA MARTIN, E. *Histamine-N-methyl transferase polymorphism and risk for migraine*. [Madrid]: Universidad de Extremadura, 2008.

(21) MAINTZ, L.; NOVAK, N. *Histamine and histamine intolerance*. American Journal of Clinical Nutrition, Vol. 85, No. 5, 1185-1196. Bonn (Germany), 2007.

(22) AYUSO P, GARCIA-MARTIN E, MARTINEZ C, AGUNDEZ JA. *Genetic variability of human diamine oxidase: occurrence of three nonsynonymous polymorphisms and study of their effect on serum enzyme activity*. Pharmacogenet Genomics 2007;17(9):687-93.

(23) *Effects of histamine and diamine oxydase activities on pregnancy: a critical review*. Oxford Journals, Human Reproduction Update, Vol. 14. 2008.

(24) SOTA OMOIGUI, M.D. The *Biochemical Origin of Pain: The origin of all Pain is Inflammation and the Inflammatory Response. PART 2 of 3 – Inflammatory Profile of Pain Syndromes*. Los Angeles, 2007.

(25) APREA, P.; ALETTI, S.; CHIALE, C. *Intoxicación histaminica por consumo de pescados*. Instituto Nacional de Medicamentos. Buenos Aires, 2003.

(26) NIVEN, C.F.; JEFFREY, M.B.; CORLETT, JR. *Differential plating medium for quantitative detection of histamine-producing bacteria*. Pub Med Central, 1981.

(27) PAN, B.S.; JAMES, D.G. *Histamine in marine products: production by bacteria, measurement and prediction of formation*. Rome (Italy), 1985.

(28) LEHANE, L.; OLLEY, J. *Histamine fish poisoning revisited*. [Austràlia]: National Office of Animal and Plant Health, Agriculture, Fisheries and Forestry, 2000.

(29) *FDA & EPA Safety Levels in Regulations and Guidance*. U.S. Department of Heath & Human Services. 2001.
<http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/Seafood/FishandFisheriesProductsHazardsandControlsGuide/ucm120108.htm>
[Accessed: 9 May 2011]

(30) VIDAL, C.; TITUS, F.; GUAYTA-ESCOLIES, R. *Evaluación del Déficit de DiAminoOxidasa (DAO) en pacientes con*

migraña. *Estudio MigraDAO*. Barcelona, 2010.

(31) SCHWELBERGER, H.G. *Histamine intolerance: a metabolic disease?*. Suïssa, 2009.

(32) MAINTZ, L. [et al.]. *Effects of histamine and diamine oxidase activities on pregnancy: a critical review*. Bonn (Germany), 2008

(33) MAINTZ, L.; BENFADAL, S.; ALLAM, J.P. *Evidence for a reduced histamine degradation capacity in a subgroup of patients with atopic eczema*. Bonn (Germany), 2005.

(34) ALLERGY UK. *Histamine intolerance*. Kent (UK), 2011. <http://www.allergyuk.org/fs_histamine.aspx> [Accessed: 11 May 2011]

(35) Síntomas de la migraña. [On-line]. Barcelona: Biofuncionalismo, 2011. <http://biofuncionalismo.com/> [Accessed: 12 May 2011]

(36) *Síntomas de histaminosis alimentaria*. [On-line]. Barcelona: Biofuncionalismo, 2011.<http://biofuncionalismo.com/wp-content/uploads/2011/02/histamina1.jpg> [Accessed: 12 May 2011]

(37) MILLÁN-GUERRERO, R.; RODRÍGUEZ, B. *A280V polymorphism in the histamine H3 receptor as a risk factor for migraine*. Colima (Mexico), 2011. <http://www.ncbi.nlm.nih.gov/pubmed/21376262>

(38) *ABP1:amiloride binding protein 1*. [On-line]. <http://egp.gs.washington.edu/data/abp1/> [Accessed: 14 May 2011]

(39) GARCÍA-MARTÍN, E.; MENDOZA, J. *Severity of ulcerative colitis is associated with a polymorphism at diamine oxidase gene but not at histamine N-methyltransferase gene*. España, 2006.

(40) *Histamine intolerance: medicines*. [On-line]. Amsterdam: Histamine Intolerance, 2011. <http://www.histamine-intolerance.info/medicines.php> [Accessed: 14 May 2011]

(41) *Medicamentos inhibidores de la enzima DAO*. [On-line]. Barcelona: Biofuncionalismo, 2011. <http://biofuncionalismo.com/la-histamina-y-los-medicamentos/> [Accessed: 14 May 2011]

(42) WILD SCHOLTEN, M. *Medicines which must be avoided by patients with histamine intolerance*. Holanda, 2010.

(43) LINSALATA, M. [et al.]. *Polyamines, diamine oxidase, and ornithine decarboxylase activity in colorectal cancer and in normal surrounding mucosa*. Bellis (Italy): Publmed, 1993.

(44) FOGEL W.A.; LEWINSKI, A.; JOCHEM J. *Histamine in food: is there anything to worry about*. Poland, 2007

(45) KOFLER, L.; ULMER, H.; KOFLER, H. *Histamine 50-Skin-Prick Test: A Tool to Diagnose Histamine Intolerance*. Austria, 2011.

(46) ROKKAS, T.; VAJA, S. *Postheparin plasma diamine oxidase in health and intestinal disease*. London, 1990.

(47) LEGGE, M; DUFF, G.B. *Plasma diamineoxidase levels in pregnancy complicated by threatened abortion*. New Zeland, 1981.

(48) BAMBA, T.; SASAKI, A.; HOSODA, S. *Evaluation of diamine oxidase activity (DAO) in the rat intestinal mucosa by measuring expired $^{14}CO2$ after oral administration of ^{14}C-putrescine*. Japan, 1993.

(49) KEHOE, C.; FAUGHNAN, M.; GILMORE, W. *Plasma Diamine Oxidase Activity Is Greater in Copper-Adequate than Copper-Marginal or Copper-Deficient Rats*.

Irlanda, 2000.

(50) SCIOTEC. *Enzyme immunoassay for the quantitative determination of histamine-degradation activity by DiAmineOxidase (DAO) in serum and EDTA-plasma*. Austria, 2008.

(51) ORGANIZACIÓN PANAMERICANA DE LA SALUD. *Manual de mantenimiento para equipo de laboratorio*. [Whashington], 2005. P. 16-18. ISBN: 92 75 32590 1

(52) VECIANA NOGUÈS, M.T.; VIDAL CAROU, M.C. "Dieta baja en histamina". A: *Nutrición i dietética clínica*. Barcelona: Elsevier Masson, 2008. P. 443 – 451. ISBN 978 84 458 1843 5

(53) LATORRE MORATALLA, M.L. [et al.]. *Histamina i otras aminas biógenas en queso rallado*. Santiago de Compostela, 2007.

(54) SCIOTEC. *DAOsin. Histamingehalt unterschiedlicher Nahrungsmittel*. Vienna: 2008.

(55) NOVELLA-RODRÍGUEZ. [et al.]. *J. Food Science*. 68, 750-55, 2003.

(56) BOVER-CID, S. *Aminas biógenas en producto cárnicos: un repaso a su origen, importancia y control*. Barcelona, 2005.

(57) G. SCHWELBERGER, H. *Metabolism of histamine*. <http://docs.google.com/viewer?a=v&q=cache:OmmSqr5dZWMJ:www.ehrs.org.uk/schwelberger.pdf+http://www.ehrs.org.uk/schwelberger.pdf&hl=ca&gl=es&pid=bl&srcid=ADGEESjyURmgkct0dwfVRJTmV0tPYZ1yF4C6z0fbvjZnPmQDorFbXP5Zdc75whDokQV0cAHUo7XOwex5nkDmljnozvJ2FEP38KZq2oKATpU6LNVUeGfe1aXpbwcMxzbPFzfrth8YpMvj&sig=AHIEtbQ2TBn16WWpfQT3Pe4Kck6NslLUOw> [Accessed 12 May 2011]

(58) GALLEGUILLOS, M. *Aminas biogenicas*. [On-line]. Santiago de Chile, 1994. <http://www.fao.org/docrep/field/003/AB482S/AB482S22.htm> [Accessed 16 May 2011]

(58.1) FISTERER, M. [et. al.]. Diagnosis and Treatment of Histamine Intolerance. Heilbronn (Germany), 2007.

(58.2) CRISTIANE, M.G. [et. al.]. *Bioactive amines in Chicken breast and thigh alter slaughter and Turing storage at 4 +/- 1ºC and in Chicken-based meat products*. Brasil, 2001.

(59) NEGRO ALVAR EZ, J.M; MIRALLES LOPEZ, J.C. *Alimentos que pueden producir una urticaria aguda por mecanismo NO Alérgico*. Murcia, 2004.

(60) *Histidina*. [On-line]. Jackson (Mississipi, USA): Baptist Health Systems, 2011. <http://www.mbmc.org/healthgate/GetHGContent.aspx?token=9c315661-83b7-472d-a7ab-bc8582171f86&chunkiid=125017>[Accessed 16 May 2011]

(60.1) MORENO-ARRIBAS, M.V. Instituto de Fermentaciones Industriales, CSIC. *Control de la formación de aminas biógenas durante la elaboración y crianza del vino*. Madrid, 2007.

(61) ZIMATKIN, S.M; ANICHTCHIK, O.V. *Alcohol-histamine interactions*. Grodno, 1999.

(62) JARISCH; WANTKE. "Wine, heath and food: Headaches". A: *Wine Science: principles, practice, perception*. EUA, 2000. P. 598. ISBN 0-12-379062-X

(63) SÁNCHEZ DE ENCISO, M. [et. al.]. *Migraña o jaqueca*. [On-line]. Lugo: Fisterra Salud, 2011. <http://www.fisterra.com/salud/1infoconse/migrana.asp > [Accessed: 16 May 2011]

(64) SHETH, K. *Migraña*. [On-line]. Baltimore: MedlinePlus, 2010.

<http://www.nlm.nih.gov/medlineplus/spanish/ency/article/000709.htm>
[Accessed: 16 April 2011]

(65) WANTKE, F.; GÖTZ, M.; JARISCH, R. *Histamine-free diet: treatment of choice for histamine-induced food intolerance and supporting treatment for chronic headaches*. Àustria, 1993. [Accessed: 22 November 2010]

(66) MARTNER-HEWES, P.M. [et. al.]. *Vitamin B-6 nutriture and plasma diamie oxidase activity in pregnant Hispanic teenagers*. Los Angeles, 1986.

(67) ALAN, C.; CLEMETSON, B. *Histamine and Ascorbic Acid in Human Blood*. New York, 1980.

(67.1) *NuaDHA 1000*. [On-line]. Logroño: Nua Biological Innovations SL, 2011. <http://www.nua-dha.com/> [Accessed: 14 June 2011]

(68) GRUNDON, N. [et. al.]. *Nutrient deficiency and toxicity symptoms*. Vic.: CSIRO Publishing. 1997. p37 – 51.

(69) MISSBICHLER. A. [et al.]. *Supplementation of enteric coated Diamine Oxidase improves intestinal degradation of food-born biogenic amines in case of histamine intolerance*. Vienna, 2010.

(71) Histamine Intolerance. [On-line]. Viena (Àustria): Nutridis, 2011.
< http://www.nutridis.at/eng/histamin.shtml > [Accessed: 19 May 2011]

(72) KOMERICKI, P. [et al.]. *Histamine intolerance: lack of reproducibility of single symptoms by oral provocation with histamine: a randomised, double-blind, placebo-controlled cross-over study*. Vienna (Austria): Publmed, 2010.

(73) CIANCHETTI, C. [et. al.]. *Tratamiento de los ataques de migraña mediante la compresión de las arterias temporales superficiales empleando un dispositivo*. Cagliari (Italy), 2009.

(74) *Migracalm: Valoración médico-legal y neurológica de su difusión informativa como producto sanitario para tratamiento paliativo de las migrañas* [Spain] Vol. 5 (2009), núm 1. ISSN: 1697-543X