Table 6. *Cont.*

Study	Trial Design	Intervention	Control	Sample size	Duration of Intervention	Reported Outcomes
Izquierdo-Casas, 2019	Randomized DBPC study	3 × 0.6 mg DAO	Placebo	82	C1 without an intervention (30 days) + C2 with intervention (30 days)	A significant reduction in number ($p < 0.001$) and duration ($p < 0.05$) of migraine episodes in intervention group compared with baseline. A decrease in the percentage of patients using selective 5-HT receptor agonists (triptans).
Schnedl, 2019	Open label interventional study	3 × 0.3 mg DAO	N/A	28	28 + 28 (follow-up)	Significant reduction in frequency and intensity of symptoms. 61% of patients showed mild increase in serum DAO levels (NS). During follow-up, without DAO supplementation, the symptoms sum score increased again and serum DAO levels slightly decreased.

Despite the promising results, studies dealing with DAO exogenous supplementation are scarce. In addition, the studies conducted investigated only a small sample of patients. It is therefore necessary to confirm the clinical significance of exogenous supplementation of the DAO enzyme by more robust, well-designed clinical trials.

Other Potential Sources of DAO

DAO need not be necessarily of animal origin. In 2020, Comas-Basté carried out screening of the ability of the family of the *Leguminosae* (legumes) plant to break down histamine. The goal was to identify plants with DAO enzyme activity (in vitro) and then to consider their potential usage as an active component of enzyme supplements. Lyophilization of the sprouts kept their enzyme activity unchanged for at least 12 months. The results show that in the future certain edible legumes could be suitable for the manufacture of supplements with DAO content for the management of HIT [83].

3.3. Antihistamines

The treatment of patients with antihistamines is empirical. There exist no randomized clinical trials that prove the contribution of this therapy in HIT. Therapeutic dosages and the choice of the generation and type of antihistamine (H_1/H_2) are in the competence of the clinician after the manifestation of the symptoms (gastrointestinal, neurological, dermatological) are taken into account; in consideration of effectiveness and safety however, 2nd or 3rd generation of H_1 antihistamines should take precedence. H_2 blockers could be used in patients with dominant gastrointestinal symptoms (hyperacidity and reflux as manifestations of HIT are also questions to discuss).

Treatment with antihistamines should be conscious and time-limited and should help create a picture of whether H_1/H_2 receptor blockade attenuates manifestations [1]. However, it may also be used as a therapeutic-diagnostic test.

3.4. Complementary Strategies in HIT Management

Some authors regard supplementation of cofactors of the DAO enzyme as optional adjunctive therapy. Vitamin C, copper or vitamin B6 supplementation may be considered [32,33,40,84].

Supplementation with probiotic microorganisms could lead to such modulations of microbiome that would reduce the production of the microbial enzyme L-histidine decarboxylase. The precondition therefore is the administration of strains that do not produce L-histidine decarboxylase. In an ideal case, these would be strains capable at the same time of degrading histamine (or other biogenic amines). Clinical trials assessing the possible impact of probiotic administration in HIT are not found in literature up to the present.

Arising from experimental trials, it would seem at present that members of *Bifidobacterium* genus could be considered as candidates for appropriate supplementation, but studies confirming this assumption are warranted [44,46].

4. Conclusions

HIT represents a set of diverse symptoms that appear following the ingestion of food with a content of such amounts of histamine that usually do not provoke symptoms in a healthy person. Manifestations may be caused by various pathophysiological mechanisms, or a combination of them. It would seem that symptoms typical for HIT in an individual may potentiate the presence of other disorders such as, e.g., celiac disease or *H. pylori* infection. The diagnosing of HIT therefore requires a complex time-demanding multidisciplinary approach, including the systematic elimination of disorders with a similar manifestation of symptoms. A low-histamine diet is currently a suitable (not however sole) diagnostic and at the same time therapeutic measure. Recently, evidence has been growing regarding the therapeutic contribution of food for special medical purposes containing a DAO enzyme of animal origin. H_1/H_2 antihistamines may also be considered in management of HIT, with the daily dosage (usually higher than the standard) determined by a clinician on the basis of the patient's clinical condition. Pharmacological treatment should have a limited time duration. The aim of the therapeutic approach should be to develop such dietary habits which will not in the future lead to the triggering of symptoms.

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Histamine Intolerance in Children: A Narrative Review.

Wojciech Nazar, Katarzyna Plata-Nazar, Katarzyna Sznurkowska and Agnieszka Szlagatys-Sidorkiewicz. Nutrients.

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Review

Histamine Intolerance in Children: A Narrative Review

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Abstract: Histamine intolerance is defined as a disequilibrium of accumulated histamine and the capacity for histamine degradation. This clinical term addresses a non-immunologically mediated pathology when histamine ingested with food is not particularly high, however its degradation is decreased. This paper aims to provide a narrative review on etiopathology, epidemiology, possible diagnostic algorithms and diagnostic challenges of histamine intolerance in children. The clinical picture of histamine intolerance in children is similar to that observed in adults apart from male predominance found in paediatric patients. Both in children and adults, a histamine-reduced diet is typically the treatment of choice. Diamine oxidase supplementation offers another treatment option. There is no symptom or test pathognomonic for histamine intolerance. Nevertheless, manifestations of chronic gastrointestinal symptoms, measurements of diamine oxidase deficits, positive results of histamine provocation tests and improvement in symptoms with histamine-reduced diet considerably increase the probability of histamine intolerance diagnosis. These factors have been included in the proposed diagnostic algorithm for histamine intolerance. In children histamine intolerance most likely co-occurs with allergies and bowel diseases, which creates an additional diagnostic challenge. As the evidence for children is poor further research is needed the determine epidemiology, validate diagnostic algorithms and establish possible treatment options regarding histamine intolerance.

Keywords: children; histamine intolerance; nutrition; diagnostic algorithm; epidemiology

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1. Introduction

Histamine intolerance—HIT—is defined as a disequilibrium of accumulated histamine and the capacity for histamine degradation [1]. This clinical term addresses a non-immunologically mediated pathology when histamine ingested with food is not particularly high, but its degradation is decreased [1,2]. Thus, some individuals are unable to degrade ingested histamine properly, which subsequently causes sensitivity to normal or even low histamine levels in food. Research on this topic has significantly accelerated during the last decade and the awareness of histamine intolerance has been growing among researchers and in the general public [3]. However, to date, no review on HIT in children has been published. As there are only a few research papers on HIT in children, this review was also based on data from studies on adult cohorts. Nevertheless, HIT seems to be a highly relevant issue in clinical paediatrics. This paper aims to provide a narrative review on the etiopathology, epidemiology, possible diagnostic algorithms as well as diagnostic challenges of histamine intolerance in children. The differences between the paediatric and adult populations are also highlighted.

2. Histamine Metabolism

Histidine decarboxylase catalyses the production of histamine from histidine (Figure 1). Histamine is metabolised by two primary enzymes: diamino oxidase, DAO, and histamine-N-methyltransferase, HNMT [3,4]. HNMT is responsible for intracellular histamine

metabolism, while DAO is a secretory protein that metabolises histamine extracellularly [5]. DAO has a higher expression than HNMT [3], being the primary barrier for intestinal histamine absorption [5].

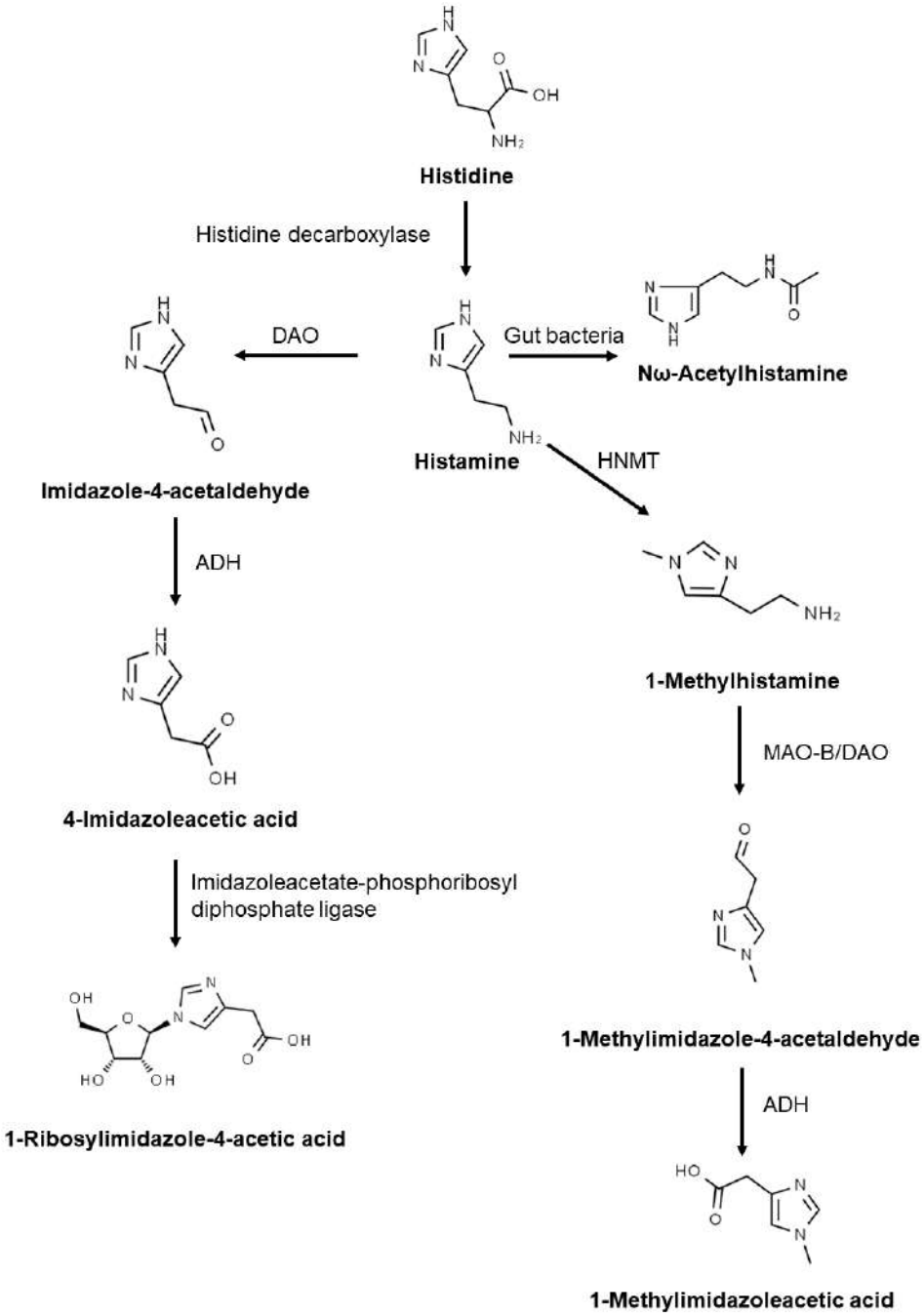

Figure 1. Histamine metabolism. DAO: diamine oxidase; MAO: monoamine oxidase B; HNMT: histamine-N-methyltransferase; ADH: aldehyde dehydrogenase.

Imidazole acetaldehyde produced by DAO is subsequently metabolised by aldehyde dehydrogenase, ADH, to imidazole acetic acid. Acetic acid is then degraded into 1-ribosylimidazole-4-acetic acid. In the second metabolic pathway, N-methylhistamine produced by HNMT is oxidised by monoamine oxidase B leading to N-methyl imidazole acetaldehyde that is further transformed into methyl-imidazole acetic acid by ADH. Histamine can also be metabolised to Nω-acetylhistamine by gut bacteria [4,6].

3. Histamine Content in Foods

Based on food lists created by Rosell-Camps et al. for children on histamine-reduced diets [7] and available scientific database [1,8,9], lists of foods to be allowed (Table 1) and avoided (Table 2) on histamine-reduced diets were created. Some fish (fresh and processed), as well as other highly processed and fermented foods (mainly some cheese) dominate the high histamine list, while the low histamine list is made up predominantly of fresh foods and foods with minimal processing.

Table 1. Food allowed on a histamine-reduced diet [1,7–9].

Food	Histamine Content: Mean [mg/kg]	Histamine Content: Range [mg/kg]
Water	-	-
Coffee	-	-
Tea	-	-
Bread	ND	-
Cereals	ND	-
Oats	ND	-
Pasta	ND	-
Rice	ND	-
Yoghurt	ND	-
Asparagus	0.34	ND–1.42
Beans	ND	-
Broccoli	ND	-
Carrot	ND	-
Cauliflower	ND	-
Courgette	ND	-
Cucumber	ND	-
Lettuce	ND	-
Mushroom	ND	-
Onion	ND	-
Potatoes	ND	-
Pumpkin	0.28	ND–1.90
Apple	ND	-
Banana	ND	-
Cherry	ND	-
Peach	ND	-
Pineapple	ND	-
Plum	ND	-
Grapefruit juice	0.31	ND–1.74
Orange juice	0.46	ND–1.32
Pineapple juice	2.44	ND–4.61
Herbs and spices	ND	-
Pepper	ND	-
Vegetable oil	-	-
Vinegar	-	-
Olives	-	-
Fresh meat	ND	-
Cooked meat	0.3	ND–4.8
Poultry	3	-
Mozzarella	ND	-
Cream cheese	3	-

ND: not detected; -: no measurement.

Table 2. Food to be avoided on a histamine-reduced diet [1,7–9].

Food	Histamine Content: Mean [mg/kg]	Histamine Content: Range [mg/kg]
Cod (fresh)	-	2–77
Tuna (frozen)	ND	-
Tuna (smoked or salted)	ND	-
Tuna (canned)	0.33	1–402
Mackerel (frozen)	-	1–20
Mackerel (smoked or salted)	-	1–1788
Mackerel (canned)	-	ND–210
Herring (frozen)	-	od 1 do 4
Herring (smoked or salted)	-	5–121
Herring (canned)	-	1–479
Sardine (frozen)	ND	-
Sardine (smoked or salted)	-	14–150
Sardine (canned)	-	3–2000
Shellfish/Shrimp paste	328	-
Fish sauce	574.7	-
Parma ham	1100	-
Sobrassada/Soppresata	21.9	-
Saucisson	71	-
Salami	-	1–654
Fermented ham	-	38–271
Fermented sousage	21.9	ND–650
Parmesan (cheese)	40.64	10–581
Blue cheese	376.6	-
Gouda (cheese)	-	10–900
Emmental (cheese)	-	5–2500
Roquefort (cheese)	9.9	-
Camembert (cheese)	-	0–1000
Cheddar (cheese)	-	0–2100
Sauerkraut/fermented cabbage	37	0–229
Soy derivatives	307	ND–307
Chocolate	0.58	-
Vanilla	-	-
Citrus	-	-
Kiwi	ND	-
Nuts	0.45	ND–11.86
Strawberry (dry)	-	-
Pineapple (dry)	-	-
Papaya (dry)	-	-
Spinach	31.77	9.46–69.71
Tomato (fresh and sauce)	22	ND–22
Eggplant	39.42	4.17–100.6
Eggs	-	-

ND: not detected; -: no measurement.

4. Histamine Intolerance or Histamine Intoxication?

In HIT, histamine accumulation in intestinal mucosa and blood plasma is caused by decreased histamine degradation, resulting most commonly from low DAO activity. Additionally, tissue HNMT is inhibited by histamine metabolites [7]. Thus, HIT can occur even when food with moderate or even low amounts of histamine are ingested.

This should be differentiated from the situation when individuals presenting with normal histamine degradation enzyme activity ingest large quantities of histamine-rich food (mainly fish) and develop histamine-induced symptoms, which is classified as histamine intoxication [3].

Histamine acting on its H_1–H_4 receptors [10] is a common denominator in both pathologies, which results in the appearance of histamine-mediated symptoms [3].

The recent meta-analysis shows that the mean histamine content in foods causing histamine intoxication is about 1100 mg/kg (95% confidence interval 422–2900 mg/kg) and almost all intoxications (98%) result from fish consumption [11]. Legal limits for histamine content in food products (mainly fish) are set, in the majority, at between 100 and 400 mg/kg [12]. Thus, the histamine content of food causing intoxication is substantively higher than stated in food safety regulatory guidelines.

For comparison, it appears like foods that can be allowed on a histamine-reduced diet contain less than 5 mg/kg of histamine (Table 2). On the other hand, most recommendations for histamine-reduced diet list foods with a wide range of histamine content, including some foods which may contain histamine concentrations near the legal limits for histamine content in foods. (Table 2) [12].

5. Primary (Genetic) Histamine Intolerance

HIT can be a genetic condition (Figure 2). In this case, it is caused by single nucleotide polymorphisms, SNPs, in the DAO gene. Expression of this gene results in altered protein production with lower enzymatic activity than usual. In the adult population, the most important SNPs in the DAO gene causing this deficit are rs10156191, rs1049742, rs2268999 and rs1049793 [3,13,14]. SNPs in the promoter region that decrease the DAO gene expression (rs2052129) have also been reported [13]. Similarly to the adult population, the DAO SNP rs1049793 is also associated with lower DAO activity in children and leads to higher serum histamine levels in paediatric patients with allergic rhinitis [15].

The relationship between the SNPs in the HNMT gene (N-methyltransferase C314T allele) and allergic diseases was investigated in children in several studies [15–19]. It appears that HNMT SNPs are associated with more severe courses of atopic dermatitis and allergic rhinitis while for asthma and bronchial hyperresponsiveness the results are contradictory.

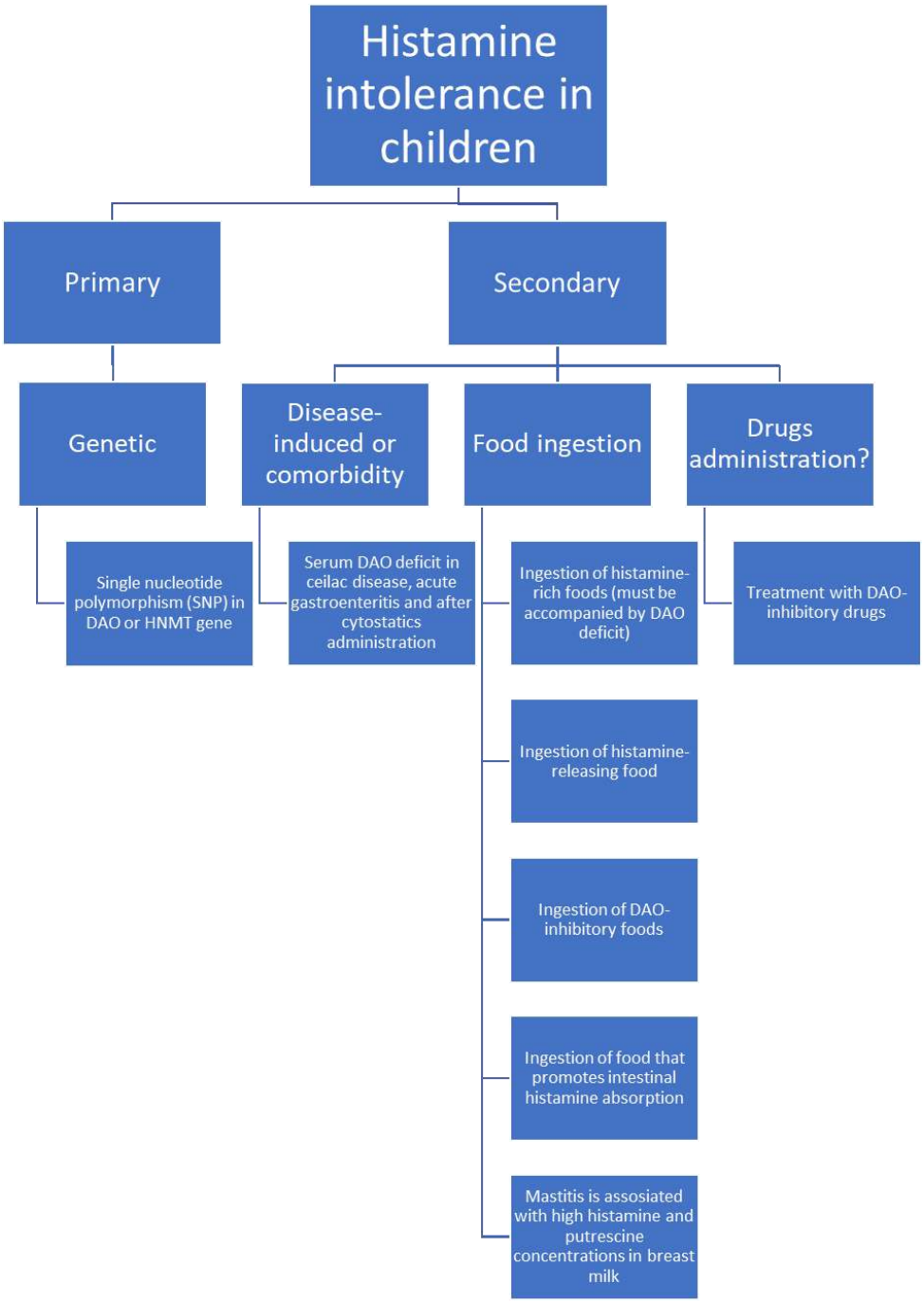

Figure 2. Possible histamine intolerance aetiologies in children.

6. Secondary Histamine Intolerance Aetiology

6.1. Disease-Induced Histamine Intolerance

DAO deficit was found in children undergoing cyclophosphamide administration in neuroblastoma paediatric patients [20], in celiac disease [21], in acute gastroenteritis [22] and during protracted diarrhoea [23]. In adults, decreased DAO excretion was reported in other diseases including chronic urticaria, viral hepatitis [1] and inflammatory bowel diseases [3]. These pathologies also occur in childhood [24–26] but insofar no evidence of DAO deficit in those conditions has been reported in children, although, as one report describes, histamine intolerance was diagnosed in a child with viral intestinal infection [27].

Thus, it appears like DAO deficiency may be caused by various factors such as the presence of a primary disease or cytostatic treatment. The common denominator is intestine damage. Similar primary factors cause secondary lactose deficiency described as reduced lactase activity [28]. Lactase, an enzyme responsible for lactose digestion, is produced, similarly to DAO, by intestinal cells. Also similarly to DAO deficiency, symptoms of lactose malabsorption, LM, include flatulence, diarrhoea, abdominal pain as well as systemic symptoms like headaches [29,30]. Moreover, the exclusion of the same dietary products may lead to an improvement in symptoms. For example, a cheese-reduced diet reduces both lactose and histamine intake. It has also been reported that HIT may be accompanied by fructose malabsorption, displaying the same symptoms and caused by the same factors as LM and HIT [30]. Therefore, several questions arise:

- Are food intolerances (e.g., lactose or fructose malabsorption) and histamine intolerance frequently comorbid?
- Could disaccharide malabsorption and histamine intolerance be caused by the same primary intestine-damaging disease?
- And, most importantly: is HIT heavily underdiagnosed?

Interestingly, the enzymatic activity of diamine oxidase and disaccharidases in small intestine biopsies of children strongly correlate with each other: DAO and lactase ($r = 0.80$), DAO and maltase ($r = 0.70$) as well as DAO and sucrase ($r = 0.55$) [31]. Additionally, it was found that in adults increasing expiratory hydrogen in lactose intolerance is associated with additional histamine or fructose intolerance and that histamine intolerance frequently accompanies disaccharide malabsorption (HIT was present in 38% of lactose intolerant patients [32] and 36.9% of patients with carbohydrate malabsorption [30]). Nevertheless, evidence is limited and the questions stated above have to be answered in future thorough investigations of these interactions.

6.2. Food Consumption

Ingested food may cause abnormal histamine accumulation in several ways (Figure 2):

- Fish, sauerkraut, smoked meat products and some cheeses contain large amounts of histamine and may trigger HIT symptoms due to even slight overavailability of histamine [1,3,7,33–35]. Histamine's presence in these foods is a result of histidine decarboxylation by microorganisms that exhibit histidine decarboxylase activity. This process occurs during food production [5]. To diagnose HIT, ingestion of histamine-rich food must be accompanied by a DAO deficit. Otherwise, histamine intoxication should be diagnosed.
- Some products can likely trigger histamine release. Examples are citrus fruits, papaya, strawberries, egg white, chocolate, some types of nuts, fish, and pork [1].
- Food rich in other biogenic amines, like tyramine or putrescine, usually accompanied by histamine, may cause competitive DAO inhibition and in combination with usually tolerable histamine amounts cause HIT [1,3]. Examples include fish, fermented sausage or sauerkraut.
- Putrescine most probably promotes histamine liberation from the intestinal mucosa [1]. Examples of high putrescine content food include cheese, fermented sausages, fish sauces or citrus fruits, green pepper, wheat germ and soybean sprouts [36,37].

One should also keep in mind that some foods can cause acquired DAO deficit via several mechanisms simultaneously. For example, fish is a histamine-rich, histamine-releasing and DAO-inhibitory food product.

6.3. Breastfeeding

Exclusive breastfeeding for about 6 months is recommended and should be followed by the introduction of complementary foods until weaning when the child is 12 months old or older [38]. There is no direct evidence on whether histamine present in the mother's food may trigger histamine intolerance in children. Perez et al. report that occasionally breast milk histamine concentration as well as other biogenic amines like putrescine increase when breastfeeding women are diagnosed with mastitis [39]. This molecule may act as a DAO inhibitor increasing the risk of decreased histamine metabolism [1]. To date, the earliest symptom onset of HIT was reported in a 6-months old child [7], which most probably coincided with the introduction of complementary foods [38]. Thus, the question arises whether increased concentrations of biogenic amines transferred in breast milk are high enough to cause histamine intoxication or induce histamine intolerance in an infant.

6.4. Drugs Administration

Certain drugs have been claimed to inhibit DAO activity and contribute to HIT pathogenesis. This list includes morphine, non-steroidal anti-inflammatory drugs, acetylcysteine, acetylsalicylic acid, clavulanic acid, isoniazid and cimetidine [1]. As many of these drugs are used in paediatric diseases [40,41], iatrogenic DAO inhibition in children should also be considered, especially if the drugs are used long term or for treating chronic conditions. However, there is no evidence on this issue yet. Nevertheless, some drugs are excluded in histamine-reduced diets for children (Table 3) [7].

Table 3. Drugs mediating histamine intolerance and excluded on histamine-reduced diet in children, adopted from Rosell-Camps et al. [7].

Type of Drug/Substance	Example
Contrast media	-
Muscle relaxants	Pancurorium, alcuronium, D-tubocurarine
Anaesthetics	Thiopental
Analgesics	Morphine, pethidine, NSAIDs, ASA, metamizole
Local anaesthetics	Prilocaine
Cardiotonics	Dobutamine, dopamine
Antihypertensives	Verapamil, alprenolol, dihydrazine
Antiarrhythmics	Propafenone
Diuretics	Amiloride
Antibiotics	Cefuroxime, isoniazid, pentamidine, clavulanate, chloroquine
Mucolytics	Ambroxol, acetylcysteine
Bronchodilators	Aminophylline
Cytostatics	Cyclophosphamide
Antidepressants	Amitriptyline
Prokinetics	Metoclopramide
Antihistamines	Cimetidine

7. Epidemiology of Histamine Intolerance in the Paediatric Population

It is estimated that the prevalence of HIT is approximately 1% worldwide and that about 80% of those patients are adults [1]. In children, a lower diagnosis rate is possible, as children most probably do not consume as much fish, cheese or fermented sausages as adults and the symptoms may not be displayed clearly enough to diagnose HIT. Nevertheless, the true prevalence of HIT in children may be the same as in the adult population. It is also claimed that due to multifaced symptoms and many organs involved, HIT prevalence is most likely underestimated [1].

In one study involving children, about 8% of children who report chronic abdominal pain and have a history of histamine-rich foods consumption had decreased serum DAO concentrations [42]. Males seem to predominate in the paediatric population which is different from the adult population [7,42,43]. However, all these hypotheses need to be verified in larger cohorts. Also, the question arises about the minimum age at which HIT

diagnosis can be made. As of now, a 15-month-old child is the youngest patient diagnosed with HIT [27]. However, another study claims that the symptoms of HIT were observed in a 6-month-old patient [7].

8. Histamine Intolerance Diagnosis in Children

As of now, two publications proposing a diagnostic scheme for paediatric HIT are available. Hoffman et al. propose the following diagnostic criteria: (1) patient has chronic abdominal pain; (2) patient has serum DAO concentration $\leq$10 IU/mL; (3) the suspected HIT symptoms improve after histamine-reduced diet; (4) positive result of histamine provocation test [42].

On the other hand, Rosell-Camps et al. recruited: (1) patients with chronic abdominal pain; (2) whose symptoms improve on a histamine-reduced diet; (3) who may have serum DAO concentration $\leq$10 U/mL [7].

The first stage of diagnosis is consistent between the studies. Gastrointestinal symptoms seem to be the most common among paediatric patients with HIT. These include chronic, diffuse abdominal pain, diarrhoea, vomiting and flatulence [7,42]. The same observation was made in the adult population, where symptoms including abdominal distension (92%), postprandial fullness (73%), diarrhoea (71%), abdominal pain (68%) and constipation (55%) were observed in the majority of the studied population [43].

However, when the second stage is considered, only about 50% of children who have decreased DAO activity report improvement in symptoms with a histamine-reduced diet [42] (Table 4). On the other hand, Rosell-Camps et al. reported that all patients with decreased DAO activity responded well to a histamine-reduced diet [7]. Therefore, it seems that the DAO activity measurement should follow the histamine-reduced diet trial, not the other way around. This scheme is also consistent with the ones proposed by Maintz et al. or Comas-Basté et al. for the adult population [1,3]. However, researchers suggest that the patient should be presenting at least two symptoms of histamine intolerance. It is unknown if this criterion was fulfilled by patients enrolled by Hoffman et al. [42], while in the study carried out by Rosell-Camps et al. all patients met this criterion [7].

Table 4. Comparison of recent studies on histamine intolerance in children.

Clinical Outcome	Number of Patients	
	Rosell-Camps et al. [7]	**Hoffman et al. [42]**
Abdominal pain	16 (100%)	31 (100%)
DAO deficit	14 (87.5%)	31 (100%)
Males	11 (68.8%)	17 (54.8%)
DAO deficit and positive response to histamine-reduced diet	14 (100%)	16 (43.2%)
High serum histamine level	1 out of 8 measured (12.5%)	22 (71.0%)
High urine histamine level	1 out of 8 measured (12.5%)	13 (41.2%)

As a histamine-reduced diet helps to improve symptoms in paediatric patients without DAO deficit [7], while not all patients with DAO deficit respond to a histamine-reduced diet [42], it seems that in the paediatric population decreased DAO concentration is not pathognomonic for HIT. The same issue, as well as high variations in prevalence of DAO deficit in the studied populations were observed in adults [44,45].

Moreover, Hoffman et al. claim that during a double-blind placebo-controlled trial only one out of seven patients developed symptoms of HIT and thus the test result was interpreted as positive [42]. This is consistent with another study based on the adult population. It shows that the histamine provocation test results are not reproducible and its use to diagnose HIT may be inappropriate [46].

In addition to these findings, it was observed that children's serum DAO concentrations do not correlate with serum or urine histamine concentrations (R^2 = 0.38 and 0.28,

respectively) [42]. A similar outcome was observed by Rosell-Camps et al. as in eight patients who had undergone measurements only one child had urine and blood histamine concentrations above physiological level [7].

Kacik et al. implement a completely different diagnostic scheme, with patients divided into allergy and pseudoallergy groups based on their serum IgE concentration [2]. It was found that low serum DAO is associated with low total and specific IgE concentration, thus no allergy, and it was concluded that the most probable diagnosis is histamine intolerance [2]. However, the DAO concentration in the pseudoallergy group (n = 8) was still very high (46.40 $\pm$ 7.19 IU/mL) in comparison to $\leq$10 IU/mL which has been proposed as the cut-off value for the diagnosis of DAO deficit [42]. Contrary to two previous studies [7,42], the most common symptoms in the pseudoallergy group were respiratory (75%), skin (50%) and symptoms appearing after food ingestion (50%). However, the digestive system symptoms were present in only 25% of the non-allergic children, compared to 100% or nearly 100% in other studies [7,42,43]. IgE concentration, both total and specific, can be helpful in the diagnosis of allergy, but reduced DAO activity is also noticed for example in celiac disease [21]. Moreover, there is no mention if patients were treated with a histamine-reduced diet and if symptoms improved [2]. The symptoms appearing after food ingestion can be attributed to many other conditions, for example lactose intolerance [47]. Consequently, HIT diagnosis in low serum IgE patients cannot be straightforwardly based exclusively on low IgE concentration and lower DAO activity. Nevertheless, testing for total and specific IgE concentrations may be applied in the differential diagnosis between allergies and histamine intolerance.

Up till the present, no specific HIT diagnosis scheme in children or adults has been developed. Due to the diversity of symptoms [2,7,43] as well as lack of strong, unequivocal correlations between biochemical markers of HIT, HIT symptoms and HIT treatment methods HIT diagnosis remains a highly challenging diagnostic issue.

9. Proposed Diagnostic Algorithm for Histamine Intolerance in Children

Based on the current evidence, instead of the flow chart method proposed by Maintz et al. [1], supported by Comas-Basté et al. [3] or the diet-provocation algorithm developed by Reese et al. [48], the authors wish to propose and discuss a new approach to HIT diagnosis based on major and minor criteria fulfilment. As the proposal derives from research involving children, a diagnostic scheme for paediatric patients may be developed.

10. Symptoms of Histamine Intolerance

In our proposed diagnostic scheme, exhibiting two gastrointestinal or three overall symptoms of histamine intolerance is the necessary condition for HIT diagnosis and the starting point of the diagnostic path (Table 5). Maintz et al., in their study present a different approach and suggest possible HIT diagnosis when the patient reveals at least 2 symptoms of histamine intolerance [1]. Rosell-Camps et al. noticed that paediatric patients with HIT intolerance display symptoms other than the digestive system including pruritus, rash, bronchospasm, cough, headache, nausea, and tachycardia [7]. This is consistent with the adult population, in which such symptoms, although less common than gastrointestinal ones, are not rare [43]. Also, no symptom is reported by 100% of the patients [43]. Nevertheless, an adult patient typically displays a larger number of symptoms simultaneously, ranging from 2 to 21, most frequently from 8 to12 symptoms. For children, the average number of symptoms revealed amounts to three [7]. The gastrointestinal symptoms are the most frequent and their occurrence is more indicative for HIT than symptoms from other organ systems [7,43].

Table 5. Proposed algorithm for histamine intolerance diagnosis in children.

Must-Have Criteria
Presenting ≥ 3 symptoms of histamine intolerance in total or ≥2 gastrointestinal symptoms
≥2 Major criteria
Positive histamine oral provocation test OR positive 50-skin-prick test when other possible pathologies giving positive result are excluded serum DAO deficit (≤10 IU/mL) OR symptoms improvement after DAO supplementation (4–8 weeks) OR symptoms improvement after DAO inhibitory drugs dismission OR identification of single nucleotide polymorphism responsible for DAO/HNMT deficit OR decreased DAO activity in colon biopsy Symptoms improvement after histamine-reduced diet (4–8 weeks)
Additional criteria that increase the probability of histamine intolerance diagnosis
Correlation between specific food consumption and symptomatology based on a diet diary High concentration biomarkers of histamine metabolism in urine, blood or stool samples Exclusion of mastocytosis (tryptase) Exclusion of food allergies (skin prick test) Exclusion or confirmation of other underlying diseases relevant to presented symptoms

At this stage of developing the diagnostic scheme, the severity and frequency of symptoms required to consider the possibility of HIT diagnosis have not yet been determined and further research is needed.

11. Major Criteria

Histamine-reduced diet is easy and inexpensive to administer as well as widely available, compared to experimental serum DAO measurements, colon biopsy or SNPs investigation that are expensive, invasive, require trained personnel and cannot be performed in all laboratories. Also, patients who find histamine-reduced diet improves their symptoms adhere to it after four weeks [42], which indicates well whether the therapy has been successful or not. Moreover, the diagnostic value of a histamine-reduced diet is well evidenced [3]. On the other hand, a histamine-reduced diet is not appropriate for some patients with DAO deficit [42] and it sometimes helps patients who do not have DAO deficit [7]. What is more, the ''histamine-reduced'' diet tends to also reduce the intake of other substances. For example, histamine-reduced diets tend to also reduce biogenic amine consumption or at least contains reduced amounts of biogenic amines [1,3]. Nevertheless, a histamine-reduced diet appears to be the most efficient test, although biochemical confirmation of DAO deficit also provides a valuable diagnostic clue.

DAO supplementation is also claimed to be a valuable diagnostic marker. However, there are no studies regarding its use in children, although it seems to be an effective way for treating HIT in adults [3] and thus it can be also considered as the first-step histamine-specific test for the paediatric population, too.

Interpretation of histamine oral provocation test is sometimes confusing and lacks reproducibility [42,46]. Nevertheless, despite its serious side-effects. the test can be a useful indicator of problems with histamine digestion, as it shows the direct causative effect of a large histamine dose on the patient's body.

Some authors [3,48–50] also propose a 50-skin-prick test. A positive result can be indicative of HIT, however, any other possible diseases such as systemic mastocytosis or allergies have to be excluded and DAO inhibitory drugs must be discontinued before the

test is performed. Thus, it can be useful when HIT is an isolated, primary disease only. With HIT as a comorbid condition, the 50-skin-prick test becomes inconclusive [50].

As a result, even the fulfilment of at least two major criteria cannot be used for a conclusive HIT diagnosis. Nevertheless, if the patient meets at least two of the criteria, HIT becomes a highly probable diagnosis. Finally, if three major criteria are fulfilled, the diagnosis of HIT can be made, as all possible histamine-specific diagnostic tests groups indicate histamine intolerance.

12. Minor Criteria

Some factors make HIT diagnosis even more probable but are less indicative of problems related to histamine-mediated symptoms specifically. Again, their fulfilment only increases the probability of HIT occurrence and does not allow for unequivocal diagnosis.

A food diary can help to diagnose histamine intolerance. The intake of specific food can be noted by parents\patients' caregivers of younger patients or by adolescent patients themselves. To aid data collection younger patients may for example highlight drawings of foods they have eaten today, while for older ones a checklist can be provided. However, if it is the patient\patient's caregiver who requests a diagnosis of HIT based on their reports, the diary's usefulness can vary greatly, depending on its content. Some patients may report time between specific food ingestion and symptoms or provide an hour-by-hour diary, while some will just report foods eaten and symptoms experienced in a given day. On the other hand, a physician can advise the patient to complete a 24- or 48-h thorough diet-to-symptoms diary. It is crucial to provide detailed instructions and make the patient aware that the temporal relation between ingested food and symptoms is important. However, one has to remember that 24 or 48 h maybe a too short period of time and patients might not be fully compliant, leading to only partial notes and resulting in an incorrect diagnosis. Also, to date, there is no established protocol for keeping such a diary. Hence, the diagnostic value of diary data is case-dependent.

Biomarkers of histamine metabolism in urine or blood samples can also be helpful in diagnosis. However, the correlations with DAO concentration are weak [42] and their diagnostic usefulness is still being investigated [3,51]. Moreover, it is difficult to provide clear guidance on when tests to exclude allergies or mastocytosis should be made, as it is indicated in the algorithm of Maintz et al. [1].

13. Comorbidities

In the light of the proposed diagnostic criteria, it is worth emphasizing that HIT may be, and in most cases probably is, a comorbidity. This is supported by studies correlating DAO/HNMT deficit (measured by SNPs) or increases in blood serum histamine concentrations with the severity of allergic diseases like atopic dermatitis, allergic rhinitis or asthma and bronchial hyperresponsiveness [15,16,18,19]. Additionally, DAO deficits were observed in bowel diseases, for example, celiac disease or acute gastroenteritis in children [21,22] and recurrent urticaria, colon adenoma, carbohydrate malabsorption as well as food allergies in adults [30,32,52–56]. Also, the DAO activity level was proposed as a bowel integrity marker [20,21]. As these are allergic and gastrointestinal diseases, the frequency or severity of histamine-mediated symptoms increases most likely due to the elevation of serum histamine concentration, leading to possible co-occurrence of histamine intolerance. Such possibility poses an additional diagnostic challenge and was included as the last additional criterion in the proposed HIT diagnosis scheme (Table 5).

14. Treatment of Histamine Intolerance

According to recent studies, a histamine-reduced diet is a treatment of choice for HIT (Figure 3, [7,42]). However, its effectiveness in symptom improvement in children varies. This choice of treatment is consistent with studies on adults with HIT [3]. Similarly, the effectiveness varies, but in general, the response is rather good [3]. Additionally, Rosell-Camps et al. report successful treatment of more severe cases of HIT in children with H_1

and H_2 antihistamines as well as oral zinc supplementation as a combination therapy along with a histamine-reduced diet [7].

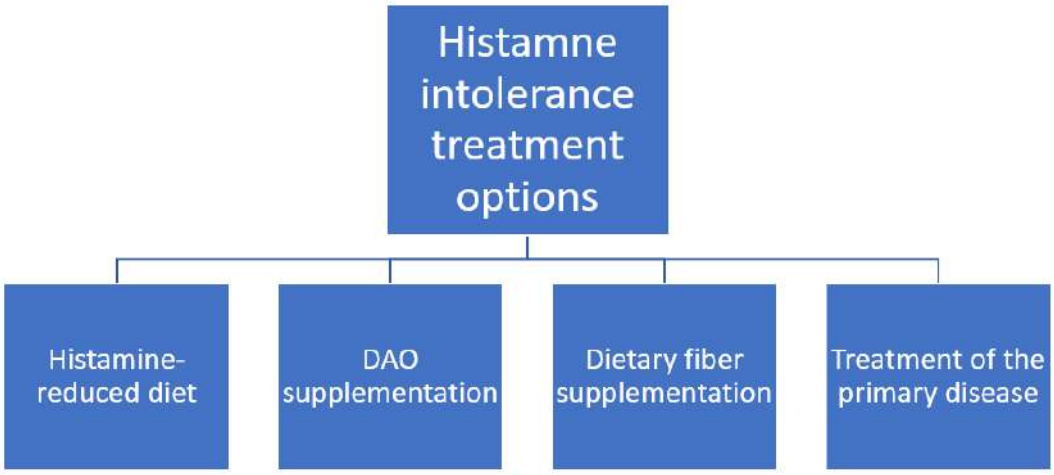

Figure 3. Histamine intolerance treatment options.

For adults, DAO supplementation is also proposed and the results are promising [1,3]. However, there is no study on a paediatric population that evaluates this treatment method. Some companies offer DAO supplements [57], but currently it is not possible to provide patients with evidence-based recommendation on this topic.

During cyclophosphamide administration in neuroblastoma paediatric patients, the pre-administration of dietary fibre inhibited the influence of cyclophosphamide on DAO activity [20], which shows a potential treatment option of drug-induced HIT. Also, it might be applied in other bowel-disease-induced DAO deficits [53–55]. Nevertheless, this therapy needs to be investigated more thoroughly to enable its assessment and drawing reliable conclusions.

15. Conclusions

Histamine intolerance has to be considered in children with non-specific gastrointestinal complaints and histamine related symptoms. Although decreased DAO activity seems to be the most relevant finding in patients with HIT, its significance as a diagnostic marker needs to be verified in large prospective cohort studies. A histamine-reduced diet is a treatment of choice for HIT, but other treatment options like DAO or dietary fibre supplementation might be suggested to patients who do not respond to an elimination diet. Secondary HIT accompanying allergies and bowel pathologies could be responsible for worsening the symptoms of these conditions.

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Evaluation of symptoms and symptom combinations in histamine intolerance

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Background/Aims: Food intolerance/malabsorption, particularly histamine intolerance (HIT), may cause nonspecific functional gastrointestinal and extraintestinal symptoms. We evaluated gastrointestinal and extraintestinal symptoms in patients with HIT. **Methods:** In an analysis of outpatients' charts we identified 133 patients, who presented with recurring nonspecific functional gastrointestinal, extraintestinal symptoms, and a diamine oxidase value <10 U/mL, indicative of HIT. A standardized anonymous questionnaire with symptoms of HIT based on known symptoms and the 4 histamine receptors including gastrointestinal, cardiovascular, respiratory and skin complaints was developed, and sent by mail to the patients. **Results:** In the 62 patients that completed the questionnaire, bloating was the most common and most serious symptom. Other commonly reported gastrointestinal symptoms were postprandial fullness, diarrhea, abdominal pain, and constipation. The presence of 2 from a list of 24 symptoms resulted in 276 various symptom combinations. From calculated 2.024 possible combinations of 3 symptoms the patients with HIT presented 1.975 combinations. **Conclusions:** The knowledge of this wide variability of symptoms and complex symptom combinations in patients with HIT may help to clinically recognize and diagnose HIT. **(Intest Res 2019;17:427-433)**

Key Words: Diamine oxidase; Histamine; Irritable bowel syndrome; Gluten; Gastrointestinal diseases

INTRODUCTION

Food intolerance/malabsorption syndromes are reported in up to 20% of the population in westernized countries and, particularly histamine intolerance (HIT) may cause nonspecific GI complaints and extraintestinal symptoms.[1] In HIT a disproportionate amount of histamine in the body is thought to result from the consumption of food with high histamine content, and a reduced ability of mainly the enzyme diamine oxidase (DAO) to digest histamine.[2] The clinical diagnosis of HIT is challenging and the symptoms may occur according to the known 4 receptors of histamine.[3] Here, we describe various symptoms and complex symptom combinations in patients with HIT. This may help to clinically recognize and diagnose HIT.

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METHODS

In a retrospective analysis of outpatients' charts, we identified 133 patients (male:female, 30:103; median age, 39 years; age range, 18–81 years), who presented with recurring functional nonspecific abdominal complaints and who had a DAO value <10 U/mL (median, 5.8 U/mL; range, 1.5–9.9 U/mL). In our outpatient setting we decided to include serum DAO determination in the evaluation of patients who present with recurring functional nonspecific abdominal complaints.[4] A thorough

anamnesis, concerning abdominal complaints and a timely relation to ingestion of histamine-containing food or drinks, including pharmaceutical treatments which might influence HIT, was performed. All of the patients were examined for and did not show lactose intolerance, fructose malabsorption, *Helicobacter pylori* infection or celiac disease.

A registered dietician was consulted to introduce and observe, using a food diary, a histamine-elimination diet for 2 weeks. If the patients were free of or had noteworthy improvement of GI symptoms, together with a DAO value <10 U/mL at first presentation, then the diagnosis of HIT was established.[5] All patients received written information about HIT and the dietician helped to develop an individually tailored long-time diet to ensure nutritional adequacy and to provide sustained relief.

In the morning, at the first presentation, blood drawings were performed after overnight fasting (>12 hours) and determination of DAO in serum was made with a radio extraction assay (Sciotec Diagnostic Technologies, Tulln, Austria) within 3 days. We used hydrogen (H_2) breath tests for exclusion of lactose intolerance and fructose malabsorption (Gastrolyzer; Bedfont Scientific Inc., Kent, England). Either histologic evaluation of gastric mucosa or an enzyme-linked IgA immunosorbent assay (ELISA; Serion, Würzburg, Germany) were done and showed absence of *H. pylori* infection. For screening of celiac disease antibodies against tissue transglutaminase were determined with anti-tTG IgA ELISA (Euro-Diagnostica AB, Malmö, Sweden). All patients >50 years old were screened by colonoscopy and no pathology was present. None of the patients showed signs of infection.

A standardized anonymous questionnaire, regarding symptoms the patients experienced before the diagnosis of HIT and/or what complaints they have due to ingesting foods with high histamine content, was established. This questionnaire was based on known symptoms and the 4 histamine receptors according to the literature,[2,3] and it was sent by mail to the patients. Every questionnaire listed 23 symptoms in 4 categories including GI, cardiovascular, respiratory and skin complaints, and for every symptom a severity score from 0 (no symptoms) to 5 (very intense) was included. Space was provided for patients to add other symptoms. Of 133 selected patients 69 (51.9%) returned the questionnaire, but 7 envelopes were returned unopened. Therefore, 62 questionnaires (46.6%) were included in this anonymous evaluation.

Qualitative data are presented as absolute and relative frequencies; quantitative parameters are summarized as mean and SD or, median and interquartile range (IQR) according to distribution, respectively. Data distribution was assessed by the Shapiro-Wilk test and the severity of symptoms is stated as the median of the reported symptom severities. Statistical analyses were performed with SPSS version 23.0 (IBM Corp., Armonk, NY, USA) and R version 3.4.2 (R Core Team, Vienna, Austria) was used to determine the frequency of combinations of symptoms. Written informed consent was obtained from each patient included in the study. The study conforms to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethical Committee of the Johannes Kepler University in Linz, Austria (approval No. K-107-16).

RESULTS

Bloating was the most common symptom among these patients (92%) and was observed as the most severe symptom with a severity score of 4 (Table 1). Other common HIT-related GI symptoms included: postprandial fullness (73%), diarrhea (71%), abdominal pain (68%), and constipation (55%) as shown in Fig. 1. Eighteen patients (29%) added other symptoms in the space provided (burning sensation in mouth, on tongue, or anus, migraine, shaking-heavy legs, weakness, leg edema, listlessness, fatigue, insomnia, reduced power of con-

Table 1. Symptom Severity Score in Patients with Histamine Intolerance

Symptom	Symptom severity score
Bloating	4
Abdominal pain, intestinal colic, diarrhea, postprandial fullness, dysmenorrhea, flush, belching, palpitations, rhinorrhea	3
Constipation, pruritus	2.5
Nausea, emesis, rash, swollen reddened eye lids, headache, dizziness, nose congestion, sneezing, dyspnea	2
Hypotonia	1.5
Collapse	1

Score will range 0 (no symptoms) to 5 (very intense). None of the symptoms was indicated with a symptom severity code 5.

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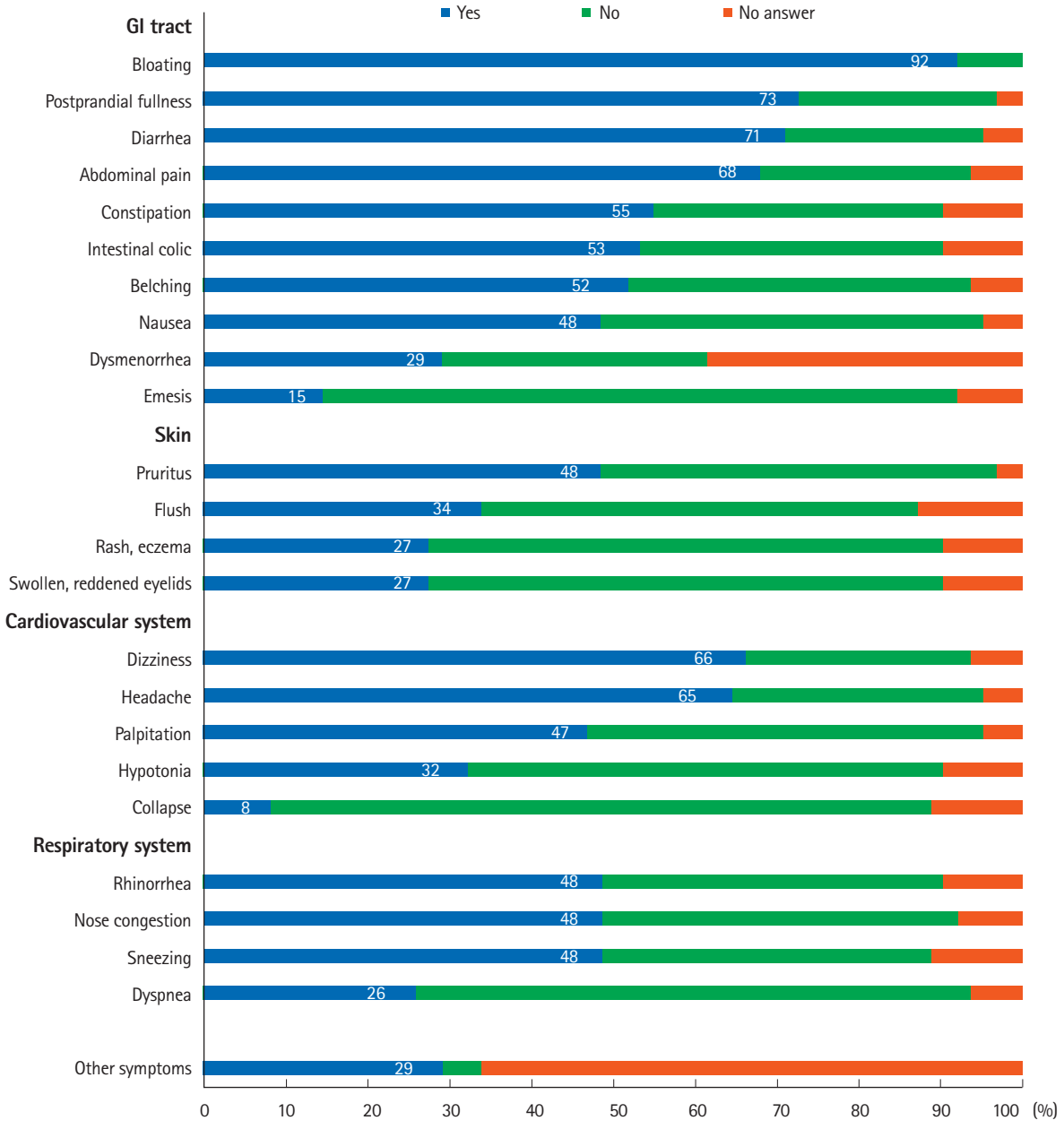

Fig. 1. Frequency and distribution of symptoms in patients with histamine intolerance.

centration, heartburn, dry skin, ophthalmitis, anxiety, suffocating, sore throat, hoarseness, cardiac arrhythmia, and arterial hypertension) and assigned them a high symptom severity score of 4. Two of these patients added 2 other symptoms.

According to the symptom categories, all the GI symptoms were mentioned most frequently, followed by cardiovascular symptoms. The presence of 2 of the 24 symptoms in all 4 categories resulted in 276 various combinations. Of the GI symptom combinations, bloating was the most frequent in combination with other GI symptoms, and 115 various combinations were reported to occur in more than 25% of patients (Table 2).

Two patients showed only 3 or fewer symptoms, but 96.8% of patients with HIT presented with more than 3 symptoms. The median of the number of symptoms was 10 (IQR, 7), and the mean value was 11.1 symptoms (SD, ±4.8). Less than 10 symptoms were indicated by 40.3% of patients, 14.5% of patients had 10 symptoms and 45.2% showed more than 10 symptoms (Fig. 2). From the calculated 2.024 possible combinations of 3 symptoms, patients presented with 1.975 combinations, and only 49 combinations were not displayed. From the 10.626

Table 2. Most Common Combinations of 2 Symptoms in Patients with Histamine Intolerance

Symptom combinations	Percent of patients	Symptom combinations	Percent of patients
Bloating - postprandial fullness	69	Diarrhea - nausea	42
		Diarrhea - nose congestion	
		Diarrhea - sneezing	
		Dizziness - constipation	
		Dizziness - intestinal colic	
		Dizziness - palpitation	
		Bloating - palpitation	
		Postprandial fullness - intestinal colic	
		Postprandial fullness - nose congestion	
		Abdominal pain - nose congestion	
Bloating - diarrhea	66	Diarrhea - intestinal colic	40
Bloating - abdominal pain		Headache - intestinal colic	
		Headache - nausea	
		Postprandial fullness - nausea	
		Abdominal pain - nausea	
Bloating - dizziness	63	Diarrhea - constipation	39
Bloating - headache		Diarrhea - palpitation	
		Diarrhea - pruritus	
		Diarrhea - belching	
		Dizziness - belching	
		Dizziness - nausea	
		Headache - constipation	
		Abdominal pain - belching	
		Abdominal pain - rhinorrhea	
		Abdominal pain - sneezing	
Abdominal pain - dizziness	55	Dizziness - nose congestion	37
		Dizziness - pruritus	
		Dizziness - sneezing	
		Headache - belching	
		Headache - nose congestion	
		Postprandial fullness - constipation	
		Postprandial fullness - sneezing	
		Postprandial fullness - pruritus	
		Abdominal pain - palpitation	
Postprandial fullness - abdominal pain	53	Constipation - intestinal colic	35
Bloating - intestinal colic		Dizziness - rhinorrhea	
		Headache - palpitation	
		Headache - pruritus	
		Postprandial fullness - rhinorrhea	
Diarrhea - dizziness	52	Abdominal pain - pruritus	34
Bloating - belching		Intestinal colic - nausea	
		Intestinal colic - nose congestion	
		Intestinal colic - sneezing	
		Rhinorrhea - sneezing	

(*Continued to the next page*)

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Table 2. Continued

Symptom combinations	Percent of patients	Symptom combinations	Percent of patients
Diarrhea - headache Diarrhea - abdominal pain Dizziness - headache Bloating - constipation Postprandial fullness - diarrhea Postprandial fullness - headache	50	Intestinal colic - belching Intestinal colic - rhinorrhea Bloating - flush Bloating - hypotonia Belching - sneezing Postprandial fullness - palpitation Pruritus - nose congestion Pruritus - sneezing Headache - rhinorrhea Headache - sneezing Rhinorrhea - nose congestion	32
Bloating - nose congestion Bloating - rhinorrhea	48	Constipation - palpitation Nausea - belching Nausea - nose congestion Nausea - sneezing Belching - pruritus Postprandial fullness - flush Postprandial fullness - hypotonia Pruritus - palpitation Pruritus - rhinorrhea Palpitation - nose congestion	31
Bloating - nausea Bloating - pruritus Bloating - sneezing Postprandial fullness - dizziness Abdominal pain - headache Abdominal pain - intestinal colic	47	Diarrhea - flush Nausea - pruritus Belching - nose congestion Flush - headache Nose congestion - sneezing	29
Diarrhea - rhinorrhea Postprandial fullness - belching	45	Intestinal colic - pruritus Intestinal colic - palpitation Bloating - dysmenorrhea Bloating - other symptoms Constipation - belching Constipation - nose congestion Nausea - rhinorrhea Belching - rhinorrhea Dizziness - hypotonia Palpitation - sneezing	27
Abdominal pain - constipation	44	Abdominal pain - dysmenorrhea Abdominal pain - hypotonia Diarrhea - swollen, reddened eyelids Belching - hypotonia Belching - palpitation Pruritus - flush Headache - hypotonia Palpitation - rhinorrhea	26

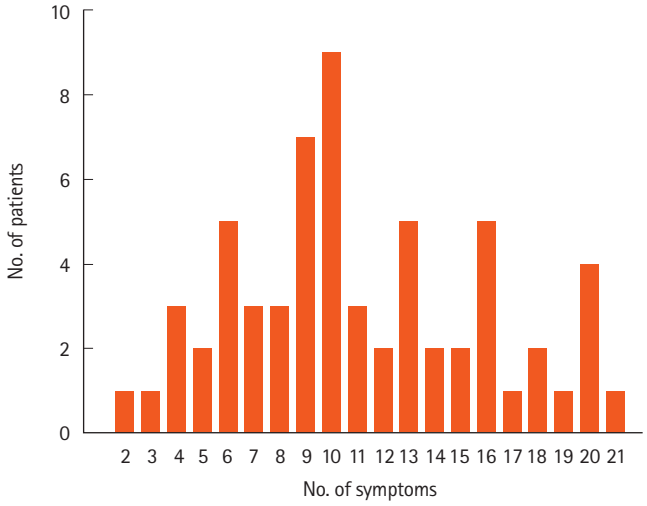

Fig. 2. Number of symptom combinations in patients with histamine intolerance.

possible combinations of 4 symptoms, 9.899 combinations were presented and 727 combinations did not occur.

DISCUSSION

HIT is assumed to be due to a GI-DAO deficit and the name was created with reference to the term lactose intolerance. A disproportionate amount of histamine in the body is thought to result from the consumption of food with high histamine content, and a reduced ability of mainly the enzyme DAO to digest histamine.[6] The clinical diagnosis of HIT is challenging but patients with low serum DAO values, 2 or more GI symptoms described for HIT, and a reduction of symptoms due to a histamine-reduced diet may be diagnosed with HIT.[4,5] In the present study we describe the wide variability of GI, extraintestinal and combinations of symptoms associated with HIT. Polymorphisms identified for the genes coding for DAO and for histamine receptors may help explain these symptoms.[7,8] Complex symptom combinations may influence disease expression and the individual response to diets or treatments.

Disorders such as IBS are one of the main reasons for consultation in primary care and IBS is associated with high symptom burden causing a reduced quality of life. The diagnosis of IBS solely relies on self-reported symptoms by patients, and is in many cases self-diagnosed and self-treated.[9] Currently Rome IV criteria as classification and diagnostic criteria in IBS are used but they have limitations in clinical practice since many patients do not demonstrate the required criteria. In Rome IV the recurring symptom of abdominal pain with change in bowel habits, including diarrhea, constipation, bloating and distension, was described as main IBS symptom.[10] We here found bloating to be the most frequent and most severe symptom in HIT. Frequently, patients also reported postprandial fullness, diarrhea, abdominal pain and constipation which resemble IBS-linked symptoms. However, IBS patients were shown to believe that food, including histamine-containing food, triggers their GI symptoms.[11]

Another new, symptom-based disorder is non-celiac gluten sensitivity (NCGS) and it is associated with the consumption of gluten-containing products.[12] Since there are no diagnostic criteria available for NCGS they are also referred to as "people without celiac disease avoiding gluten."[13] It was assumed that people with NCGS are a group of patients with IBS who are self-diagnosed and perform self-treatment with a gluten-free diet.[14] However most gluten-containing foods and drinks also contain histamine and/or they are consumed with added histamine-containing seasonings. We described that GI and extraintestinal symptoms in NCGS resemble those which can be found in HIT.[15]

Functional dyspepsia (FD) is a disorder with a heterogeneous group of symptoms in the epigastric region and again, with absence of any organic disease. For FD a number of explanations was employed but pathophysiology is unknown and despite all attempts the treatment of FD remains insufficient.[16] Abdominal pain and postprandial fullness are described in FD as main symptoms[17] and patients with HIT reported these also to be prominent symptoms (Table 2).

However, a symptom is an experience observed as different from normal and depends very much on the individual patients' subjective interpretation. Symptoms alone or symptom complexes are rarely, if ever, diagnostic.[9] Although, included patients experienced recurring symptoms caused by food ingestion with high histamine content, in this study a recall bias cannot be entirely excluded. So far, no laboratory values have been found to correlate with symptoms in IBS, NCGS, or FD. Although, serum DAO values are not fully established to reflect GI-DAO activity[1] and determination of DAO in serum with currently available assays has limitations,[18] the diagnosis of HIT may be supported with measurements of serum DAO.[4,5]

Since there are symptom correlations and parallels in IBS, NCGS, and FD with HIT, determination of serum DAO values in well-defined patients with recurring functional non-specific GI symptoms in IBS, NCGS, and FD are necessary. In conclusion, the knowledge of this wide and complex variability of symp-

toms in patients with HIT may assist clinically recognizing and diagnosing histamine intolerance.

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CONFLICT OF INTEREST

W.J.S. received speaking honoraria from Sciotec. The other authors declare no competing interests.

AUTHOR CONTRIBUTION

Study design: Schnedl WJ, Enko D, Mangge H. Patient recruitment and data collection: Schnedl WJ. Laboratory data determination: Schenk M, Mangge H. Data analysis: Schnedl WJ, Lackner S, Holasek SJ. Discussion of results: Schnedl WJ, Schenk M, Holasek SJ, Mangge H. Writing the manuscript: Schnedl WJ, Lackner S, Enko D. Approval of final manuscript: all authors.

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ARTICLE

Clinical nutrition

Histamine-reduced diet and increase of serum diamine oxidase correlating to diet compliance in histamine intolerance

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Abstract

Diagnosis of histamine intolerance (HIT) has been based on low serum diamine oxidase (DAO) values, functional gastrointestinal disorders and improvement of symptoms with a histamine-reduced diet (HRD). In a retrospective analysis of outpatients' charts we identified 101 patients with HIT. After a median of 13 months, a questionnaire was distributed to the patients so that they could be classified into four diet-compliance groups. Calculated with all 101 patients we found an increase of serum DAO values due to a HRD. In the 63 patients that completed the questionnaire, we found that 50 patients had improvement of symptoms or no continuing symptoms. A significant increase of serum DAO levels was found in the patients with strict and occasional diet compliance. Therefore, we demonstrate that a HRD is not only improving symptoms in HIT, but is causing an increase in serum DAO values that correlates with the degree of diet compliance.

Introduction

The diagnosis of histamine intolerance (HIT) is clinically challenging because HIT is causing various clinical symptoms mainly after ingestion of histamine-rich food and, HIT is thought to be due to a reduced activity of the enzyme diamine oxidase (DAO) [1]. Although serum DAO values are not established to reflect gastrointestinal DAO activity, the diagnosis of HIT can be supported with measurements of serum DAO [2]. We demonstrate that a histamine-reduced diet (HRD) is not only improving symptoms, but is increasing serum DAO correlating with the degree of diet compliance.

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Methods

In an analysis of outpatients' charts at a follow-up visit after a median of 13 months (range: 2–44) we identified 101 white patients, who presented with functional abdominal complaints and a serum DAO value < 10 U/mL at the first visit (male/female = 34/67, median age = 53, and range: 20–81 years). They received written information about HIT and a registered dietician helped to develop an individually tailored HRD according to the literature [3–5].

At the follow-up visit a questionnaire was distributed to patients so that they could be classified into four diet-compliance groups, which were determined as strict (HRD every day), occasional (HRD 3 days a week), rare (HRD once a week), and no diet (Fig. 1). Seventy-two patients (71.3%) returned their anonymous information and, 29 patients (28.7%) did not answer the questionnaire. Additionally, they were asked about the development of symptoms and 2 groups were created: 50 patients with an improvement or who were free of symptoms and 13 patients with unchanged symptoms since diagnosis (Fig. 2).

Determinations of DAO in serum were made with a radio extraction assay (Sciotec Diagnostic Technologies, Tulln, Austria). For individual diagnosis of single or combined food intolerance/malabsorption, all of the patients were examined for and did not show lactose intolerance, fructose malabsorption, *Helicobacter pylori* infection or celiac disease [6]. All patients >50 years old presented no pathology

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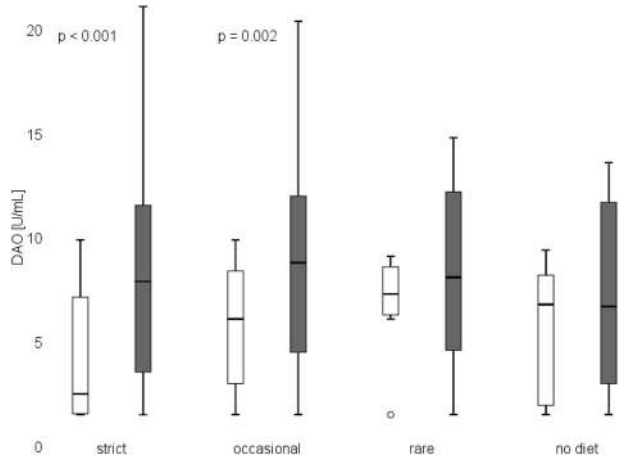

Fig. 1 Boxplots of serum DAO values at first visit and at follow-up visit after a HRD, divided into diet compliance groups. □ at first visit ■ at the follow-up visit

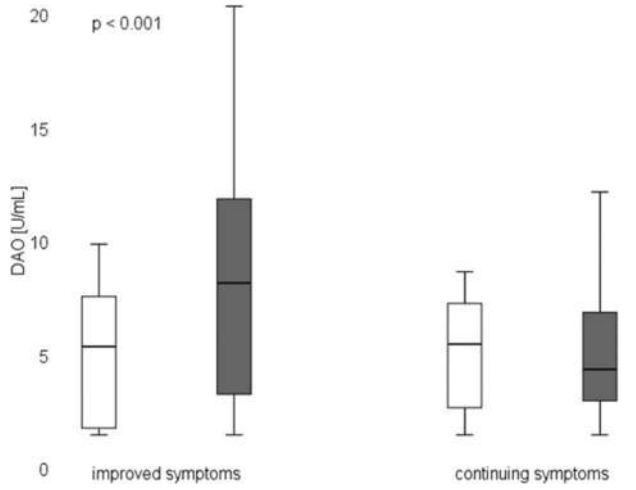

Fig. 2 Boxplots of serum DAO values of 63 patients at first visit and at the follow-up visit after following a HRD with improved and with continuing symptoms. None of the patients with strict diet compliance indicated continuing symptoms. The diet compliance groups occasional, rare and no diet are contained in both symptom groups. □ at first visit ■ at the follow-up visit

in screening by colonoscopy. Body mass index and routine laboratory data did not change from first to control visits.

Statistical analysis was performed with SPSS version 23.0 (IBM, Paris, France). Shapiro–Wilk test revealed that the data were not normally distributed. Data analysis were performed with the nonparametric Wilcoxon signed-rank test for related samples. The Kruskal–Wallis test for the duration of histamine-reduced dieting time was used. To compare the distribution of the compliance groups over the observation period four time groups were created and the chi-squared test was performed. The study was approved by the Ethical Committee of the Johannes Kepler University in Linz, Austria.

Results

In all, 101 included patients the median of serum DAO values increased significantly from 5.8 U/mL (range: 1.5–9.9) to 7.5 U/mL (range: 1.5–25.3) after initiating the HRD ($p < 0.001$). Of the 101 patients 66 demonstrated an increase in DAO values (65%), 8 had unchanged DAO (8%) and 27 had a decrease in DAO (27%). A significant increase of DAO was found in the 27 with strict and 29 patients with occasional compliance (Fig. 1). The groups with rare and no compliance (9 and 7 patients, respectively) did not show significant changes in DAO ($p = 0.401$ and $p = 0.345$). The patients with strict compliance had the highest increase in DAO from a median of 2.5 to 7.9 U/mL. Subgroup analysis of 29 patients, who did not return their questionnaires, showed an increase of median DAO from 5.6 to 6.3 U/mL ($p = 0.022$).

Sixty-three patients reported their symptomatology after initiating a HRD, 50 of these indicated improvement of symptoms (79%). Of these 50 patients, 33 also had an increase in DAO (52%), 6 reported improved symptoms even though their DAO was the same in the first and the follow-up visits (10%), and 11 reported improved symptoms but their DAO decreased (17%).

Combining the DAO values of all 50 patients reporting symptom improvement after following the HRD, there was a significant increase of DAO from median 5.4 U/mL (range: 1.5–9.9) to 8.2 U/mL (range: 1.5–20.4), whereas DAO in 13 patients with continuing symptoms slightly decreased ($p = 0.701$) (Fig. 2). Of the 27 patients with strict diet compliance, 21 reported their symptomatology, 12 of these patients were symptom-free and nine reported symptom improvement due to following the HRD.

Evaluating the DAO values of 101 patients based on time periods following the HRD, all except the time group >18 months, showed a significant increase of serum DAO (<7 months $p < 0.023$, from 8 to 12 months $p < 0.020$, 13–18 months $p < 0.001$, and >18 months $p < 0.067$). However, this time group >18 months had the highest DAO at the first visit.

The Kruskal–Wallis test did not reveal significant differences in dieting time duration between the compliance groups. Comparing the distribution of diet compliance groups within the time periods using the chi-squared test, no difference was found.

Discussion

The clinical diagnosis of HIT is challenging due to complex symptoms and the involvement of numerous organs [7]. However, DAO is the primary enzyme required for the degradation of ingested histamine and is synthesized by apical enterocytes located in the intestinal villi [8].

Based on the diagnosis of HIT a HRD may be developed to treat to the individual symptomatology by reducing the ingestion of histamine-containing foods [2, 9]. This aims to exclude sources that are high in histamine, which include aged, fermented foods and beverages. The list of foods with high histamine content is long and contains a variety of foods, including fruits, vegetables, seasonings, and fish, many of which may have high histamine content as fresh and/or frozen, smoked, and canned products [4]. Additionally, the histamine content in food varies considerably depending on storage time and processing [5]. Certain foods, food additives, preservatives, and medications may support the release of histamine or inhibit enzymes needed to metabolize histamine [6]. Additionally, diet recommendations should take into account the foods that are locally available [10]. A HRD is useful, simple and inexpensive to reduce HIT related symptoms [9] and we here show symptom improvement in 79% and an increase of DAO in 52% of patients with HIT.

Conclusions

We demonstrate that a HRD is not only improving symptoms but is causing an increase in serum DAO values that correlates with the degree of diet compliance. Parts of this study were used by Dr. Verena Malcher to fulfill the requirements for obtaining the degree "Dr. med." at Medical University in Graz, Austria.

Compliance with ethical standards

Conflict of interest Wolfgang J. Schnedl received speaking honoraria from Sciotec. Remaining authors declare no conflict of interest.

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Tyramine and histamine risk assessment related to consumption of dry fermented sausages by the Spanish population

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ABSTRACT

Tyramine and histamine are the main dietary bioactive amines related to acute adverse health effects. Dry fermented sausages can easily accumulate high levels of these hazards and are frequently consumed in Spain. The present work aims to assess the exposure to tyramine and histamine from the consumption of dry fermented sausages by the Spanish population and to assess the risk to suffer acute health effects from this exposure. A probabilistic estimation of the exposure to these hazards was derived combining probability distributions of these amines in dry fermented sausages (n = 474) and their consumption by the Spanish population. The mean dietary exposure to tyramine and histamine was 6.2 and 1.39 mg/meal, respectively. The risk of suffering hypertensive crisis or histamine intoxication by healthy population due to tyramine or histamine intake, respectively, exclusively from dry fermented sausages, can be considered negligible. For individuals under treatment with MAOI drugs, the probability to surpass the safe threshold dose (6 mg/meal) was estimated as 34%. For patients with histamine intolerance, even the presence of this amine in food is not tolerable and it could be estimated that 7000 individuals per million could be at risk to suffer the related symptoms after consuming dry fermented sausages.

1. Introduction

Bioactive amines are microbial metabolites, which can be found in nearly all types of foods in a wide and variable range of concentrations, even within the same type of product. Fermented food and beverages, such as dry fermented sausages, constitute one of the food products that can accumulate high amine contents, which are formed by the decarboxylation of precursor amino acids by fermentative microorganisms as well as by spoilage microorganisms (EFSA, 2011; Bover-Cid et al., 2014). In the last decades, hygienic improvements at all stages of the food chain along with other specific recommendations, such as the use of starter cultures lacking amino acid-decarboxylase potential, might have contributed to reduce the levels of these compounds in fermented meat products. However, data on biogenic amine content in dry fermented sausages on the Spanish market indicate that there are still many products that contain high levels of amines (Latorre-Moratalla et al., 2012a). In fact, different Member States of EU at the EFSA Network Meeting on Microbiological Risk Assessment informed about an increase of bioactive amine content in some fermented foods (EFSA, 2011). Therefore, the presence of these compounds in fermented foods could be still of concern from the food safety point of view (Leuschner et al., 2013). Dry fermented sausages are the most consumed fermented products in Spain, either as a snack or part of a main dish.

Tyramine and histamine are the main dietary bioactive amines associated with adverse health effects. Adverse health effects can occur both in case of high intake of these amines or when the ability to metabolize them is compromised by different causes (including enzymatic deficiencies due to genetic or physiological circumstances or enzymatic blockage). Under these circumstances they accumulate in plasma and exert bioactive effects (Maintz and Novak, 2007; Ladero et al., 2010; Kovacova-Hanuskova et al., 2015). Tyramine may increase blood pressure, especially if its exposure coincides with the antidepressant monoamine oxidase inhibitors (MAOI) drugs (Paulsen et al., 2012; Vidal-Carou et al., 2014). Histamine intoxication, formerly called scombroid or histamine fish poisoning, is caused by the ingestion of high concentrations of this amine, so that normal metabolic mechanisms are insufficient for

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their detoxification. The symptoms associated with this intoxication are allergy-like, characterized by neurological and gastrointestinal effects such as headaches, nausea, vomiting, diarrhea, by cutaneous pruritus, flush and urticaria, and by rhinorrhea and hypotension. The severity of the disorders related to both tyramine and histamine exposure is variable, but it may be considered mild since only sometimes require medical attention. The frequent misdiagnosis is reported as the main reason accounting for the poor statistics about the incidence of health disorders due to dietary amines (FAO/WHO, 2013).

Furthermore, the onset of symptoms related to histamine accumulation in blood has also been associated with a wide range of foods with relatively low histamine content. This is known as histamine intolerance, which derives from the insufficient activity of histamine detoxification systems, concretely a deficiency of DAO enzyme by genetic, pathological (e.g. inflammatory bowel diseases) or pharmacological blockade caused by the treatment with common drugs with known DAO inhibiting side effects (acetylcysteine, clavulanic acid and metoclopramide, etc.) (Jarisch, 2004; Maintz and Novak, 2007). Although the symptoms of histamine intolerance are similar to those of intoxication, some authors associate DAO deficiency with some diseases of high prevalence in the population, such as migraine, atopic dermatitis, irritable bowel syndrome, cyclic vomiting syndrome, and muscular pain (Guida et al., 2000; Maintz and Novak, 2007; Vidal-Carou et al., 2010; Izquierdo et al., 2012; Rosell-Camps et al., 2013; Tormo, 2013; Kovacova-Hanuskova et al., 2015).

The exposure assessment of any specific hazard is a key point on the risk assessment and data quality and treatment could have a significant impact on the risk estimation (FAO/WHO, 2013). Although the quantitative risk assessment is currently recognized as the relevant scientific approach to assess food safety and to provide scientific criteria for decision making in risk management and development of mitigation strategies, only few assessments have been performed regarding bioactive amines in food. Mainly, these assessments dealt with histamine in fish and fishery products (Lehaney & Olley, 2000; Sumner and Ross, 2002; FAO/WHO, 2013), and also tyramine, histamine, putrescine and/or cadaverine in fermented foods based on Austrian data (Rauscher-Gabernig et al., 2009, 2012; Paulsen et al., 2012; Rauscher-Gabernig et al., 2012) and EU data (EFSA, 2011). The deterministic calculations (i.e. point estimates) of the bioactive amine exposure used in most of the above mentioned studies, did not provide exposure level probability. However, a stochastic approach would provide a more representative exposure assessment and hence, a more realistic risk assessment. Therefore, the current work aims to assess the exposure of Spanish consumers to tyramine and histamine from dry fermented sausages by means of a probabilistic estimation, and to quantify until which extend such exposure contributes to reach the maximum tolerable levels generally recognised as safe.

2. Materials and methods

2.1. Data on tyramine and histamine contents in dry fermented sausages from the spanish market

Data about contents of tyramine and histamine in dry fermented sausages from retail Spanish market were obtained from the database of our own research group (Vidal-Carou et al., 1990; Hernández-Jover et al., 1997; Bover-Cid et al., 1999; Miguelez-Arrizado et al., 2006; Latorre-Moratalla et al., 2008, 2012a). A total of 474 samples of different kinds of dry fermented sausages were considered: *Salchichón* (n = 357), *chorizo* (n = 87), *salami* (n = 18) and *sobrasada* (n = 12). All these products are manufactured by fermentation and ripening from pork meat and fat with other additional ingredients (e.g. pepper or red pepper, sugar, wine, garlic, preservatives, etc.) with or without the addition of starter cultures. The determination of bioactive amines in all samples was performed by ion-pair HPLC or UHPLC methods coupled to fluorescence detection (Hernández-Jover et al., 1996; Lavizzari et al., 2006; Latorre-Moratalla et al., 2009).

2.2. Data on consumption of dry fermented sausages by Spanish population

Data about consumption of dry fermented sausages was extracted from the Spanish national dietary survey (Encuesta Nacional de Ingesta Dietética) carried out by the Spanish Agency for Consumer Affairs, Food Safety and Nutrition (AECOSAN, 2011). This survey includes a sample of 3000 individuals randomly selected within the Spanish population, 1500 men and 1500 women aged between 18 and 64 years old. Consumption data (i.e. serving size) of the selected food categories (*salchichón*, *chorizo*, *salami* and *sobrasada*) were expressed in grams. As the toxic effects of tyramine and histamine are of acute nature, the intake was calculated on a meal basis (i.e. grams per meal per person). Only the meals where dry fermented sausages were consumed were considered.

2.3. Exposure assessment

Various probability distributions were fitted to tyramine and histamine contents of Spanish dry fermented sausages and consumption data collected from Spanish population using @Risk 7.0 (Palisade Corporation, NewField, NY). The goodness of fit was evaluated using the Chi-square (χ^2) test. The best-fitting distributions describing tyramine or histamine contents and dry fermented sausage consumption were selected as an input for the assessment of the exposure to these compounds by the probabilistic estimation using the Monte Carlo simulation technique with 10,000 iterations.

2.4. Hazard characterization

The maximum tolerable safety levels as an approximation of the no adverse health effect level adopted in the EFSA Scientific Opinion (EFSA, 2011) for different types of population were considered. These threshold limits were obtained from studies published in the literature based on toxicological data of dietary amines, clinical studies with volunteers, clinical cases and other expert opinions about tolerance or intoxication levels. For tyramine the thresholds were: 6 mg/meal/person for patients treated with MAOI drugs, 50 mg/meal/person for patients receiving third generation of MAOI drugs, so called RIMA (reversible inhibitors of MAO-A); and 600 mg/meal/person for healthy individuals. For histamine, the safe threshold considered for healthy population was 25 mg/meal/person as the most conservative level. In the case of patients with histamine intolerance, even small amounts of this amine in food may cause adverse effects, so as the EFSA (2011) stated, “only levels below detectable limits can be considered as safe”.

To quantify the contribution of the exposure to tyramine and histamine from dry fermented sausages to reach the maximum tolerable levels for healthy and sensitive population a ratio between the exposure level and those thresholds was calculated.

3. Results and discussion

3.1. Distribution of tyramine and histamine contents in dry fermented sausages from the Spanish market

Fig. 1 shows the distribution of tyramine contents (mg/kg) in

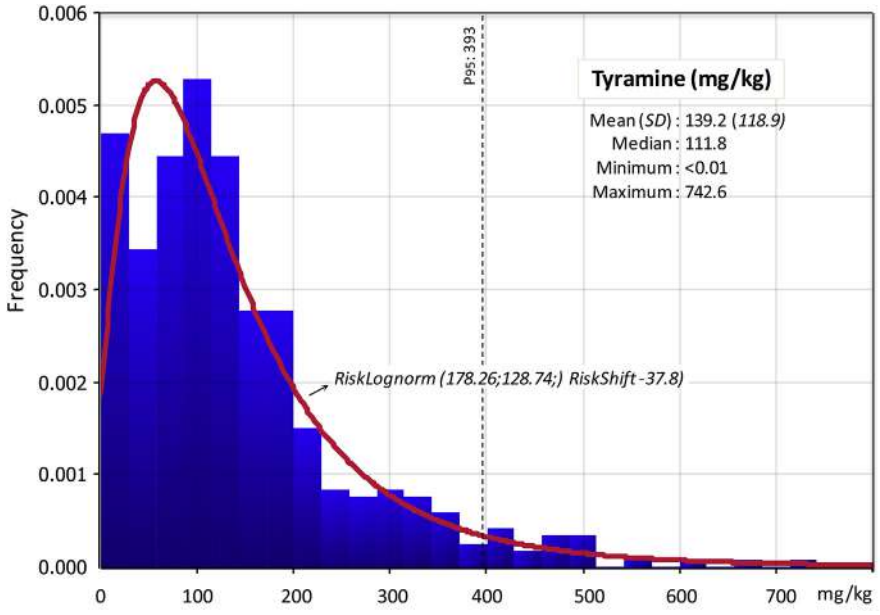

Fig. 1. Distribution of tyramine contents (mg/kg) in Spanish dry fermented sausages.

retail Spanish dry fermented sausages. Tyramine was the most frequent and abundant bioactive amine found in retail dry fermented sausages (detected in the 99.5% of samples) following a *lognormal* distribution with the parameter estimates shown in Table 1. The mean value was 139 mg/kg (relative standard deviation, RSD of 86%) and the range was from not detected (<0.01 mg/kg) to 742 mg/kg, though 95% of samples did not exceed 400 mg/kg. No significant differences were found among contents of tyramine depending on the type of sausage ($p > 0.05$), neither no significant trend was found when assessing tyramine contents as a function of years. Tyramine is extensively reported as the main bioactive amine found in dry fermented sausages, in which is usually produced by fermentative microbial population, mainly lactic acid bacteria (LAB) and more rarely coagulase negative staphylococci (Aymerich et al., 2006; Talon and Leroy, 2011; Latorre-Moratalla et al., 2012b). Latorre-Moratalla et al. (2010) reported that 48% of LAB and 13% of staphylococci isolated from spontaneously dry fermented sausage are able to decarboxylate tyrosine to form tyramine. Likewise some strains of spoilage microbiota have also been described as strongly tyraminogenic (Latorre-Moratalla et al., 2012b).

The occurrence of histamine in retail Spanish dry fermented sausages was less frequent (in the 66% of samples) and usually at lower levels than tyramine. Histamine contents followed a *beta general* distribution (Table 1). The mean value was 27 mg/kg (RSD of 215%) and the 95-percentil 143 mg/kg (Fig. 2). Among samples containing histamine, 57% did not exceed 10 mg/kg. In some particular samples, high histamine contents were found, reaching 475 mg/kg generally accompanied by high amounts of other bioactive amines, such as tyramine, putrescine and cadaverine (data not shown). *Chorizo* sausage showed the highest histamine levels, although the mean value was not statically different when compared with the other products ($p > 0.05$). As in the case of tyramine, histamine contents were not significantly different according to the year of analysis. Some strains of a reduced number of enterobacteria or LAB have the capability to produce histamine in dry fermented sausages. However, the presence of these specific bacteria in this kind of food is not very common unless specific contaminations occur (Roig-Sagués et al., 1996; Bover-Cid et al., 2001). Therefore, high contents of this amine in dry fermented sausages are usually considered as a hygienic indicator of poor

Table 1
Distributions used as inputs for the exposure assessment model and the resulting outputs for dietary exposure of consumers to tyramine and histamine.

	Distributional assumption[a]
Inputs	
Tyramine contents (mg/kg)	Log Normal (178.26[b];128.74[c]; shift [-37.832])
Histamine contents (mg/kg)	Beta General (0.19[d];10.79[e]; 0.01[f]; 1510.4[g])
Consumption (g/serving size)	Gamma (1.97[h]; 22.1[i]; shift [1.90])
Outputs	
Exposure of tyramine (mg/meal)	Pearson5 (2.70[h]; 14.75[i]; Shift [-2.4])
Exposure of histamine (mg/meal)	Log Normal (6.77; 304.2; Shift [-0.000005])

[a] Probability distributions best fitting available data (lowest χ^2 according to @risk).
[b] Mean.
[c] Standard deviation.
[d] α_1.
[e] α_2.
[f] Minimum.
[g] Maximum.
[h] Shape α.
[i] Scale β.

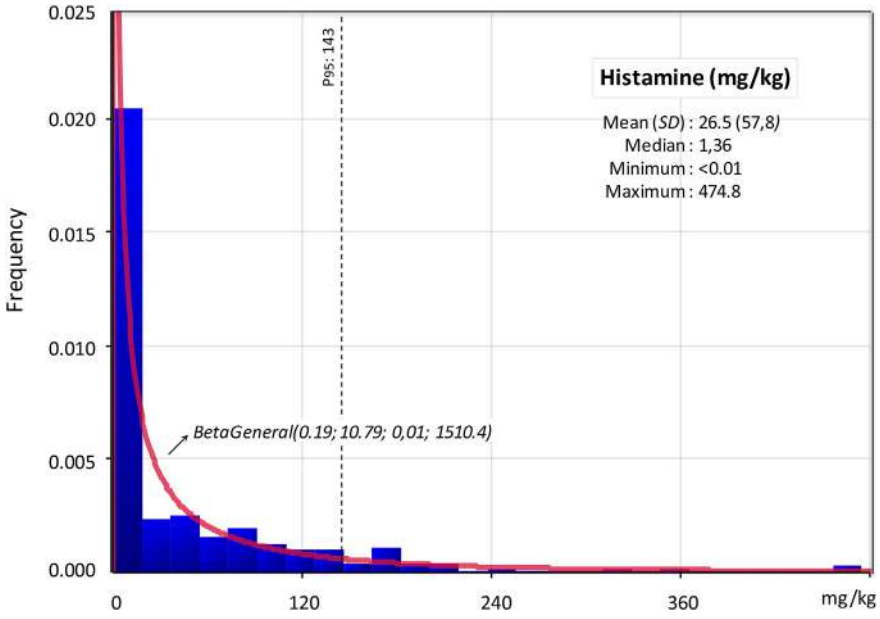

Fig. 2. Distribution of histamine contents (mg/kg) in Spanish dry fermented sausages.

microbiological quality of raw materials and/or improper manufacturing processes.

The large variability of tyramine and histamine contents observed in retail Spanish dry fermented sausages could be explained by multiple factors such as the microbiological quality of raw materials, which varies in each production batch; ingredients and additives (sugar, curing agents, spices, etc.). Additionally, diameter of sausage and technological ripening conditions (temperature and relative humidity) can also influence the phenomena associated with aminogenesis, including microbial growth, acidification, proteolysis and activity of decarboxylases (Suzzi and Gardini, 2003; Spano et al., 2010; Singh et al., 2012). Therefore, the probabilistic exposure assessment from data about biogenic amine in retail products becomes the most suitable approach to capture and deal with the actual variability of the occurrence of these hazards.

3.2. Distribution of the consumption of dry fermented sausages

According to the last extensive national dietary survey performed in Spain (AECOSAN, 2011) a wide variability in the amount of sausage consumption was recorded, ranging from 2 to more than 250 g/meal. The mean consumption was 45 g/meal (RSD of 73%) and the 95-percentile 100 g/meal (Fig. 3). Consumption data described a *gamma* distribution (Table 1). According to this survey, the 19% of meals contain some kind of dry fermented sausages as starter, main dish or snack, although the serving size changed in each case. Concretely, the product most often consumed is *chorizo*

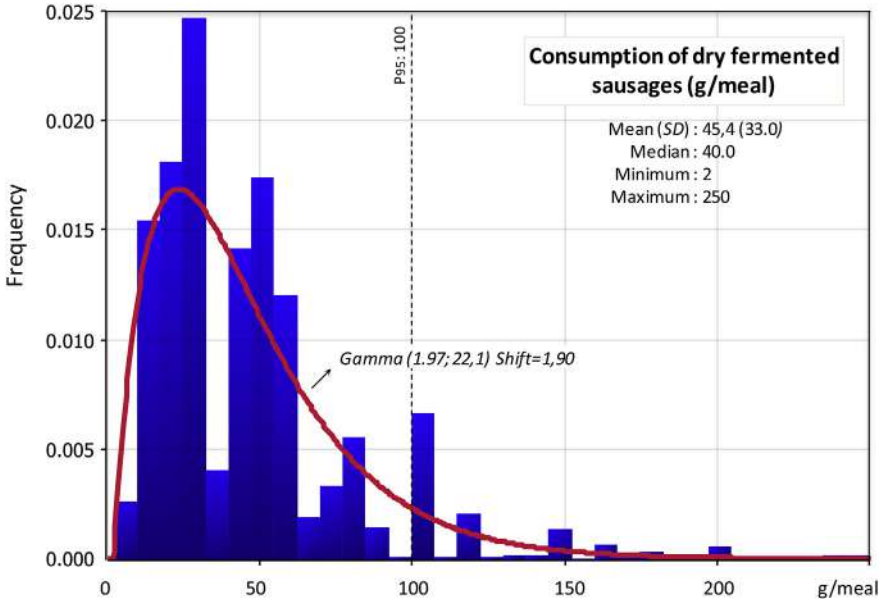

Fig. 3. Distribution of dry fermented sausage consumption by the Spanish population (g/meal).

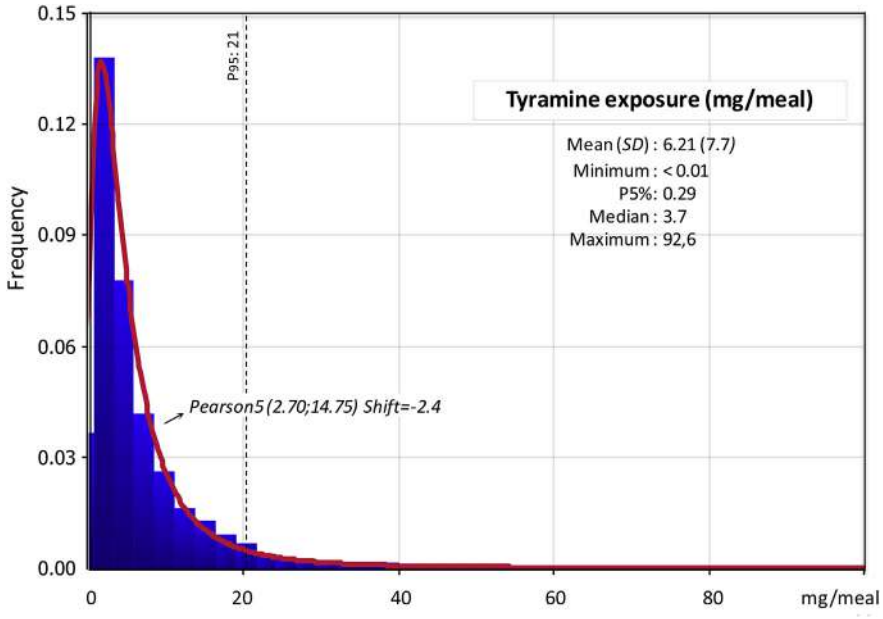

Fig. 4. Results of tyramine exposure (mg/meal) from dry fermented sausages by the Spanish population.

(about once a week) with a mean value of 42 g/meal/person. *Salchichón* sausages type is consumed less frequently (about once every 3 weeks) but in higher amounts (mean of 52 g/meal). *Sobrasada* and *salami* are more sporadically consumed but in similar amounts to *salchichón*. No statistically significant differences were detected in consumption according to age or gender of consumers.

3.3. Exposure assessment and hazard characterization of tyramine

The outputs of the probabilistic exposure assessment for tyramine performed by combining probability distributions of tyramine contents and sausages consumption are shown in Fig. 4.

The exposure to tyramine from dry fermented sausages followed a *Pearson5* distribution (Table 1). The mean value for tyramine exposure was 6.2 mg/meal (RSD of 124%). In the 95% of meals involving dry fermented sausages, the exposure to tyramine was below 21 mg, whereas the maximum level was 93 mg/meal.

In the assessment carried out by EFSA, tyramine exposure data on dry fermented sausages from Spain is not available and only a total European 95-percentile was reported, ranging from 17.2 to 99.3 mg/day, depending on the country (EFSA, 2011). Also considering the high level exposure (95-percentile) to tyramine of the Spanish population (21 mg/meal), this data is placed in the lower European range determined by the EFSA. This lower intake of tyramine per meal could be attributed to lower serving size of these products by the Spanish population in comparison with other EU countries, as the occurrence of tyramine in Spanish dry fermented sausages is similar in both assessments.

Table 2 shows the contribution of the exposure to tyramine from Spanish dry fermented sausages to achieve the maximum tolerable levels for healthy population and for vulnerable population under treatment with MAOI or RIMA drugs. The quantification was performed by different exposure estimations: mean, 95-percentile and maximum values. On the basis of the results obtained regarding the tyramine exposure, the risk of suffering a hypertensive crisis by the healthy population was negligible. In fact, even if it is considered a high tyramine exposure (95-percentile and maximum) only a 4 and 16% of the maximum tolerable amount (600 mg/meal) was reached, respectively. Although this contribution is apparently low, it must be taken into account that meals may also contain other food with variable bioactive amine levels (e.g. cheese, wine, etc.). The assessment of the overall exposure to tyramine by the multiple sources of this bioactive amine remains unknown.

In the case of people under treatment with RIMA drugs, the 95-percentile of exposure of tyramine (21 mg/meal) meant the 42% of the maximum tolerable level. The probability to reach an exposure of 50 mg of tyramine in a meal was very low (0.01%) and only this threshold limit was exceeded with the maximum value of tyramine exposure (92.5 mg/meal). The situation is different in those individuals treated with MAOI drugs, in which the mean exposure to tyramine by the consumption of sausages already exceeded the safe dose (6 mg/meal). According to the tyramine exposure output, the probability to surpass this tolerable exposure level per meal was estimated to be 34%.

According to the last report on antidepressant drug consumption by the Spanish population published by the Spanish Agency on Medicinal Products, the only MAOI and RIMA drugs used for the treatment of depression are tranylcypromine and moclobemide. Nowadays, up to 0.001% of the Spanish population is receiving a daily dose of these drugs, being used only as an alternative therapy in depressive patients resistant to more frequently used antidepressants (AEMPS, 2015). In view of this data and taking into

Table 2
Contribution (%) of the tyramine exposure from dry fermented sausages by the Spanish population to achieve the maximum tolerable levels generally adopted as safe by EFSA for the healthy population and for vulnerable people under treatment with RIMA (reversible inhibitor of monoamine oxidase A) or MAOI (monoamine oxidase inhibitor) drugs.[a]

Tyramine exposure (mg/meal)		Contribution (%)		
		Healthy population	RIMA patients	MAOI patients
Mean	6.2	1	12	103
95-Percentile	21	4	42	350
Maximum	92.5	16	185	1540

[a] 600 mg/meal for healthy population, 50 mg/meal for patients treated with RIMA drugs and 6 mg/meal for patients treated with MAOI drugs.

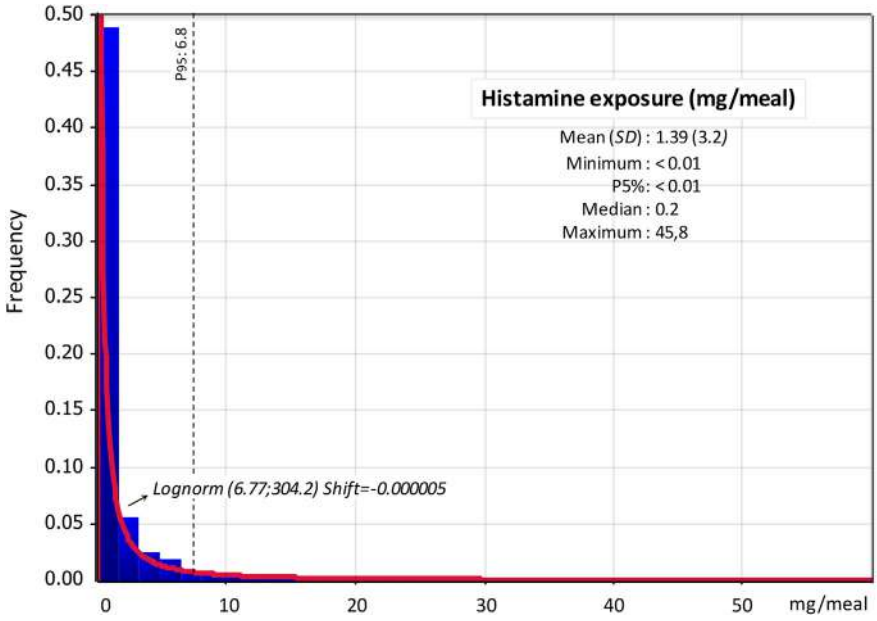

Fig. 5. Results of histamine exposure (mg/meal) from dry fermented sausages by the Spanish population.

account that approximately 46 million people in Spain are potential consumers of dry fermented sausages (i.e. total Spanish population excluding the 1.5% reported as not consumers of meat products according to ENIDE survey), 3 individuals per million (i.e. 156 individuals) would be daily exposed to a level of tyramine above the maximum tolerable threshold when taking MAOI drugs. However patients prescribed with MAOI and RIMA are usually advised to limit or avoid the consumption of dry fermented sausages. Therefore, as MAOI treated individuals could have consumption-patterns different from the data used in the present assessment (from mostly non MAOI treated people), the actual exposure to tyramine of this vulnerable population will be most probably lower than the above estimation.

3.4. Exposure assessment and risk characterization of histamine

The outputs of the probabilistic exposure assessment for histamine performed by combining probability distributions of histamine contents and sausages consumption are shown in Fig. 5. Levels of exposure to histamine from the consumption of dry fermented sausages followed a *lognormal* distribution (Table 1) with a mean value of 1.39 mg/meal (RSD of 228%). Only 5% of meals resulted in histamine intake levels higher than 6.8 mg. As in the case of tyramine, in the European exposure assessment histamine exposure data specifically for Spain is not available. The total European 95-percentile reported for histamine exposure in these type of products was from 6.4 to 37.1 mg/day, depending on the country (EFSA, 2011). Spanish exposure levels obtained in the present assessment are clearly placed within the lower interval, which could be explained, as in the case of tyramine, by the lower consumption of these products by the Spanish population in comparison with those reported for the European population.

Table 3 shows the contribution (percentage) of the exposure to histamine from dry fermented sausages to achieve the maximum tolerable level adopted for preventing histamine intoxication (25 mg/meal). Considering the mean exposure, only the 6% of the critical threshold was reached, and even considering 95-percentile of the exposure less than the 30% of this limit was reached. Based on the present results, the risk to suffer acute effects related to histamine by the consumption of Spanish dry fermented sausages is really low, since only in very rare occasions (maximum exposure value) the threshold was nearly doubled.

An additional concern associated with the occurrence of histamine in food is for people suffering from histamine intolerance, in which even the presence of this amine at very low levels is considered to be capable of triggering adverse effects. This intolerance related to a deficiency in the metabolism of histamine due to the lack of specific enzymes, what produces its accumulation in plasma and the appearance of multi-faced clinical symptoms. For this reason, for individuals with histamine intolerance only food with levels of this amine below detectable limit could be considered as safe (EFSA, 2011). Moreover, it should be taken into account that the occurrence of dietary potentiators, such as other bioactive amines or alcohol and its metabolite acetaldehyde, could also increase or enhance the susceptibility to histamine and, accordingly, the risk of adverse reactions could rise (Maintz and Novak, 2007). In the dry fermented sausages from the Spanish market considered in this study, the 66% contained histamine, and very frequently accompanied with other potentiate bioactive amines such as putrescine and cadaverine.

Some studies estimate that histamine intolerance may affect 1% of the general population (Maintz and Novak, 2007; Kovacova-Hanuskova et al., 2015). However, the increasingly widespread

Table 3
Contribution (%) of the histamine exposure from dry fermented sausages by the Spanish population to achieve the maximum tolerable levels generally adopted as safe by EFSA for the healthy population (histamine intoxication) and for histamine intolerance*.

Histamine exposure (mg/meal)		Contribution (%)	
		Healthy population	Histamine intolerance patients[a]
Mean	1.4	6	–
95-Percentile	6.8	27	–
Maximum	45.8	183	–

*25 mg/meal for healthy population.
[a] According to EFSA, for people with histamine intolerance even small amounts of histamine may cause adverse health effects and no maximum tolerable threshold has been adopted. Therefore, no contribution has been calculated.

diagnosis of histamine intolerance by DAO deficiency could augment this population percentage. In fact, it has been published recently more evidence about the relationship between a reduced capacity to metabolize dietary histamine by a deficit of DAO and health problems such as migraine, gastrointestinal disorders, skin reactions and muscle pain, among others (Guida et al., 2000; Vidal-Carou et al., 2010; Izquierdo et al., 2012; Rosell-Camps et al., 2013; Tormo, 2013). Some recent interventional studies have shown a high incidence rate of DAO deficiency (up to 80%) among this type of susceptible population (Izquierdo et al., 2012; Rosell-Camps et al., 2013). In addition, it should be considered that histamine intolerance can be a consequence of inhibition of DAO activity as a side effect caused by a number of commonly used drugs, including acetylcysteine, clavulanic acid, metoclopramide, verapamil, isoniazid, etc. (Maintz and Novak, 2007; Kovacova-Hanuskova et al., 2015). Indeed, it was estimated that approximately 20% of the European population could be taking some of the DAO inhibitor drugs (EFSA, 2011).

Considering that 46 million people in Spain are potential consumers of dry fermented sausages and that the histamine intolerance could affect at least the 1% of the population and taking into account the estimation that the 66% of retail dry fermented sausages contained histamine (percentage obtained in the present study), it could be expected that the 0.7% of Spanish population (303,600 individuals) may suffer some of the related symptomatology after the consumption of dry fermented sausages. Moreover, it should be taken into account the existence of other potential sources of histamine, such as cheese, fish or fish products, fermented beverages and some vegetables, that are fairly widespread making the risk of suffering this intolerance higher.

4. Conclusions

A reliable estimation of exposure has been achieved through the probabilistic assessment from representative Spanish data of amine contents and consumption of dry fermented sausages, in which the actual distribution of the content of the hazard and the mathematical function describing the probability of occurrence of every value is described. According to this probabilistic estimation, tyramine and histamine intake would hardly contribute to reach their maximum tolerable threshold for healthy individuals. However, sensitive people treated with MAOI drugs or with histamine intolerance by deficit of DAO would be at risk of suffering adverse effects due to the consumption of dry fermented sausages. Concretely, the maximum tolerable limit established for patients under MAOI treatment (6mg/meal) was exceeded in the 34% of meals containing dry fermented sausages. Therefore, it could be estimated that 3 habitants per million of the Spanish population could suffer adverse health effects due to the exposure to tyramine from dry fermented sausages and the concomitant consumption of MAOI drugs. This estimated risk is very low compared with that found for individuals with histamine intolerance, which rises up to practically 7000 cases per million habitants.

Due to the estimated risk of suffering adverse effects attributed to histamine in food, it seems important that food industry accepts the challenge to proceed with measures focussed on the minimization of the occurrence of histamine in food. This implies to control the potentially aminogenic microorganisms, its growth and its amino acid-decarboxylase activity during the whole production and merchandising chain. Moreover, the statement of tyramine and histamine content in food labelling would be another additional measure to prevent the occurrence of the related adverse effects of those bioactive amines in sensitive individuals, especially for histamine intolerant individuals. Additional studies are needed to estimate the maximum level of histamine and eventually other amines in food to provide histamine intolerant patients with clearly labelled products.

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Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2016.11.011.

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Serum diamine oxidase activity is associated with lactose malabsorption phenotypic variation

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Serum diamine oxidase activity is associated with lactose malabsorption phenotypic variation

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Abstract

Objectives:

Recently, an intermediate lactose intolerance (LI) phenotype based on the lactase gene (*LCT*) C/T_{-13910} polymorphism was proposed. However, a multifactorial genesis of LI phenotypic variation including endogenous and exogenous factors cannot be ruled out. Therefore, this study was conducted to investigate a possible association between serum diamine oxidase (DAO) and LI phenotypes in individuals with lactose malabsorption (LM).

Design and methods: A total of 121 ambulatory patients with LM were included in this retrospective study. The lactose hydrogen breath test (LHBT) and serum DAO activity measurements were performed on the same day. A thorough anamnesis with respect to gastrointestinal symptoms was carried out at the initial consultation.

Results: In total, 44 (36.4%) patients with a serum DAO activity < 10 U/mL showed higher H_2 levels after 60 (mean: 53.7 ± 57.6 vs 34.5 ± 31.7 parts per million [ppm], p = 0.116), 90 (mean: 70.3 ± 57.5 vs 52.7 ± 41.4 ppm, p = 0.184) and 120 minutes (mean: 98.9 ± 72.5 vs 67.9 ± 44.9 ppm, p = 0.012) during LHBT compared to 77 (63.6%) patients with a serum DAO activity ≥ 10 U/mL. Individuals with a serum DAO activity < 10 U/mL tended to report gastrointestinal symptoms during the LHBT more often (p = 0.091).

Conclusions: Our findings suggest that patients with LM and a serum DAO activity level < 10 U/mL had higher end-expiratory H_2 levels and tended to be more

symptomatic during the LHBT compared to LM patients with DAO activity levels ≥ 10 U/mL.

Key words: *Lactose intolerance*

Diamine oxidase

Breath test

Phenotypes

Abbreviations

LI, lactose intolerance; LM, lactose malabsorption; LHBT, lactose hydrogen breath test; *LCT*, lactase gene; DAO, diamine oxidase; HI, histamine intolerance; CO_2, carbon dioxide; H_2, hydrogen.

1. Introduction

Lactose malabsorption is a widespread gastrointestinal condition worldwide. The lactase enzyme, which is responsible for the cleavage of the disaccharide lactose into the absorbable monosaccharides glucose and galactose, is localized in the brush boarder of the small intestine [1]. This enzyme shows maximal activity during the perinatal period. After 2-12 years of age, a “lactase non-persistence” phenotype with low lactase activity and a “lactase-persistence” phenotype with normal lactase activity can be distinguished [2]. In individuals with “lactose non-persistence”, lactose malabsorption (LM) is defined as an inadequate digestion of lactose, whereas lactose intolerance (LI) is defined as LM combined with gastrointestinal symptoms [3].

The lactose hydrogen breath test (LHBT) is a widely used diagnostic tool for lactose malabsorption testing [4], with about one-third of lactose malabsorbers complaining of clinical symptoms during the LHBT [5]. In contrast, genetic testing for lactase non-persistence does not allow for the assessment of clinical symptoms or different clinical presentations of LI [4].

Recently, an intermediate LI phenotype based on the lactase gene (*LCT*) C/T_{-13910} polymorphism was proposed [6]. This fact raises the question of non-genetic factors being responsible for a multifactorial genesis of different LI phenotypes. Interestingly, a previous study found significant correlations between lactase and diamine oxidase (DAO) activities in small intestinal biopsies of children [7]. Based on these results, a possible relationship of DAO activity and different clinical presentations of LI may be considered.

DAO, the main enzyme in metabolizing ingested histamine, is synthesized by mature apical cells in the intestinal mucosa localized in the upper intestinal villi [8]. It is continuously released from the enterocytes and also transported from the intestinal mucosa to the blood circulation [9]. Diseases with intestinal mucosa damage lower the serum DAO activity. The decrease is associated with the severity of mucosal damage [10].

The aim of this retrospective study was to investigate a possible association between serum DAO activity and different LI phenotypes. Therefore, LHBT and serum DAO activity measurements were performed in parallel for 121 ambulatory patients with LM.

2. Materials and Methods

2.1. Study design and study population

A total of 121 consecutively-examined ambulatory adult patients with verified LM were included in this retrospective study. The inclusion criteria were: a minimum age of 18 years, the parallel performance of the LHBT and serum DAO activity measurements, a thorough anamnesis of gastrointestinal symptoms at the first consultation, and a twelve-hour overnight fasting state. Furthermore, patients were asked to refrain from smoking. Individuals with incomplete case histories or colonoscopy and/or antibiotic-based therapy at least 4 weeks before the LHBT were excluded from the study. None of the patients showed signs of active or chronic inflammatory bowel disease or were on drug intake (i.e., acetylcysteine, verapamil, cimetidin, metoclopramid) at study entry.

2.2. Ethics

The study was approved by the ethics committee of the Johannes Kepler University of Linz (Linz, Austria [trial registration number: K-107-16]) and is in accordance with the latest version of the Declaration of Helsinki.

2.3. LHBT

Stationary gas-chromatography was employed to measure the end-expiratory H_2 concentrations (Gastrolyzer, Bedfont Scientific inc., Kent, United Kingdom). The baseline (0 minutes) concentration was determined after an overnight fasting state of 12 hours. After the oral ingestion of 50 g of lactose dissolved in 200 mL of water the end-expiratory breath H_2 concentration was measured at 30, 60, 90, and 120 minutes [11, 12]. The results were expressed in parts per million (ppm). The patients were instructed to report clinical symptoms and to avoid smoking, eating or physical activity during the test. The LHBT was interpreted to be positive if the H_2 peak was ≥ 20 ppm over the baseline value [11, 13].

2.4. Serum DAO activity measurements

The serum DAO activity was determined using a quantitative radio extraction assay (DAO-REA®; Sciotec Diagnostic Technologies GmbH, Tulln, Austria). According to the literature [14, 15], a serum DAO activity < 10 U/mL is considered to be associated with a higher risk of histamine intolerance (HI) compared to a serum DAO activity ≥ 10 U/mL. The intra- and inter-assay reproducibility of the DAO radio extraction assay was < 10 and < 15% (information of the manufacturer).

2.5. Statistical analysis

For the statistical analysis, descriptive statistics were used to summarize and present the study variables. For subgroup comparisons of categorical parameters, the exact Chi-Square test was used. For subgroup comparisons of metric variables in the case of normal distribution (verified with the Kolmogorov-Smirnov test) the paired Student's t-test was calculated. For metric non-normal distributed variables the exact Mann-Whitney U-test was used. A p-value < 0.05 was considered statistically significant. Analyse-it® software version 2.30 (Analyse-it Software, Ltd, Leeds, United Kingdom) was used for statistical analysis.

3. Results

3.1. Patient characteristics

In total, 121 patients were included, of whom 80 (66.1%) were female and 41 (33.9%) were male with a mean age of 47 years. The demographic and clinical data are presented in Table 1.

3.2. Serum DAO activity

Serum DAO measurements of all patients (n = 121) showed a median value of 13.6 (range: 1.5 – 65.7) U/mL. Of these, 77 (63.6%) individuals had a serum DAO activity ≥ 10 U/mL (median: 18.4 [range: 10.3 – 65.7]), whereas 44 (36.4%) patients demonstrated a serum DAO value < 10 U/mL (median: 5.7 [range: 1.5 – 9.5]).

3.3. LI phenotypic variation

LM patients with a serum DAO activity < 10 U/mL showed higher end-expiratory H_2 levels after 60 (mean: 53.7 ± 57.6 vs 34.5 ± 31.7 ppm, p = 0.116), 90 (mean: 70.3 ± 57.5 vs 52.7 ± 41.4 ppm, p = 0.184) and 120 minutes (mean: 98.9 ± 72.5 vs 67.9 ± 44.9 ppm, p = 0.012) during LHBT compared to LM patients with a serum DAO activity ≥ 10 U/mL. Box-and-whisker plots of end-expiratory H_2 levels during the LHBT in 77 and 44 individuals with serum DAO activity ≥ 10 and DAO activity < 10 U/mL, respectively, are shown in Fig.1 and Fig. 2.

3.4. Self-reported symptoms during the LHBT

Taken together, 82 (67.8%) patients with LM reported one or more gastrointestinal symptoms (i.e., abdominal pain, diarrhea, bloating, heartburn, burping, nausea) during the lactose LHBT. Interestingly, self-reported gastrointestinal symptoms tended to be more frequent in patients (34 out of 44 [77.3%]) with a serum DAO activity < 10 U/mL compared to those patients (48 out of 77 [62.3%]) with a DAO activity ≥ 10 U/mL (p = 0.091).

4. Discussion

In the present study, 121 adult individuals with LM were investigated using LHBT and serum DAO activity measurements. To the best of our knowledge, this is the first study addressing the possible association between serum DAO activity levels and different LI phenotypes.

The serum DAO activity has been recognized as a marker of intestinal mucosal maturation and integrity [16] with low serum DAO levels reflecting mucosal injury [17, 18]. Similarly, a reduced lactase activity in the small intestine may also indicate mucosal damage [18, 19] associated with conditions such as gastroenteritis, short bowel syndrome, celiac and tropical sprue, infectious enteritis, radiation enteritis, gastrointestinal surgery or drugs [12]. As a consequence non-absorbable lactose reaches the large intestine, where it is fermented into short-chain fatty acids, carbon dioxide (CO_2), and hydrogen (H_2) by colonic bacteria [12, 20]. In turn, the H_2 production causes GI symptoms such as abdominal pain, bloating and/or diarrhea [6, 20, 21].

The measurement of H_2 in the end-expiratory breath is considered to be the most clinically significant parameter of bacterial lactose fermentation in the colon [6]. Nevertheless, the interpretation of the LHBT is limited because this method is not standardized yet [12]. Moreover, in individuals with carbohydrate malabsorption, the acidic microclimate in the colon may affect the bacterial H_2 production and cause false negative LHBT results [12, 22]. A longer orocecal transit time may be another possible reason for false negative LHBT results, because breath testing may be finished before a measurable H_2 increase is established [11, 12]. Pre-analytical poor patient preparation during the alveolar air collection may also influence LHBT measurements in patients with LI [20].

In this study serum DAO activity discriminates between two distinct LI phenotypes as defined by LHBT: lactose malabsorbers with higher end-expiratory H_2 breath levels (DAO activity < 10 U/mL) and those with lower H_2 breath levels (DAO activity ≥ 10

U/mL). Of note, individuals with LM and a DAO activity < 10 U/mL tended to be more symptomatic during LHBT ($p = 0.091$).

In a recent study, individuals with the *LCT* C/T_{-13910} genotype tended to have clinical symptoms (i.e., abdominal pain) more often during breath testing compared to those with an *LCT* T/T_{-13910} genotype [6]. Therefore, the genotype-phenotype correlation may be one explanation for the existence of different LI phenotypes. However, our data demonstrate that serum DAO activity levels also segregate into varying clinical presentations of LI. Nevertheless, the factors responsible for triggering symptoms in individuals with LI are not yet completely understood [5, 20]. Furthermore it is known that the prediction of LI based on the subjective perception of reported symptoms remains difficult [12, 23].

Two shortcomings of this study may be described. Firstly, intestinal lactase activity measurements and *LCT* genotyping (C/T_{-13910} polymorphism) were not performed. Secondly, this study is retrospective and cross-sectional in nature, representing the serum DAO activity determinations only at a single measuring point.

In conclusion, our findings suggest that patients with LM and a serum DAO activity level < 10 U/mL had higher end-expiratory H_2 levels and tended to be more symptomatic during the LHBT compared to LM patients with DAO activity levels ≥ 10 U/mL. However, prospective longitudinal studies incorporating follow-up measurements of DAO activity are required to fully elucidate the association with LI.

Conflict of interest

Wolfgang J. Schnedl is co-founder of GedoMed GmbH (Bruck an der Mur, Austria). The other authors disclose no conflict of interest regarding the publication of this article.

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Figures:

Fig. 1.

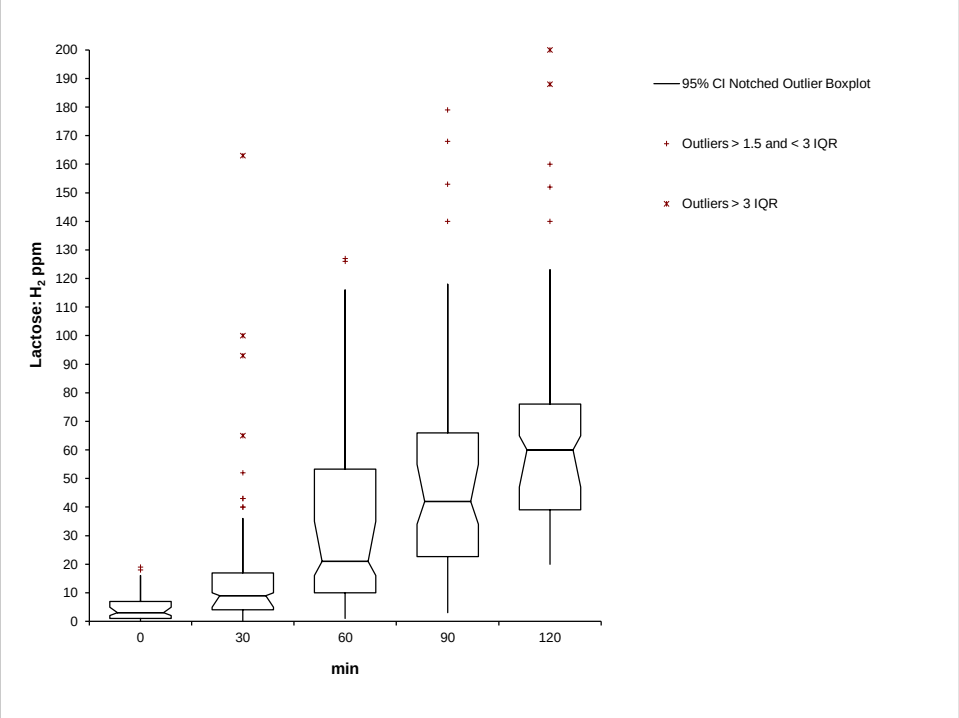

Fig. 1. Box-and-whisker plot of exhaled H_2 levels during the LHBT in 77 patients with serum DAO activity ≥ 10 U/mL. The boxes represent the 25th to 75th percentile range. The line inside the boxes represents the median value of H_2 concentrations expressed in parts per million (ppm).

Fig. 2.

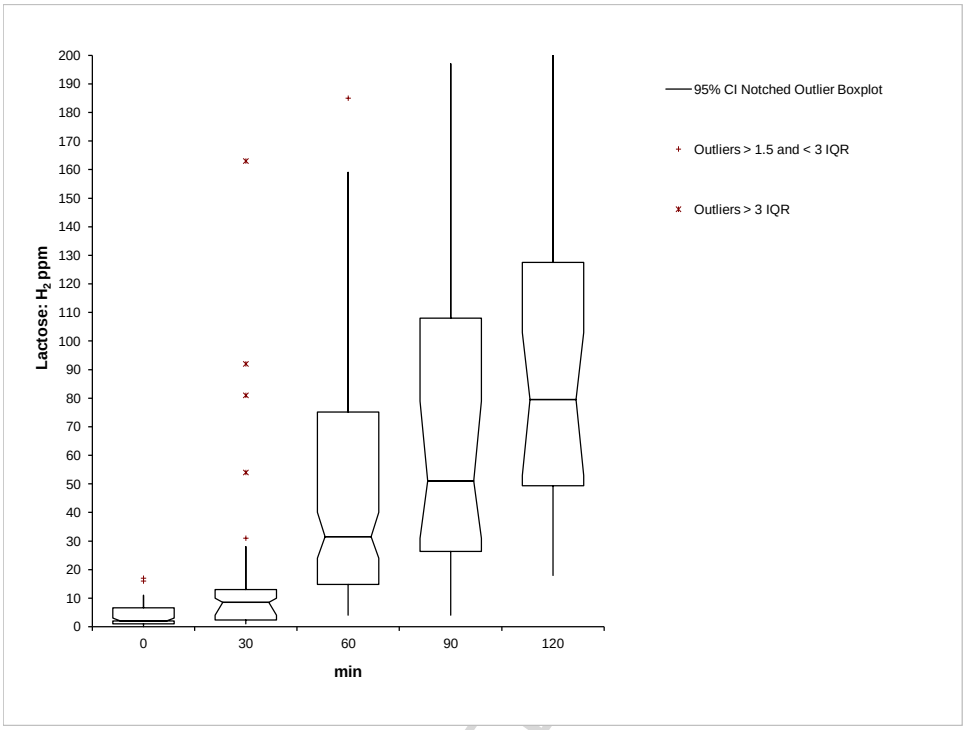

Fig. 2. Box-and-whisker plot of exhaled H_2 levels during the LHBT in 44 patients with serum DAO activity < 10 U/mL. The boxes represent the 25th to 75th percentile range. The line inside the boxes represents the median value of H_2 concentrations expressed in parts per million (ppm).

Tables

Table 1

Demographic and clinical characteristics of the patients

	Study population (n = 121)
Gender:	
Female	80 (66.1%)
Male	41 (33.9%)
Mean age in years (± SD)	47 (± 17)
Gastrointestinal symptoms:	
Abdominal pain	39 (32.2%)
Bloating/flatulence	82 (67.8%)
Diarrhea	36 (29.7%)
Obstipation	6 (4.9%)
Heartburn	4 (3.3%)
Burping	2 (1.6%)
Nausea	1 (0.8%)

SD = standard deviation.

Highlights

- Lactose breath testing and serum diamine oxidase (DAO) measurements are performed.
- Association with lactose malabsorption phenotypic variation is investigated.
- Serum DAO activity level < 10 U/mL associates with higher exhaled H_2 levels.
- Lactose malabsorbers with low DAO activity (<10 U/mL) tend to report symptoms more often.

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Concomitant Prevalence of Low Serum Diamine Oxidase Activity and Carbohydrate Malabsorption. Can J Gastroenterol Hepatol. Enko D, Meinitzer A, Mangge H, Kriegshäuser G, Halwachs-Baumann G, Reininghaus EZ, Bengesser SA, Schnedl WJ. **2016**

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Research Article

Concomitant Prevalence of Low Serum Diamine Oxidase Activity and Carbohydrate Malabsorption

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The aim of this retrospective study was to analyze the concomitant prevalence rates for lactose malabsorption (LM), fructose malabsorption (FM), and histamine intolerance (HI) in patients with so far unexplained gastrointestinal (GI) symptoms. A total of 439 outpatients, who presented unclear abdominal discomfort, underwent lactose (50 g) and fructose (25 g) hydrogen (H_2) breath tests. Additionally, serum diamine oxidase (DAO) measurements were performed. Individuals with low serum DAO activity (<10 U/mL), GI symptoms, and response to histamine-free diet were diagnosed with HI. Of all 439 patients, 341 (77.7%) were found with 7 various GI conditions. In total, 94 (21.4%), 31 (7.1%), and 100 (22.8%) individuals presented LM, FM, or HI only, whereas 116 (26.4%) patients showed an overlap of GI entities investigated here. Interestingly, 89 out of 241 (36.9%) individuals with carbohydrate malabsorption were also diagnosed with HI (LM + HI: 52 [11.8%], FM + HI: 23 [5.2%], and LM + FM + HI 14 [3.2%] individuals). In conclusion different combinations of LM, FM, and HI are present in individuals with unclear abdominal discomfort/pain. In clinical practice we suggest testing for LM, FM, and additional HI in the diagnostic work-up of these patients. Depending on these various diagnoses possible, patients should get an individualized dietary advice.

1. Introduction

Nonspecific abdominal discomfort is a common and widespread condition worldwide. Among the multitude of differential diagnoses, carbohydrate malabsorption is a frequent cause of unexplained gastrointestinal (GI) symptoms [1–3].

Lactose malabsorption (LM) results from a reduced expression or impaired activity of the enzyme lactase in the epithelium of the small intestine. Hence, the nonabsorbable disaccharide lactose cannot be cleaved into the absorbable monosaccharides glucose and galactose [3, 4]. By comparison, fructose malabsorption (FM) is caused by limited absorption capacity of the GLUT-5 protein, the major fructose transporter in the small intestine [3, 5, 6]. The undigested and unabsorbed carbohydrates reach the large intestine, where the colonic bacteria ferment the sugar molecules, which may cause GI symptoms such as abdominal pain, bloating, and/or diarrhea [3, 7].

These complaints are also the leading GI symptoms of histamine intolerance (HI) [8, 9]. Therefore, this GI condition should also be considered as a possible underlying reason of unclear abdominal discomfort [8]. HI results from a disequilibrium of the biogenic amine histamine, which occurs to various degrees in many foods, and the reduced capacity of histamine degradation. An impaired activity (<10 U/mL) of serum diamine oxidase (DAO), which is the main enzyme for

Table 1: Main demographic and clinical characteristics of the study population.

	Study population
Patients	439 (100.0%)
Gender	
Male	138 (31.4%)
Female	301 (68.6%)
Median age, years (25th, 75th percentile)	43.8 (29.9, 55.4)
Presence of gastrointestinal symptoms	
Abdominal pain/discomfort	99 (22.6%)
Bloating/flatulence	299 (68.1%)
Diarrhea	249 (56.7%)
Obstipation	24 (5.5%)
Others (nausea, emesis, burping, and heartburn)	61 (13.9%)

the metabolism of ingested histamine, causes an insufficient extracellular histamine breakdown in the GI tract [8, 10].

Using MEDLINE® database (US National Library of Medicine, Bethesda, MD, USA), we could not find studies investigating serum DAO measurements in patients with carbohydrate malabsorption. Therefore, this retrospective study was conducted to investigate concomitant prevalence rates of LM, FM, and HI in patients presenting unexplained abdominal discomfort.

2. Materials and Methods

2.1. Patients. A total of 439 case histories of outpatients, who visited the medical practice of internal medicine due to nonspecific abdominal complaints, were included in this retrospective analysis. The ethnic origin of all included individuals was Caucasian. All of them were investigated for LM, FM, and HI. Blood draw from a peripheral vein for DAO activity measurements was performed in the morning after an overnight fasting state (>12 h). None of the included patients was on histamine-free diet, had histamine releasing drugs, or had alcohol at the time of blood sampling and anamnesis. At the presentation a thorough evaluation of abdominal symptoms was made including a dietary history and the association between meal consumption and the occurrence of symptoms (Table 1).

Individuals presenting extraintestinal symptoms (e.g., migraine, dizziness, malaise, or headache) only, patients with gastritis caused by the intake of nonsteroidal anti-inflammatory drugs, patients with acute or chronic inflammatory bowel or infectious disease and individuals with elevated anti-tissue-transglutaminase (TTG) IgA antibodies were not included in this evaluation. In addition to positive TTG IgA testing, a biopsy-based histological investigation of the small intestinal mucosa was part of the diagnostic evaluation. *Helicobacter pylori* infection was tested in all patients and eradication therapy was initiated if applicable. The data on *H. pylori* were not included in this manuscript because a causative role in GI malabsorption comparable to carbohydrate malabsorption is not confirmed.

This study was approved by the Ethical Committee of the Johannes Kepler University Linz (Linz, Austria) and is in accordance with the latest version of the Declaration of Helsinki.

2.2. LM and FM. Gas chromatography (Gastrolyzer, Bedfont Scientific Inc., Kent, United Kingdom) was employed to detect patients with LM and FM. Baseline breath hydrogen (H_2) levels were measured after an overnight fasting state of > 12 hours. Lactose was given in a dose of 50 g dissolved in 200 mL of water. In the course of a following visit fructose was given in a dose of 25 g dissolved in 200 mL of water. In both tests the end-expiratory breath H_2 concentration was measured at 0 (baseline before sugar ingestion), 30, 60, 90, and 120 minutes. The results were expressed in parts per million (ppm). According to the literature [3, 11, 12], patients with a H_2 peak > 20 ppm above baseline H_2 concentrations were classified as lactose and/or fructose malabsorbers independently of their self-reported clinical symptoms during or after the breath test. Patients were instructed to avoid physical effort, smoking, or eating during the lactose and fructose breath test. Patients with a colonoscopy, an antibiotic- or a laxatives-based therapy at least two weeks before test procedures, were excluded from the breath testing.

2.3. HI. The serum diamine oxidase (DAO) activity was measured using a quantitative radio extraction assay (DAO-REA®; Sciotec Diagnostic Technologies GmbH, Tulln, Austria).

The intra- and interassay reproducibility of the DAO radio extraction assay was < 10 and < 15% (information of the manufacturer). According to the literature [8, 13], in individuals with serum DAO activity < 3 U/mL, HI intolerance was expected, while in patients with serum DAO levels between 3 and 10 U/mL, HI was considered possible. Patients with DAO levels < 10 U/mL were identified with HI only if they showed two or more GI symptoms of HI (e.g., nausea, vomiting, meteorism, and/or abdominal pain) and a positive response to a low histamine diet [8, 13].

2.4. Statistics. Descriptive statistics were performed to analyze prevalence rates for LM, FM, and HI. The exact Chi-Square test for independence was used to compare categorical variables. A p-value < 0.05 was considered statistically significant. SPSS Statistics for Windows version 22.0 (IBM SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis.

3. Results

3.1. Patient Population Characteristics. Of all 439 patients included, 138 (31.4%) were male and 301 (68.6%) were female with a median age of 43.8 years. The main demographic and clinical characteristics of the study population including the assessment of GI symptoms during the first consultation are provided in Table 1. None of the included patients showed signs of active acute or chronic inflammatory bowel disease.

Table 2: Prevalence rates of LM, FM, and HI.

GI conditions	Patients	Percent
LM	94	21.4
FM	31	7.1
LM + FM	27	6.2
HI	100	22.8
LM + HI	52	11.8
FM + HI	23	5.2
LM + FM + HI	14	3.2
Total	341	77.7

GI: gastrointestinal; LM: lactose malabsorption; FM: fructose malabsorption; HI: histamine intolerance.

3.2. DAO Serum Levels. All in all, 51 individuals (11.6%) were identified with a serum DAO level < 3 U/mL, 138 patients (31.4%) had a serum DAO level between 3 and 10 U/mL, and 250 (57.0%) individuals showed DAO serum levels ≥ 10 U/mL. No correlation was observed between serum DAO levels and the occurrence of LM ($p = 0.395$) or FM ($p = 0.615$).

3.3. Differential Diagnoses of GI Conditions. As shown in Table 2, 341 (77.7%) patients were found with 7 various GI conditions, while 98 (22.3%) individuals remained negative for any GI entity investigated here. All in all, 94 (21.4%), 31 (7.1%), and 100 (22.8%) individuals presented LM, FM, or HI only, whereas 116 (26.4%) showed a diagnostic overlap of LM, FM and HI, respectively. Interestingly, 89 out of 241 (36.9%) individuals with carbohydrate malabsorption were identified with HI.

4. Discussion

In this study, 341 (77.7%) individuals with unclear abdominal complaints presented 7 various GI conditions. To the best of our knowledge, this is the most extensive investigation on concomitant prevalence rates for LM, FM, and including HI in such a large collective of patients.

With respect to carbohydrate malabsorption, H_2 breath testing identified 241 (54.9%) patients with LM and/or FM, of which 89 (36.9%) individuals were also diagnosed with HI. These findings demonstrate that multiple combinations of carbohydrate malabsorption with HI may be associated with GI discomfort. This seems a great challenge for clinicians in view of individualized treatment options. Individuals with LM, FM and/or HI should get detailed dietary advice by registered dietitians, preferably at time of diagnosis.

In the present study and according to the literature [8, 13], individuals with serum DAO activity < 3 U/mL were expected with HI, while in patients with serum DAO levels between 3 and 10 U/mL, HI was considered possible. We observed no correlation between serum DAO levels and the occurrence of LM ($p = 0.395$) or FM ($p = 0.615$). Nevertheless, present data show, that the diagnostic overlap between LM and HI was higher compared to FM and HI. In a recent study, we found serum DAO activity associated with LM phenotypic variation [14]. We observed, that patients with LM and a serum DAO activity level < 10 U/L presented higher end-exspiratory H_2-levels in the lactose breath test compared to LM patients with DAO activity levels ≥ 10 U/mL [14]. DAO, the main enzyme in metabolizing ingested histamine, is synthesized by mature apical enterocytes, which are located in the upper intestinal villi [15]. It is continuously released from the intestinal mucosa and also transported to the blood circulation [16]. Mucosal damage in the small intestine caused by GI conditions (e.g., gastroenteritis, short bowel syndrome, GI surgery, drugs, celiac and tropical sprue) may reduce DAO and lactase activity, respectively [14, 17]. This could be one possible reason for the diagnostic overlap between LM and HI observed here.

The diagnosis of HI has its limitations. In general, the diagnostic approach of HI is difficult because the symptoms are highly variable and may affect almost all organs [9]. Moreover, standardized *in vitro* diagnostic tests for HI testing are still lacking [18]. Therapy of HI should be based on a consequent avoidance of histamine-rich food (e.g., spinach, tomatoes, long-ripened or fermented products, alcohol) or histamine liberators (e.g., citrus fruits, chocolate). A diet diary is suggested to document the improvement of symptoms during a histamine-free diet and to record the relapses in HI after dietary mistakes [8].

Not only the diagnostic approach of HI is difficult, but also limitations of the conventional lactose and fructose H_2 breath test must be mentioned. The functional H_2 breath test is considered a reliable, non-invasive diagnostic approach for patients with LM and FM [19], but the method is not standardized yet and pre-analytical poor patient preparation during the alveolar air collection may lead to false-negative test results [12]. Moreover, the acidic microclimate in the colon of patients with carbohydrate malabsorption can also cause decreased bacterial H_2 production [20]. Another influencing cofactor of the H_2 breath test is the orocecal transit time, which may also lead to false negative test results, because breath testing may be finished before a measurable H_2 increase is established [11, 12]. Furthermore an individual and subjective perception of GI symptoms, which patients associate with carbohydrate malabsorption, must be considered [12, 21]. Visceral hypersensitivity is considered to play an essential role in functional symptoms, but the causal symptom triggers are not completely understood yet [3, 19].

Two limitations of this study may be described. Firstly, activities of the intestinal histamine-degrading enzyme histamine N-methyl-transferase were not measured because no standardized kit is commercially available yet. Secondly, serum DAO levels were determined at a single measuring point, only. Therefore, a prospective longitudinal study containing follow-up measurements is required to assess the clinical course of serum DAO levels in patients with unclear abdominal discomfort.

5. Conclusions

Patients with unexplained abdominal discomfort/pain present multiple combinations of carbohydrate malab-

sorption and HI. As a consequence we suggest testing for LM, FM, and additionally HI in the diagnostic work-up of these patients in clinical practice. Depending on differential diagnostic considerations, patients should get an individualized dietary advice.

Competing Interests

Wolfgang J. Schnedl is cofounder of GedoMed GmbH (Bruck an der Mur, Austria). The other authors have no competing interests.

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Circadian profiling reveals higher histamine plasma levels and lower diamine oxidase serum activities in 24% of patients with suspected histamine intolerance compared to food allergy and controls. Pinzer, T. C., Tietz, E., Waldmann, E., Schink, M., Neurath, M. F., & Zopf, Y. Allergy. **2017**; 73(4), 949–957

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Circadian profiling reveals higher histamine plasma levels and lower diamine oxidase serum activities in 24% of patients with suspected histamine intolerance compared to food allergy and controls

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Abstract

Background: Histamine intolerance is thought to trigger manifold clinical symptoms after ingesting histamine-rich food due to reduced activity of diamine oxidase (DAO). No study has hitherto systematically assessed daily fluctuations of histamine levels and DAO activities in symptomatic patients. The aim of the study was to investigate the presence of histamine intolerance, to therefore establish day profiles of histamine levels and DAO activities, and to compare the results between patients with suspected histamine intolerance, food allergy and healthy controls.

Methods: We determined day profiles of histamine plasma levels and DAO serum activities in 33 patients with suspected histamine intolerance, in 21 patients with proven food allergy and in 10 healthy control patients. Clinical symptoms, food intolerances and further clinical and laboratory chemical parameters were evaluated.

Results: Twenty-four percent (8 of 33) suspected histamine-intolerant patients showed elevated histamine levels during the day. That might be caused by constantly and significantly reduced DAO activities in these patients compared to food-allergic and control patients. The remaining 25 patients presented normal histamine levels and DAO activities, but an increased prevalence of multiple food intolerances compared to the other subgroup of suspected histamine-intolerants. There was no correlation between subjective complaints and serological histamine parameters in patients with suspected histamine intolerance.

Conclusions: We determined by daily profiling that decreased DAO activities correlated with elevated histamine levels in a subgroup of suspected histamine-intolerants. This finding discriminates these patients from food intolerant individuals with similar clinical symptoms and strongly suggests the presence of histamine intolerance.

Abbreviations: 95% CI, 95% confidence interval; BSA, Body surface area; DAO, Diamine oxidase; ELISA, Enzyme-linked Immunosorbent Assay; FODMAP, Fermentable Oligo-, Di-, Monosaccharides And Polyols; IBS, Irritable bowel syndrome; RAST, Radioallergosorbent test; REA, Radio Extraction Assay.

Clinical trial registration number: NCT02293343.

KEYWORDS
diamine oxidase activities, day profile, food allergy, histamine intolerance, histamine levels

1 | INTRODUCTION

Abdominal pain, diarrhoea, pruritus—adverse food reactions appear in a multifaceted manner with a broad range of symptoms. Due to the increasing incidence of food intolerances in industrial nations and the associated restriction of quality of life, a close look at nutrition becomes increasingly important.[1-3]

There is a much evidence of food hypersensitivity—either expressed as immunological food allergy or nonimmunological food intolerance.[4] The prevalence of the latter averages between 15% and 20% and is thus about four times higher than the prevalence of food allergy.[4-6] Among the most common food intolerances are intolerances against fructose and lactose as well as histamine.[4,7] The frequency of histamine intolerance is not fully understood yet, but indirect evidence suggests that about 1%-3% of the population is affected.[8] Reduced activity of diamine oxidase (DAO), the key enzyme in histamine metabolism, has been hypothesized as the main factor in the development of histamine intolerance leading to the accumulation of histamine above the individual critical value.[9-12] Consequently, this is provoking disorders within a short time lag from hours up to days. High histamine levels in the body are not only caused by reduced DAO activities but also by the ingestion of histamine-rich and histamine-releasing foods such as meat, dairy products and alcohol.[2,13,14]

Histamine intolerance has already been reported as a causal trigger for cardinal gastrointestinal disorders like abdominal pain, diarrhoea and flatulence.[2,15,16] On the one hand, the patients' clinical presentation can resemble other food intolerances or allergy and is usually diagnosed under the umbrella of irritable bowel syndrome (IBS).[2,7] On the other hand, histamine intolerance is also characterized by extra-intestinal symptoms such as headache,[15] pruritus,[16] urticaria,[17] atopic eczema,[18] cardiac arrhythmia[19] and asthma[13,14] that exceed the diagnosis of IBS. As both the aetiology and the course of histamine intolerance are not sufficiently investigated, the knowledge and treatment in the medical field are not always uniform. Thus, affected patients do doctor shopping to find an appropriate explanation for their diversified complaints.

According to the current recommendations,[20] a provocation test with increasing concentrations of histamine hydrochloride can be applied under strict medical supervision for the determination of a histamine intolerance. However, side effects can be very severe and hospitalization might be required so that a provocation test should probably be limited to patients with an urgent suspicion. A simple, fast-tracked diagnostic tool could provide the first evidence for a histamine intolerance and might be helpful to select patients for a provocation test.

To some extent, low DAO activities and high histamine levels in the blood are indicators of the disease.[10-12,18] But do the complaints of the patients indeed correlate with the measured histamine parameters? So far, no study has systematically assessed daily fluctuations of histamine levels and DAO activities in symptomatic patients. Wantke et al[21] investigated daily variances of histamine levels and DAO activities in healthy volunteers, but could not observe any differences. However, a single-shot measurement of these parameters may be insufficient to detect intraday variations and clarify the presence of a histamine intolerance. Therefore, more knowledge of the daytime dynamics of histamine and DAO activity is very important. A correct diagnosis, which is ideally based on the determination of serological parameters, is the basis for an adequate therapeutic intervention, and symptom relief can be achieved through histamine-free diet,[10,22,23] antihistamines,[11,13,23] medication that blocks the effects of histamine and supplementation of DAO.[24]

The aims of this project were to determine a day profile of histamine levels and DAO activities and to evaluate differences concerning the serological parameters and clinical symptoms between the investigated study groups—suspected histamine-intolerants, proven food-allergic patients and healthy controls—to offer a better diagnostic tool for histamine intolerance.

2 | METHODS

2.1 | Subjects

Over a 12-month period, a total of 65 adult patients were enrolled in the study. Patients were recruited by special social media platforms and from the ambulance for nutritional medicine of the Department of Medicine 1 of the University Erlangen-Nuremberg, Germany. Three patient groups were acquired: (i) suspected histamine intolerance, (ii) proven food allergy and (iii) healthy controls. The first group comprised patients with reasonable suspicion of histamine intolerance. Clinical complaints under normal histamine-rich diet that resolved completely when consuming a histamine-low diet served as inclusion criterion for this group. When participants further complained about symptoms despite a histamine-low diet, they were rejected from the study. The second group covered patients with increased serum IgE as well as gastrointestinal complaints that did not improve under histamine-low diet. The third group enclosed healthy individuals without any complaints under standard diet. Exclusion criteria comprised pregnancy, lactation, being under age and the current intake of antihistamines or anti-inflammatory medication.

2.2 | Study design and setting

This study was performed in a prospective cohort design. The study protocol was approved by the local ethics committee. All participants provided written informed consent.

Four weeks before study start, all medication possibly interfering with the analyses (antihistamines, corticosteroids and anti-inflammatory medication) was paused. During a period of 1 week prior to and throughout the examinations, all groups had normal mixed diets with the aim of supplying normal amount of histamine by food and drink.

2.3 | Data collection

A 3-day nutritional diary using the Freiburger Diet Protocol (Nutri-Science GmbH, Freiburg, Germany) directly before the time of investigation was itemized in energy value as well as content of protein, fat, carbohydrates and alcohol per day by PRODI (version 6.5 expert, Nutri-Science GmbH). All patients were checked for sugar intolerances in-house or externally by validated H2 breath tests. The survey at the examination day assessed clinical symptoms, underlying diseases and both nicotine and alcohol consumption. Furthermore, IBS symptoms were recorded using questionnaires based on the Rome III criteria.[25,26]

2.4 | Sample collection and analysis

To determine a day profile of both histamine levels and DAO activities at the examination day, blood samples were taken every three hours from 6 AM until midnight by butterfly needles or peripheral venous catheters. Because of the short half-life of histamine, the blood samples were immediately cooled on ice and centrifuged (1780 g) for 10 minutes at 4°C (Rotina 35R, Hettich GmbH, Tuttlingen, Germany). Histamine plasma levels (threshold: 0.35 ng/mL/m^2 BSA, Immundiagnostik AG, Bensheim, Germany) were determined by enzyme-linked immunosorbent assay (ELISA) and DAO serum activities (threshold: 5.73 U/mL/m^2 BSA, Immundiagnostik AG, Bensheim, Germany) by radio extraction assay (REA). Both serological parameters were adapted to the subjects' individual body surface area (BSA).

Additional blood samples were taken for further investigation of a differential blood count (reference range neutrophil granulocytes <75%, eosinophil granulocytes <4%, basophil granulocytes <1%, lymphocytes <40% and monocytes <8%) and for vitamin B6 determination (reference range 5.0-30.0 ng/mL). The total quantity of IgE antibodies (reference value: <100 kUA/L) as well as specific IgE antibodies against food allergens was quantified by radioallergosorbent test (RAST), and serum tryptase (reference value: <11.4 μg/L) was measured by fluorescence immunoassay to determine a food allergy and a mast cell-activating disease (ImmunoCAP®, Phadia 250, Thermo Fisher Scientific Inc., Phadia GmbH, Freiburg, Germany).

2.5 | Statistical analysis

The statistical analysis was performed with R version 3.2.4.[27] Clinical and laboratory variables were summarized by absolute and relative frequencies for categorical variables and by means and standard deviations for continuous variables. 95% confidence intervals (95% CI) and boxplots are reported for histamine levels and DAO activities. Statistically significant differences between the three diagnosis groups were tested by means of the chi-square test and Kruskal-Wallis test, respectively. Wilcoxon signed-rank test and Dunn-Bonferroni post hoc testing were used to compare intergroup differences as well as observed and prescribed values. All statistics are based on 2-sided testing. *P*-values ≤.05 were considered statistically significant.

3 | RESULTS

3.1 | Group allocation

In summary, 64 patients (n = 54 female, 84.4%) with an average age of 38.3 ± 14.2 years were analysed. A total of 33 patients (n = 28 female, 84.8%) with an urgent suspicion of histamine intolerance were included in the study. In addition, 21 patients (n = 17 female, 81%) with a proven food allergy and a total of 10 (n = 9 female, 90%) healthy volunteers who had no complaints were recruited. As expected, the IgE antibodies were significantly increased in the food-allergic patients (361.2 ± 911.2 kUA/L) ($P < .001$), whereas the IgE antibodies were in the normal range in the suspected histamine-intolerants (29 ± 24.4 kUA/L) and healthy volunteers (14.3 ± 9.6 kUA/L). Correspondingly, proven food-allergic patients were tested positive for nut mixture (76.2%), wheat flour (47.6%), celery (42.9%), tomato (23.8%), rye flour (23.8%), soybean (14.3%) and milk protein (4.8%) and negative for chicken egg white, casein and salmon.

3.2 | Day profiles of histamine levels and diamine oxidase (DAO) activities

By recording the progression of histamine levels and DAO activities over time, 24% (8 of 33, all female) suspected histamine-intolerant patients featured elevated histamine levels and constantly reduced DAO activities. Despite the typical symptoms, the remaining 25 subjects (n = 20 female, 80%) did not show any changes in histamine levels or DAO activities, which would correspond to the definition of a histamine intolerance. In order to distinguish these patients from the patients with reduced DAO activities, they are hence referred to as "food-hypersensitive patients." Figure 1 and Table 1 demonstrate the day profiles of histamine levels and DAO activities of patients with suspected histamine intolerance, food-hypersensitive patients, food-allergic patients and healthy control patients. Diamine oxidase (DAO) activities were significantly lower in histamine-intolerants (see Figure 2) and tended to be within the normal range in the other groups. There were no significant differences between the groups regarding the bandwidth of histamine levels (see Figure 2).

3.3 | Food intolerances

The overall prevalence of food intolerances in symptomatic patients did not differ significantly between groups (see Figure 3). Splitting the

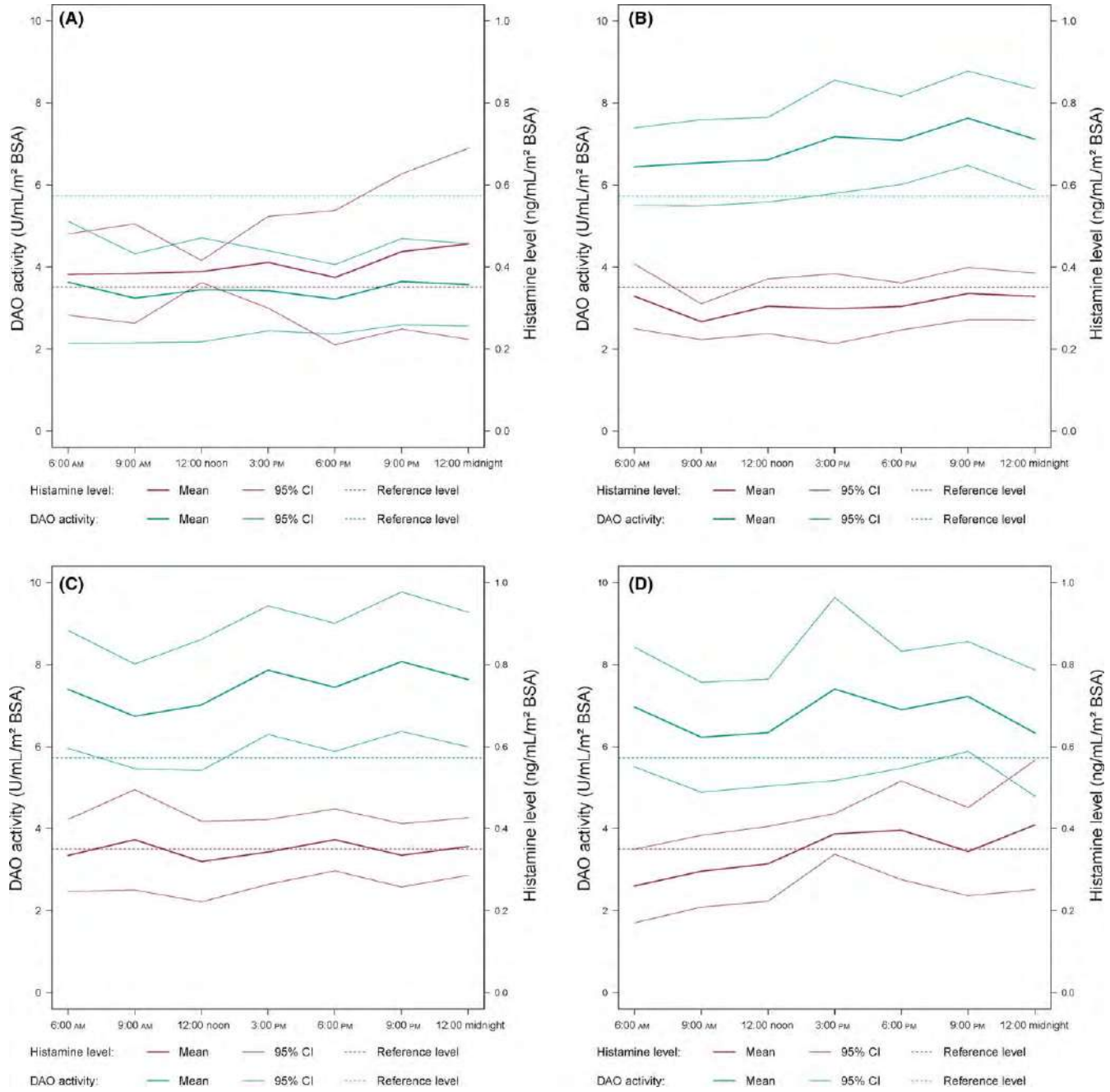

FIGURE 1 Day profiles of histamine plasma levels and diamine oxidase serum activities. For both histamine plasma levels and DAO serum activities, mean values, 95% confidence intervals and reference levels to be regarded as healthy (maximum histamine level: 0.35 ng/mL/m² BSA; minimum DAO activity: 5.73 U/mL/m² BSA) are illustrated. A, Histamine-intolerant patients, B, food-hypersensitive patients, C, food-allergic patients and D, healthy control patients. DAO, diamine oxidase; BSA, body surface area; 95% CI, 95% confidence intervals [Colour figure can be viewed at wileyonlinelibrary.com]

food intolerances against fructose, lactose and sorbitol into single and multiple intolerances revealed an intriguing result: histamine intolerance was exclusively associated with single food intolerances, whereas food-hypersensitive and food-allergic patients showed similar percentages of single and multiple food intolerances (see Figure 3).

3.4 | Variety and diversity of clinical symptoms

To assess the health status, clinical symptoms were recorded in categories: allergic rhinitis including oral allergy syndrome, skin changes, gastrointestinal alterations as well as asthmatic symptoms and headache (see Table 2). In general, histamine-intolerant, food-hypersensitive and food-allergic patients presented a wide variety of symptoms. No differences between these groups were seen in the prevalence of symptoms (see Table 2). Further self-reported disorders, for example palpitations, flush, heartburn, nervousness, fatigue, increased sweating, muscle and joint pain, were infrequent (<15% each), except for flatulence (histamine-intolerant patients: 12.5%; food-hypersensitive patients: 25%; food-allergic patients: 19%). Likewise, their prevalence did not vary between the groups ($P > .05$, not reported in Table 2).

TABLE 1 Day profiles of histamine plasma levels and diamine oxidase serum activities

	6:00 AM	9:00 AM	12:00 noon	3:00 PM	6:00 PM	9:00 PM	12:00 midnight
Histamine plasma levels (ng/mL/m^2 BSA)							
Histamine-intolerant patients	**0.38**	**0.38**	**0.39**	**0.41**	**0.37**	**0.44**	**0.46**
Food-hypersensitive patients	0.33	0.27	0.3	0.3	0.3	0.34	0.33
Food-allergic patients	0.33	**0.37**	0.32	0.34	**0.37**	0.33	**0.36**
Healthy control patients	0.26	0.3	0.31	**0.39**	**0.4**	0.34	**0.41**
DAO serum activity (U/mL/m^2 BSA)							
Histamine-intolerant patients	**3.62**	**3.23**	**3.44**	**3.42**	**3.21**	**3.64**	**3.56**
Food-hypersensitive patients	6.44	6.54	6.62	7.18	7.09	7.63	7.11
Food-allergic patients	7.4	6.74	7.02	7.87	7.45	8.07	7.64
Healthy control patients	6.97	6.23	6.34	7.41	6.9	7.22	6.33

DAO, diamine oxidase; BSA, body surface area.

Mean values are reported. Values outside the reference levels to be regarded as healthy (maximum histamine level: 0.35 ng/mL/m² BSA; minimum DAO activity: 5.73 U/mL/m² BSA) are bold.

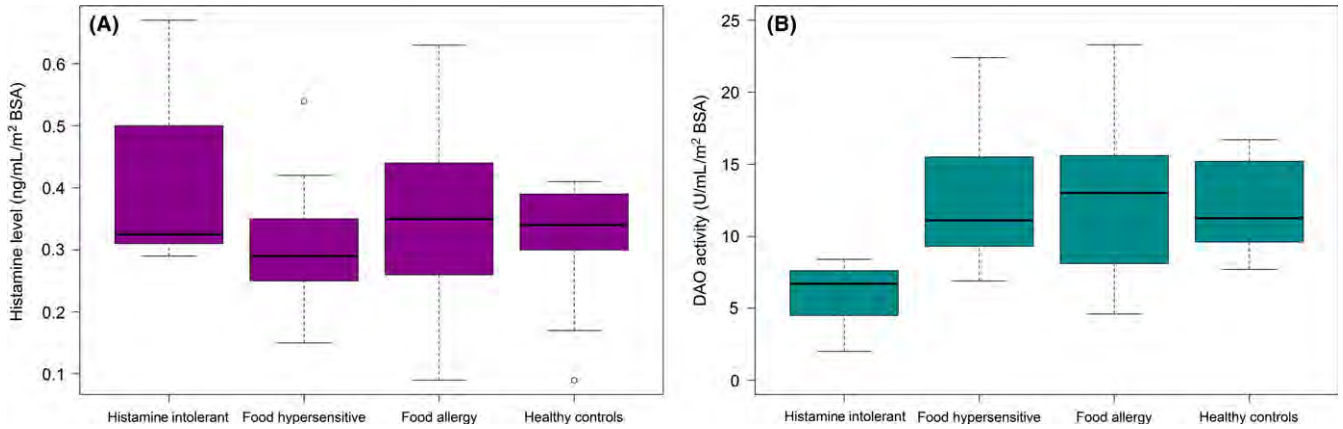

FIGURE 2 Comparison of histamine plasma levels and diamine oxidase serum activities. *P*-values of Wilcoxon signed-rank test for (A) histamine plasma levels: n.s., and (B) diamine oxidase serum activities: histamine-intolerant patients – food-hypersensitive patients: $P = .002$; histamine-intolerant patients – food-allergic patients: $P < .001$; histamine-intolerant patients – healthy control patients: $P < .001$. DAO, diamine oxidase; BSA, body surface area [Colour figure can be viewed at wileyonlinelibrary.com]

3.5 | Nutritional behaviour, alcohol and nicotine consumption

Regarding the daily intake of calories, histamine-intolerants consumed 2431.2 ± 362.3 kcal per day and food-hypersensitive patients 2873.3 ± 1218.1 kcal per day. The energy intake of food-allergic patients was 2862.9 ± 1552.8 kcal per day and 2081.7 ± 818.6 kcal per day in healthy volunteers. Thus, food-hypersensitive patients consumed significantly more calories per day compared to controls ($P = .02$). A tendency to higher calorie intake per day was also determined for food-allergic patients in comparison with controls ($P = .06$). The detailed analysis of the percentage of daily intake of macronutrients revealed no differences with regard to protein (histamine-intolerants: 14.5% ± 2.8%/d; food-hypersensitive patients: 16.6% ± 4.1%/d; food-allergic patients: 16% ± 3.5%/d; controls: 15.3% ± 3.1%/d; $P = .53$), fat (histamine-intolerants: 31.8% ± 4.7%/d; food-hypersensitive patients: 38.4% ± 6.1%/d; food-allergic patients: 37.1% ± 5.5%/d; controls: 37.6% ± 8.5%/d; $P = .09$) and carbohydrates (histamine-intolerants: 50.4% ± 6.1%/d; food-hypersensitive patients: 40.9% ± 8.3%/d; food-allergic patients: 42.1% ± 8.8%/d; controls: 44.5% ± 8.8%/d; $P = .07$).

71.9% of the study population consumed alcohol and 14.1% nicotine on a regular basis. No statistical significant intergroup differences were observed for both alcohol (histamine-intolerants: n = 6, 75%; food-hypersensitive patients: n = 15, 60%; food-allergic patients: n = 17, 81%; controls: n = 8, 80%; $P = .40$) and nicotine consumption (histamine-intolerants: n = 1, 12.5%; food-hypersensitive patients: n = 2, 8%; food-allergic patients: n = 3, 14.3%; controls: n = 3, 30%; $P = .41$).

3.6 | Irritable bowel syndrome and primary diseases

Figure 4 illustrates the distribution of IBS subtypes based on the Rome III criteria in histamine-intolerant, food-hypersensitive and food-allergic patients. Food hypersensitivity was associated with an increased risk for IBS with diarrhoea (IBS-D) in comparison with histamine intolerance. The food-allergic patients could rarely be categorized in IBS.

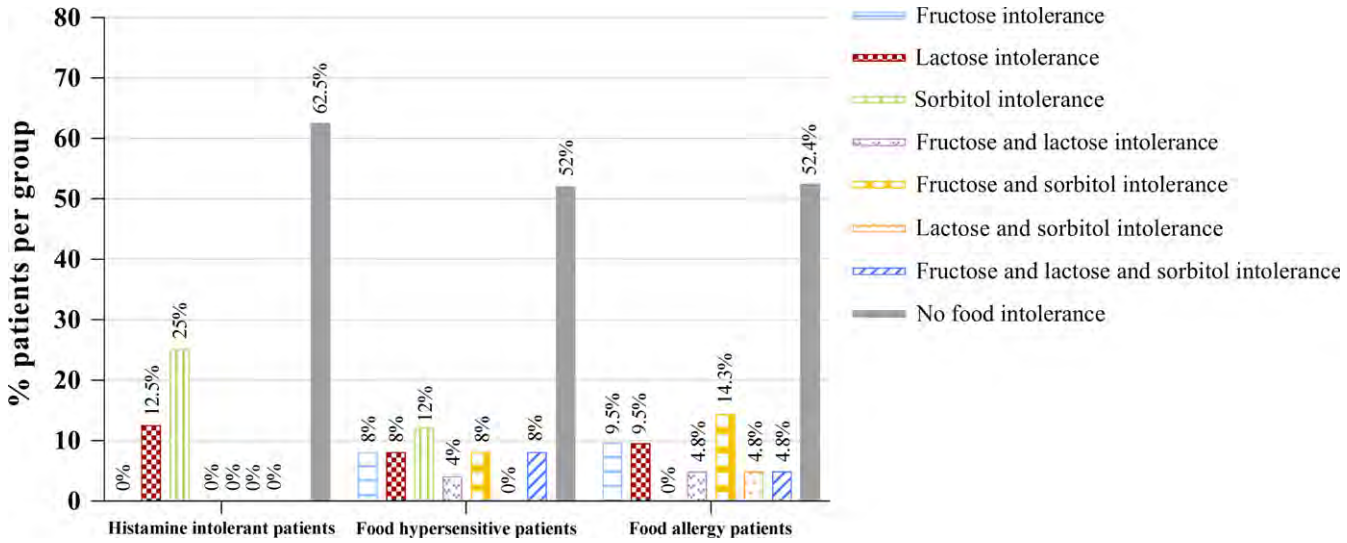

FIGURE 3 Prevalence of food intolerances. Relative frequencies of single and multiple food intolerances against fructose, lactose and sorbitol are shown [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Spectrum of histamine and allergy-related clinical symptoms

	Histamine-intolerant patients	Food-hypersensitive patients	Food-allergic patients	*P*-values
Allergic rhinitis				
Runny nose	3 (37.5%)	11 (44%)	10 (47.6%)	.89
Stuffy nose	3 (37.5%)	7 (28%)	9 (42.9%)	.57
Itchy nose	3 (37.5%)	6 (24%)	9 (42.9%)	.39
Red eyes and swollen eyelids	4 (50%)	9 (36%)	8 (38.1%)	.78
Watery eyes	3 (37.5%)	4 (16%)	6 (28.6%)	.38
Sneezing	3 (37.5%)	7 (28%)	10 (47.6%)	.39
Swollen airways	3 (37.5%)	5 (20%)	9 (42.9%)	.23
Oral allergy syndrome	4 (50%)	10 (40%)	13 (61.9%)	.33
Skin changes				
Itchy skin	5 (62.5%)	13 (52%)	7 (33.3%)	.27
Urticaria	3 (37.5%)	5 (20%)	4 (19.1%)	.53
Skin rash	3 (37.5%)	10 (40%)	7 (33.3%)	.90
Gastrointestinal alterations				
Nausea and vomiting	5 (62.5%)	12 (48%)	9 (42.9%)	.64
Stomach pain	3 (37.5%)	18 (72%)	11 (52.4%)	.16
Diarrhoea	4 (50%)	18 (72%)	16 (76.2%)	.37
Asthmatic symptoms				
Cough	0 (0%)	4 (16%)	5 (23.8%)	.30
Shortness of breath	2 (25%)	6 (24%)	5 (23.8%)	1.00
Wheezing	0 (0%)	1 (4%)	4 (19.1%)	.13
Headache	4 (50%)	14 (56%)	10 (47.6%)	.85

Absolute and relative frequencies and *P*-values of chi-square test are reported.

We found similar frequencies of primary diseases (hypothyroidism, asthma, atopic dermatitis, depression, gastrointestinal and cardiovascular diseases, endometriosis, fibromyalgia) in the symptomatic groups ($P > .05$, data not shown). Migraine exclusively appeared in food-hypersensitive patients (8%).

3.7 | Laboratory values

Differential blood count, vitamin B6, magnesium and zinc were within the normal range in all groups. Serum tryptase levels were below 20 μg/L in the entire study population (histamine-intolerants:

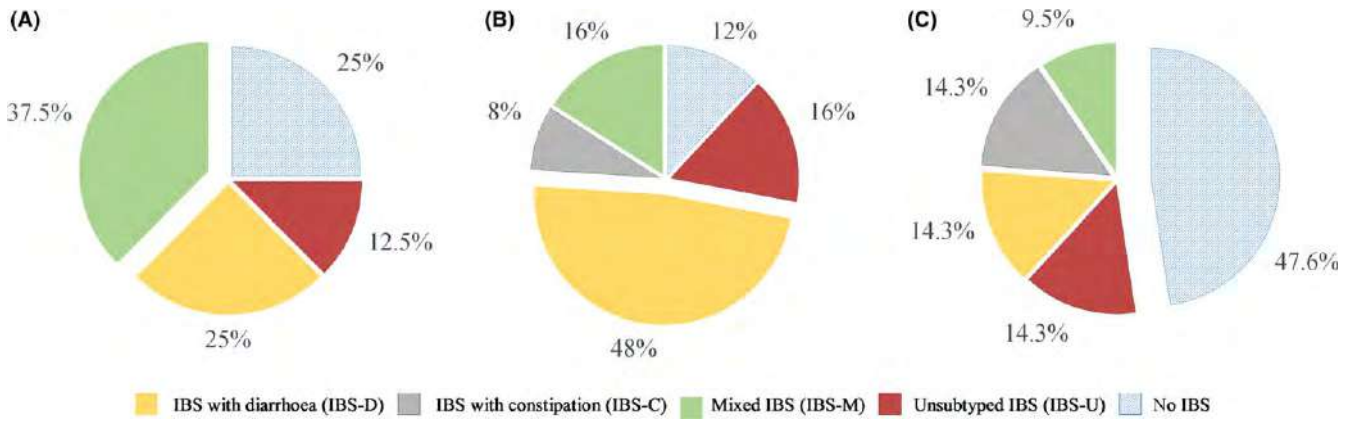

FIGURE 4 Subtype distribution of irritable bowel syndrome based on the Rome III criteria. Proportions of patients are displayed. A, histamine-intolerant patients, B, food-hypersensitive patients and C, food-allergic patients. IBS, irritable bowel syndrome [Colour figure can be viewed at wileyonlinelibrary.com]

4.58 ± 2.86 μg/L; food-hypersensitive patients: 6.57 ± 8.91 μg/L; food-allergic patients: 4.65 ± 1.69 μg/L; controls: 6.66 ± 3.46 μg/L) except for one food-hypersensitive patient (46.1 μg/L).

4 | DISCUSSION

A plethora of symptoms has been reported in patients after consuming histamine-rich and histamine-releasing foodstuffs due to histamine accumulation based on reduced activity of DAO, the main enzyme in histamine metabolism.[8,10,28,29] But is there reliable evidence that histamine intolerance exists? No diagnosis was as critically discussed as the presence of histamine intolerance. To address this issue, we determined day profiles of histamine plasma levels and DAO serum activities in patients with urgent suspicion of histamine intolerance compared to patients with proven food allergy and healthy volunteers.

For the first time, we were able to demonstrate that there are patients who can be classified as histamine-intolerants according to the definition.[9-12] In 24% (8 of 33) suspected histamine-intolerants, constantly and significantly reduced DAO activities triggered elevated histamine levels throughout the day. We observed that the most common clinical symptoms of histamine intolerance are diarrhoea, nausea and vomiting, headache, itchy skin, oral allergy syndrome as well as red eyes and swollen eyelids (≥50%). These findings appear to be consistent with literature data as gastrointestinal, skin and respiratory problems as well as headache have been described to be characteristic for histamine intolerance.[4,8,28] Like other work groups,[30] we could not find any differences in the complexity of the symptoms between patients with histamine intolerance, food hypersensitivity or food allergies. This is probably due to the nonspecific pathology, great variability and individual complaints of the patients. Unfortunately, we could not observe any correlations between subjective complaints and measured histamine parameters. Our current results show that it is difficult to differentiate between histamine intolerance and other food intolerances by clinical presentation alone. Additional laboratory chemical examinations are necessary.

In patients with a proven food allergy, increased histamine levels are expected compared to healthy controls, which was not the case in our study. Immunologically mediated food allergy is based on significantly increased serum levels of IgE antibodies against food antigens that cause the immediate reactions (type I hypersensitivity) via mediator release, for example histamine, from mast cells.[30,31] However, we did not ask the patients to consume allergenic food components and thus trigger an allergic reaction with histamine release from ethical point of view.

Based on our repeated determination, we could demonstrate that histamine plasma levels are subjected to constant fluctuations between normal and pathologic values during the day in our healthy controls. This great variety most likely depends on the quantity of the ingested histamine-rich food. In accordance with previous studies,[10,28] our healthy subjects showed normal DAO activities. Fluctuations in histamine levels do not seem to be of any clinical relevance as long as sufficient DAO activity is available. We suspect that an individual histamine sensitivity is responsible for the patient's discomfort. Even though no significant differences in the histamine levels between the groups could be detected, the patients with a laboratory-based suspicion of histamine intolerance presented persistently increased histamine values over the course of the day. This is probably due to the significantly reduced DAO activities. The intraday fluctuations emphasize the difficulties in diagnosis of histamine intolerance as single-point values might be interpreted incorrectly (false high or low). Repeated determination of histamine levels and DAO activities on several days therefore could be further pursued in the clinical course. In our study, a clear demarcation of histamine intolerance appeared best at noon so that this time point might be recommended for the blood samplings. An arithmetic mean could possibly be standardized.

A study including 439 patients with unclear abdominal discomfort identified fructose (5.2%) and primarily lactose (11.8%) intolerance as a frequent concomitant in histamine intolerance.[32] In conformity with this study, we also demonstrated that carbohydrate intolerances are frequently associated with histamine intolerance. Interestingly, there was a frequent co-occurrence of histamine and sorbitol intolerance (25%).

A histamine-free diet is the method of choice in the explorative diagnosis and therapy of histamine intolerance.[10,22,23] In addition, a new diet low on FODMAPs has gained increasing popularity in recent years. The acronym FODMAP—Fermentable Oligo-, Di-, Monosaccharides And Polyols—refers to the carbohydrates fructose, lactose, fructans and galactans as well as sugar alcohols, such as sorbitol and mannitol, which are ingredients of numerous foodstuffs.[33,34] They are thought to trigger gastrointestinal disorders, in particular diarrhoea and flatulence, due to the induction of luminal distension and increased intestinal permeability.[33,34] Thus, a low FODMAP diet is considered highly effective in the treatment of functional gut symptoms and IBS, respectively.[33,34] In our study, the 25 patients without serological indication of histamine intolerance had multiple proven food intolerances against fructose, lactose or sorbitol and possibly other, yet unknown, food hypersensitivities. According to the Rome III criteria, most of them matched the subtype IBS with diarrhoea. These patients would possibly benefit more from a low FODMAP diet.

The mere presence of gastrointestinal complaints does not allow conclusions about the genesis of the disease, although the diagnosis of an IBS is very frequently.[2,7,30] The prevalence of IBS is significantly higher in women than in men.[35] There was also a high rate of symptomatic young and middle-aged (18-65 years) women in our study population (83.3%) who were assigned to the IBS category according to the Rome III criteria.[25,26] Evidence suggests associations between a histamine-rich diet and IBS.[2] That is why symptom relief under histamine-poor diet is not highly specific for histamine intolerance, but may also occur in IBS. One of our food-hypersensitive patients showed increased tryptase activity, hinting towards that other, for example mast cell-activated diseases, could be present in this patient.[36] In clinical practice, frequent and known differential diagnoses for histamine intolerance should be investigated at an early stage.

To compare the patients' nutritional status, we analysed the daily intake of macronutrients and calories. The DACH reference values for the supply of nutrients, which were elaborated by expert associations from Germany, Austria and Switzerland, recommend an optimal distribution of >50% carbohydrates, 15% protein and 30% fat in daily nutrition.[37] Female patients at the age of 25-50 years with mild physical activity should consume about 2100 calories per day.[37] Our findings suggest that histamine-intolerant patients comply with the recommended optimal nutrition in all aspects ($P > .05$). In contrast, our so-called food-hypersensitive and food-allergic patients had a normal protein uptake ($P = .08$; $P = .22$), but a significantly higher caloric ($P = .001$; $P = .004$) and fat ($P < .001$; $P < .001$), and lower carb uptake ($P < .001$; $P = .001$). Systematic studies investigating nutritional differences between patients with histamine intolerance and patients with other food intolerances or allergies are currently lacking.

We did not find any noticeable deviations of micronutrients including vitamin B6, magnesium and zinc in histamine-intolerant patients, and there seems to be no association between the concentration of micronutrients and DAO activities.

5 | CONCLUSIONS

We conclude from our data that: (i) a more differential diagnosis of histamine intolerance is possible, (ii) there is no correlation between subjective complaints and serologically detectable histamine parameters, (iii) the multifaceted clinical symptoms of histamine intolerance resemble other food intolerances or allergies, and (iv) repeated determination of histamine levels and DAO activities on several days should have a greater clinical value in diagnostic investigation than the measurement at only one single time point.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest

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REVIEW

Histamine intolerance and dietary management: A complete review

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KEYWORDS
Amine;
Diamine oxidase;
Histamine;
Intolerance;
Mast cell

Abstract
Background: Present in several types of food, bioactive amines are described as organic bases of low molecular weight, which constitute a potential health risk. An awareness of amine levels in foods today is therefore important in relation to food safety and patient care. This review aims to emphasise the need to unify the information on the content of biogenic amines in foods and prevent patients' misunderstanding.
Methods: Selective literature search for relevant publications in PubMed and other scientific data bases combined with further data from the World Wide Web on histamine and other amines content in foods.
Results: Available reference sources do not reflect a homogeneous consensus, and the variation between foods makes it impossible for dieticians to accurately estimate amines content to correctly advise patients.
Conclusions: To achieve the goal of collecting reliable information, all methods and tools used in analytical studies should be standardised and information exposed to patients should be verified.

Introduction

Bioactive amines are described as organic bases of low molecular weight produced by the metabolism of plants, animals and microorganisms. They have vasoactive, psychoactive and toxicological characteristics and constitute a potential health risk. The concentration of amines formed in foods depends on the type of microorganisms present, the action of decarboxylase enzymes produced by microorganisms on specific amino acids and favourable conditions for enzymatic activity. The presence of these chemical metabolites has been suggested as a quality indicator in routine analyses for food production and marketing monitoring.[1]

Biogenic amines are present in low concentrations or are not detected in fresh food (below 10 μg/g); however, in food of animal origin such as fish, meat, eggs, cheese and fermented foods, they can be present in high concentration (above 50 μg/g) able to induce chemical poisoning.[2]

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The most important biogenic amines found in food are: histamine, tyramine, tryptamine, phenethylamine and cadaverine, the synthesis of which occurs by decarboxylation of the precursor amino acids histidine, tyrosine, tryptophan, phenylalanine and lysine, respectively.[3]

Based on the mean content of the most toxic biogenic amines (histamine and tyramine), the food safety relevance of the considered food categories can be ranked in the following decreasing order – for histamine: 'dried anchovies', 'fish sauce', 'fermented vegetables', 'cheese', 'other fish and fish products' and 'fermented sausages'; and for tyramine: 'fermented sausages', 'fish sauce', 'cheese', 'fermented fish' and 'fermented vegetables'. Based on the consumer exposure to the most toxic biogenic amines, the food safety relevance of the considered food categories can be ranked in the following decreasing order – for histamine: 'other fish and fish products', 'fermented sausages', 'cheese', 'fish sauces' and 'fermented vegetables'; and for tyramine: 'beer', 'cheese', 'fermented sausages', 'fermented fish meat' and 'preserved meat'.[4]

Histamine is also contained in mast cells and basophils, and its biological effects are usually seen only when it is released in large amounts in the course of allergic and other reactions.[5]

Amines can be formed by transamination of aldehydes and ketones, hydrolysis of nitrogen compounds, thermal decomposition or by decarboxylation of amino acids.[6] The decarboxylation process can proceed through two biochemical pathways: decarboxylation through endogenous (naturally occurring) decarboxylase enzymes or by exogenous decomposition through enzymes released by microflora. The production of amines by the exogenous process is considered far more significant.[7]

According to their biosynthetic pathway, bioactive amines are classified into[1]:

1) Biogenic: they are formed by bacterial enzymatic decarboxylation of amino acids (histamine, serotonin, tyramine, phenethylamine, tryptamine, putrescine, cadaverine and agmatine).
2) Natural: spermine and spermidine are formed ''*in situ*'' in the cells as they are required.

It is noteworthy that since histamine is stored in mast cells, it could be classified as biogenic and natural.

There is a natural mechanism for bioactive amine catabolism. They are oxidised by amine oxidades (monoamine oxidases (MAO) and diamine oxidases (DAO)).[8] Amine oxidases are enzymes which catalyse the oxidative deamination of mono-, di- and polyamines with the formation of an aldehyde, ammonia and hydrogen peroxide: $RCH_2NH_2 + O_2 + H_2O$ $RCHO + H_2O2 + NH3$.[7]

The metabolic function of these enzymes is the breakdown of a number of biologically active amines. The enzymes are divided into two separate groups:

The first group is the flavin co-factor dependent enzymes known as monoamine oxidases (MAO).[7]

The so-called 'trace amines' are synthesised in humans from their corresponding amino acids (tyrosine, phenylalanine and tryptophan, respectively) by decarboxylation. Their catabolism is mainly mediated by monoamine oxidase (MAO). Two MAO isozymes exist, A and B, with different locations and substrate specificity. MAO-A predominates in the stomach, intestine and placenta and has polar aromatic amines (as noradrenalin and octopamine) as preferred substrates. MAO-B predominates in the brain and selectively deaminates non-polar aromatic amines (as phenethylamine and dopamine).[4]

Tyramine is a substrate for either form of MAO, MAO-A is responsible for intestinal metabolism of tyramine, thereby preventing its systemic absorption. Tyramine and phenethylamine are also subjected to N-methylation by N-methyltransferases, generating the sympathetic neurotransmitter, noradrenaline. Tyramine can be further converted into octopamine.[9]

The second group is the copper amine oxidases or diamine oxidases (DAO), which are found in animal tissue and plasma, plants, yeasts, fungi and bacteria.[7]

Humans metabolise histidine to urocanic acid through the activity of L-histidine ammonium lyase, to form glutamate and then α-ketoglutarate, which enters the citric acid cycle, or to histamine through the activity of histidine decarboxylase. There are two ways of histamine metabolism in the human body. Nitrogen in the imidazole cycle is methylated by histamine N-methyltransferase at the formation of N-methylhistamine, which is further oxidised by monoamino oxidase to N-methylimidazolylacetic acid. This enzyme is very selective for histamine detoxification and involves S-adenosylmethionine as donor of methyl group. Histamine is oxidised by diamino oxidase to imidazolylacetic acid, which is bound to ribose.[5]

The biogenic amine content of some foods has been widely studied because of their potential toxicity. Histamine has been implicated as the causative agent in outbreaks of food poisoning where intoxication results from the ingestion of foods containing excessive amounts of histamine. Tyramine and phenethylamine have been identified as the initiators of hypertension during treatment with monoamino oxidase inhibitor drugs and of dietary-induced migraine in susceptible individuals.[4]

The accumulation of biogenic amines in food depends on the availability of free amino acids and the presence of microorganisms with decarboxylase activity on amino acids.[10] Amine formation also depends on food intrinsic and extrinsic parameters such as: temperature and pH, oxygen tension, availability of carbon sources, presence of vitamins, co-enzymes, concentration of free amino acids and fermentable carbohydrates.[11]

Individual differences in enzyme activities besides varying amine concentrations in food may account for different tolerance levels.[12]

In general, increased sensitivity against biogenic amines is due to a weakened enzymatic amine degradation caused by genetic or acquired impairment of MAO, DAO, histamine-N methyltransferase (HNMT) function.[4]

Impairment of DAO activity either due to genetic predisposition, gastrointestinal diseases, or due to medication with DAO inhibitors results in high histamine blood levels, which consequently overload the internal hepatic inactivation system of histamine-N methyltransferase,[12] and leads to histamine intolerance causing numerous symptoms mimicking an allergic reaction even after the ingestion of small amounts of histamine tolerated by healthy individuals.[13]

DAO has been shown to be a secretory protein predominantly synthesised in renal proximal tubular and intestinal epithelial cells and it is stored in plasma membrane associated vesicular structures. Therefore, it has been proposed that DAO might be of primary importance for inactivation and scavenging of extracellular histamine originating from ingested histamine rich food.[14]

Individuals with respiratory and coronary heart diseases, hypertension problems or vitamin B12 deficiency are at risk because they are sensitive to smaller amounts of amines. People with gastrointestinal problems (gastritis, irritable bowel syndrome, Crohn's disease, gastric and colon ulcers) are also at risk since the activity of the oxidases in their bowels is generally lower than in healthy individuals. People using drugs MAO, DAO and polyamine oxidase (PAO) activity inhibitors may also be affected because they prevent amine catabolism.[1]

Other diseases, such as mastocytosis and mast cell activation syndrome (MCAS), are also related to histamine, as Mast Cells (MCs) are the main source of histamine in the human intestine.[15]

Mastocytosis is divided into cutaneous mastocytosis (CM), systemic mastocytosis (SM), and local MC tumours (mastocytoma and MC sarcoma), all of them alterations of the MC.[16]

MCs are tissue-fixed effector cells of allergic and other inflammatory reactions. Mast cell activation (MCA) occurs in a number of different clinical conditions, including primary mast cell disorders, IgE-dependent allergies and atopic diseases, other hypersensitivity or immunologic reactions, and mastocytosis. MCA can be documented by a substantial increase in the serum tryptase level above baseline. Apart from tryptase, other mediators, may also serve as useful parameters of MCA. These include, among others, histamine (in plasma and urine) and histamine metabolites (in urine).[17]

When symptoms are recurrent, are accompanied by an increase in mast cell-derived mediators in biological fluids, and are responsive to treatment with mast cell-stabilising or mediator-targeting drugs, a MCAS may be diagnosed.[17]

Therapy is based on the consequent conduction of a histamine-free diet. A histamine-free diet, if necessary, supported by antihistamines or the substitution of DAO, leads to an improvement of symptoms.[13]

Alcohol and long-ripened or fermented (and therefore histamine-rich) food, such as aged cheese, cured meat, and yeast products; histamine-rich food, such as spinach or tomatoes; or histamine liberators, such as citrus fruit, should be avoided.[13]

In addition, the histamine-free diet can be complemented with adjuvant administration of H1 and H2 antagonists and histamine degradation can be supported by the administration of vitamin C and vitamin B-6, which leads to an increase in DAO activity.[13]

Histamine intolerance sufferers have different thresholds, i.e. tolerance levels, so the next step after completing a successful elimination diet is to establish their threshold level, with the aim of gradually improving it over a period of time.[18]

These amines do not represent a health hazard unless they are consumed in large quantities or if the natural catabolism mechanism of one or more amines is inhibited. In this case, poisoning occurs and thus it is important to determine amine profile and content in food since these substances can trigger toxicological processes.

We therefore sought to review the actual histamine and other biogenic amines content of a number of food tables and judge the reference source that physicians might consult in advising patients with histamine and other amines intolerance.

Methods

Search strategy

The present text was a review. It focuses on scientific literature about histamine intolerance and related diseases. Thus, a bibliographic search was made on PubMed data base and other scientific data bases, such as Scielo, Embase, Cochrane, Clinicaltrials.gov and Scopus, using the following MeSH terms and keywords: ''histamine''[MeSH Terms] OR ''histamine''[All Fields] AND intolerance[All Fields]; bioactive[All Fields] AND (''amines''[MeSH Terms] OR ''amines''[All Fields]); amine oxidase (copper-containing)''[MeSH Terms] OR (''amine''[All Fields] AND ''oxidase''[All Fields] AND'' (copper-containing)''[All Fields]) OR ''amine oxidase (copper-containing)''[All Fields] OR (''diamine''[All Fields] AND ''oxidase''[All Fields]) OR ''diamine oxidase''[All Fields]; mast cells''[MeSH Terms] OR (''mast''[All Fields] AND ''cells''[All Fields]) OR ''mast cells''[All Fields] OR (''mast''[All Fields] AND ''cell''[All Fields]) OR ''mast cell''[All Fields]. This research strategy was adapted to each search engine.

The studies undertaken on histamine were reviewed in January 2016. The search was done by two independent researchers who subsequently corroborated the results found.

Inclusion/exclusion criteria

The following types of studies were included: food composition tables, food analytical studies and laboratory analysis, reviews, table compilations and proposals of content in food for the general population.

The exclusion criteria were as follows: duplicated studies or non-related with the topic, controversial biomarkers to get and support results or conclusions, opinions, expert's opinions, letters, conference papers and editorial papers.

Tables were divided in three. Table 1 shows a comparison between reviews,[19–32] table compilations and proposals of histamine content in food for the general population and food analytical studies and laboratory analysis. Table 2 is similar to Table 1, but shows other amines content in food and Table 3 collects those foods that were excluded from Tables 1 and 2 under the following criteria: less common foods or only 2 out of 14 references included the food in their list, both had the same colour recommendation or on the contrary had opposite colour recommendations.

For tables that provided the amount of histamine in mg/kg per food, low content was considered to be

Table 1 Comparison between reviews, table compilations and proposals of histamine content in food for the general population and food analytical studies and laboratory analysis.

Food group	Food	Food composition table, food analytical study and laboratory analysis			Compilations of laboratory analysis		Reviews, table compilations and proposals of content in food for the general population								
		Ref. 19,20	Ref. 21	Ref. 13	Ref. 22	Ref. 23	Ref. 24	Ref. 18	Ref. 25	Ref. 26	Ref. 7	Ref. 27	Ref. 28	Ref. 29	Ref. 30
Cereal and tuber	Barley											X			X
	Buckwheat											X			X
	Corn						X					X	X		X
	Malt						X								X
	Potato						X						X		X
	Rice					X	X								X
	Wheat					X	X	X				X			X
	Yeast						X	X				X	X	X	
Fruit	Avocado				X	X	X			X		X	X	X	X
	Banana				X		X					X	X		X
	Cherry												X	X	X
	Coconut												X	X	X
	Dried figs											X	X		X
	Grapefruit				X							X	X		X
	Guava						X								X
	Kiwi	X			X		X	X				X	X	X	X
	Lemon						X	X				X	X		X
	Mandarin				X								X		X
	Mango											X			X
	Olives					X	X					X	X	X	X
	Orange				X		X					X	X		X
	Papaya				X		X	X				X	X		X
	Pear						X					X	X		X
	Pineapple				X		X	X				X	X	X	X
	Plum							X				X	X	X	X
	Raspberry						X					X	X		X
	Strawberry				X		X	X				X	X	X	X
Vegetable	Broccoli												X		X
	Cabbage									X		X	X		X
	Capsicum												X	X	
	Cauliflower												X		X
	Cucumber				X							X	X		X
	Eggplant			X	X	X	X			X		X	X	X	X
	Green peas		X									X	X		X
	Leek											X			X
	Mushroom					X	X					X	X	X	X
	Onion											X	X	X	
	Pickle											X	X	X	X
	Sauerkraut			X	X	X	X	X		X		X	X	X	X
	Spinach	X	X	X	X	X	X					X	X	X	X
	Tomato				X		X	X		X		X	X	X	X
	Turnip greens											X	X		X
	Zucchini				X								X		X
Dairy	Acidified whey						X					X			
	Butter				X		X	X							X
	Cheese (fresh)				X		X						X		X
	Cheese (semi/hard)				X	X	X	X		X					
	Cheese Brie										X	X	X	X	X
	Cheese Camembert			X					X		X	X	X	X	X
	Cheese Cheddar	X		X					X	X	X	X	X		X
	Cheese Edam										X		X		
	Cheese Emmental			X		X			X				X		
	Cheese Feta						X			X					X
	Cheese Gouda			X					X		X		X		
	Cheese Gruyere								X			X	X		
	Cheese Parmesan			X								X	X	X	X
	Cheese Raclette									X		X			
	Cheese Roquefort								X	X		X	X		
	Cheese Swiss	X		X							X	X	X		X
	Milk (fresh)				X	X	X			X			X		X
	Milk (pasteurised)					X	X	X	X				X		
	Milk - Coconut							X							X
	Yoghurt				X	X	X	X		X		X	X	X	X
Legume	Beans					X	X	X				X		X	X
	Chickpeas					X	X	X				X			X
	Lentils					X	X	X				X			X
	Soya beans											X			X
Fish	Canned anchovies				X	X	X						X	X	X
	Canned tuna	X			X		X				X		X	X	X
	Crab									X					X
	Fresh blue				X	X	X	X							X
	Fresh white				X	X	X	X		X					X
	Frozen blue				X		X						X		X

Table 1 (*Continued*)

	Frozen white				X (green)	X (red)	X (green)			X (green)			X (red)		X (red)
	Oysters									X (red)					X (green)
	Prawns									X (red)				X (red)	X (red)
	Shellfish				X (red)		X (red)	X (red)		X (red)					
	Smoked salmon/fish				X (red)		X (red)			X (red)			X (red)	X (red)	X (red)
	Tuna									X (red)			X (yellow)	X (red)	X (yellow)
Meat	Bacon											X (green)	X (yellow)	X (red)	
	Chicken							X (green)		X (green)			X (green)		X (green)
	Cold meat				X (red)	X (red)	X (red)	X (red)							X (red)
	Duck									X (green)					X (yellow)
	Fresh meat				X (green)	X (green)	X (green)			X (green)			X (green)		X (green)
	Ham (cooked)			X (green)	X (yellow)	X (green)	X (red)	X (red)		X (red)		X (red)	X (red)	X (red)	X (red)
	Ham (Iberic)				X (yellow)		X (red)			X (red)		X (red)	X (red)		
	Rabbit											X (red)	X (green)		X (green)
	Salami			X (green)						X (red)		X (green)	X (red)	X (red)	X (red)
	Sausage	X (green)		X (green)		X (red)	X (red)	X (red)	X (red)	X (red)			X (red)	X (red)	X (red)
	Smoked meat									X (red)			X (red)	X (red)	X (red)
	Turkey				X (yellow)		X (red)			X (green)			X (green)		X (red)
Egg	Cooked egg (white)				X (yellow)		X (green)					X (yellow)			
	Raw egg (white)				X (red)		X (green)	X (red)							
	Yolk				X (green)		X (green)	X (green)					X (green)		X (green)
Nuts	Almond												X (green)	X (red)	X (red)
	Dried fruit and nuts				X (red)		X (red)	X (red)						X (red)	
	Peanut											X (yellow)	X (red)		
	Pistachio											X (red)	X (green)		
	Poppy											X (red)			X (green)
	Sesame seeds												X (yellow)	X (red)	X (red)
	Sunflower seeds											X (yellow)	X (yellow)		
Fats	Coconut oil				X (green)		X (green)								X (red)
	Margarine				X (green)		X (green)								X (red)
	Olive oil				X (green)		X (green)								X (red)
Sweets	Chocolate (milk/dark)	X (green)				X (green)	X (red)	X (red)				X (red)	X (red)	X (red)	X (red)
	Cocoa	X (green)			X (red)		X (red)	X (red)				X (red)	X (red)	X (red)	X (red)
	Honey						X (green)							X (red)	
	Jam				X (yellow)		X (green)					X (yellow)		X (red)	X (red)
Drinks	Coffee						X (green)						X (green)		X (green)
	Cola type drinks												X (red)		X (red)
	Fruit Juices					X (green)						X (red)	X (red)	X (red)	X (red)
	Green tea				X (green)		X (yellow)	X (red)					X (green)		X (green)
	Orange juice				X (yellow)							X (green)	X (red)		X (red)
	Red/Black tea				X (yellow)		X (yellow)	X (red)		X (red)			X (green)		X (green)
	Tomato juice				X (yellow)		X (red)					X (yellow)	X (red)		X (red)
	Vegetable drinks				X (green)										X (red)
Condiments	Baking powder											X (red)			X (green)
	Colorant/Preservative							X (red)							X (red)
	Curry				X (red)							X (yellow)			X (red)
	Ketchup		X (yellow)	X (green)								X (yellow)			X (red)
	Meat extract												X (red)		X (red)
	Mustard				X (red)					X (red)		X (yellow)		X (red)	X (red)
	Soy sauce				X (red)		X (red)						X (red)	X (red)	X (red)
	Tomato sauce		X (green)		X (red)	X (yellow)	X (red)					X (yellow)		X (red)	X (red)
	Vanilla											X (red)			X (green)
	Vinegar (balsamic)				X (red)	X (red)	X (red)			X (red)		X (green)		X (red)	
	Vinegar (white/red wine)			X (green)		X (red)	X (red)	X (red)		X (red)		X (green)	X (red)	X (red)	X (red)

* Red: high/very high (>20 mg/kg); yellow: moderate (5–20 mg/kg); green: low content (<5 mg/kg).

<5 mg/kg (green); moderate content 5–20 mg/kg (yellow); and >20 mg/kg as high content (red).

Results

Search results

A total of 23 references were retrieved in this review. After reading all the sources of information we were led to the exclusion of nine of them for not following the proposed criteria or being duplicated. Thus, only 14 studies were considered legible for review and have been included after a double revision. All studies reviewed have shown low-medium evidence as a whole.

Discussion

We found that histamine and other biogenic amines are present in a vast majority of foods. Available reference sources do not reflect a homogeneous consensus, and the variation between foods makes it impossible for dieticians to accurately estimate amines content to correctly advise patients.[33]

It has been shown how in the reviews, compilation tables and proposals of foods content for the overall population, three different recommendations (in response to high, moderate or low histamine content) were found for the same food. This was the case of strawberries, blue cheese, cooked ham, yoghourt, frozen blue fish or green tea.

It can also be seen, when comparing those compilation tables with laboratory analytical studies, how histamine

content recommendations for the same food can be opposed (very high vs. very low content). Foods such as kiwi, spinach, canned tuna, sausages, cocoa and tomato sauce showed this contrast.

It may also occur that even laboratory analytical studies show opposite results, as with spinach, Cheddar and Swiss cheese and ketchup.

Even the European Rapid Alert system for Food and Feed database reports concentration ranges in different sub-samples of the same sample e.g. 50–500 mg/kg, 102–180 mg/kg, 27–152 mg/kg, of 147 mg/kg, below 5–208 and below 10–1000 mg/kg (for fish samples).[4]

Data from outbreaks show big variation in concentrations leading to adverse effects in the consumer. These uncertainties may lead either to an underestimation of the adverse effect to occur in sensitive people or to an overestimation of the risk in healthy people due to biogenic amines, since only the risk assessment of the individual biogenic amines is feasible at the moment.[4]

That situation can lead patients to assume erroneous or insufficiently verified information, and generates incomplete or ineffective treatments. This becomes disturbing when two-thirds of those using the internet to find health information claim it has some impact on their healthcare decisions,[34] and when searchers assure the internet information they obtain is, in most cases, trustworthy.[35]

The majority of health-related Internet searches by patients are for specific medical conditions.[36] Many concerns have been raised about the quality of online consumer health information, and the possibility that poor information has detrimental effects on health. A systematic review of 79 studies investigating the quality of online health information revealed that the methodology and rigour of these studies varies widely, as do the findings.[37] The information is often incomplete and sometimes inaccurate, although good quality material can be found.

Therefore, instructing patients with histamine intolerance, DAO deficit and mast cell diseases to limit their intake of histamine and other amines containing products would seem to be a reasonable recommendation. However, following such a recommendation will be challenging for several reasons. First, simply knowing that a product contains histamine or other amines does not allow an accurate estimate of its content. Second, ingredient lists are generally not present on fast food items, making it difficult to identify the

Table 2 Reviews, table compilations and proposals of other amines content in food for the general population.

Food group	Food	[25]		[7]	[28]	[31]	[26]	[30]	[32]	[29]
		Triptamine	Tiramine	Tiramine						
Cereal and tuber	Alfalfa					X		X		
	Kumara					X		X		
	Potato	0			X	X		X		
Fruit	Apple	0.53			X	X	X			
	Apricot				X	X		X		
	Avocado		2.3		X	X		X	X	
	Banana	1.13	0.7		X	X	X	X	X	
	Blackcurrant				X	X		X		
	Cherry				X	X		X		
	Coconut				X			X	X	
	Dates				X	X		X	X	
	Dried figs				X	X		X	X	
	Grapefruit				X	X	X	X		
	Grapes				X	X		X	X	
	Kiwi				X	X		X	X	
	Lemon				X	X	X	X	X	
	Mandarin				X	X		X		
	Olives				X	X		X	X	X
	Orange	0.1	1		X	X	X	X	X	
	Papaya				X	X	X	X	X	
	Passionfruit				X	X		X	X	
	Peach				X	X		X		
	Pear				X	X	X	X		
	Persimmon					X		X		
	Pineapple	0.62			X	X	X	X	X	
	Pomegranate	0.47				X		X		
	Plum				X	X		X		
	Raspberry		5		X	X		X		
	Rhubarb				X	X		X		
	Rockmelon				X	X		X		
	Strawberry	0.47			X	X	X	X		
Vegetables	Asparagus				X	X		X		
	Broccoli				X	X		X	X	
	Cabbage	0.77			X	X		X		
	Carrot	1.58			X	X				
	Cauliflower	1.98			X	X		X	X	
	Cucumber	1.28			X	X		X		
	Eggplant				X	X		X	X	X
	Green peas				X	X		X		
	Lettuce				X	X		X		
	Marrow					X		X		
	Mushroom					X	X	X	X	
	Onion	0.92			X	X				

Table 2 (*Continued*)

	Pickle				X	X		X		
	Sauerkraut		2		X	X		X		
	Spinach				X	X		X	X	
	Tomato	0.93	0.4		X	X				
	Turnip greens	2.12			X	X		X		
	Zucchini				X	X		X		
Dairy	Cheese Brie		26	39.8	X			X		X
	Cheese Camembert	2	12	Trace	X			X		X
	Cheese Cheddar	0.1	21-27	24-108.	X		X	X		
	Cheese Edam	8	31	Trace	X					
	Cheese Gouda	7	29	29	X					
	Cheese Limburger	16	12		X					
	Cheese Roquefort	20	36		X		X			
	Cheese Swiss	19	41		X			X		
	Mozzarella	10	16		X					
	Yoghurt		0.13		X			X		
Legume	Broad beans					X		X	X	
	Tofu/Tempeh				X			X		X
Fish	Canned tuna	0.1	0		X			X		
	Fresh white				X		X	X		
	Frozen				X		X	X		
	Sardine				X			X		
	Smoked salmon/fish				X			X		X
	Tuna				X		X	X		X
Meat	Bacon				X					X
	Ham (cooked)						X	X		X
	Pork (fresh/untreated)				X			X		
	Sausages	36	12		X			X		
	Turkey				X			X		
Nuts	Almonds				X			X	X	
	Cashew nuts				X		X	X		
	Macadamia nuts				X			X	X	
	Peanut				X			X	X	
	Pecan				X			X		
	Pine nuts				X			X	X	
	Pistachios				X			X	X	
	Sesame seeds				X			X	X	
	Sunflower seeds				X			X	X	
	Walnut				X		X	X	X	
Sweets	Chocolate (dark)		0.07			X	X	X		X
	Cocoa				X		X		X	
	Maple syrup				X			X		
	Sugar				X			X		
Drinks	Coffee				X			X		
	Cola type drinks				X			X		
	Pear juice					X		X		
	Tomato juice				X	X		X	X	X
	Vegetable drinks				X	X		X		
Condiments	Basil					X		X		
	Soy		0.18		X			X	X	X
	Vinegar (white/red wine)				X			X		

* Content (mg/kg).
* Red: high/very high; yellow: moderate; green: low content.

presence of amines. Third, amine-free products may require more effort to identify.[33]

To achieve the goal of collecting reliable information, all the methods and tools should be standardised.[38] Standardisation is a *sine qua non* of information pooling. However, scientific, and other constraints make it difficult to impose uniform procedures across studies.[39] In this case, each assessed nutrient must be defined in the same way, the units of measurement must be comparable, and the methods used to assess nutrient value must be the same or comparable.[38] It is important to recognise that it is not always necessary to use precisely the same methods and tools for data collection in order to achieve valid data integration across studies. Rather, what is crucial is that the information conveyed by each data set is 'inferentially equivalent'.[39]

Nutrient values in the food composition databases must be updated frequently and new foods and recipes need to be added promptly so that the results are precise and accurate also over time.[38] We recommend that manufacturers analyse their products for amines content and make these data available for incorporation into nutrient databases. Food manufacturers should also lower amines content of popular products. We also recommend that policymakers mandate that amines content of foods be included on the

Table 3 Foods excluded from Tables 1 and 2.

	Two green recommendations	Two yellow or red recommendations	One green and one yellow/red recommendations
Food excluded from Table 1	Apricot, Peach, Asparagus, Carrot, Celery, Lettuce, Rice milk, Soy milk, Lamb, Sunflower oil, Sweetener, Pepper.	Bread crumbs/cubes, Dates, Grapes, Lime, Passion fruit, Cream Tilsit, Sour cream, Yoghurt (fruit), Broad beans, Surimi, Calf liver, Chicken liver, Duck liver, Foie gras, Pork (fresh/untreated), Venison, Viscera, Hazelnut, Almond oil, Avocado oil, Peanut butter, Sesame oil, Walnut oil, Chocolate (white), Energetic drinks, Flavour enhancer, Ginger, Miso.	Rye, Pumpkin, Cream, Yoghurt (soy/rice), Split peas, Tofu/Tempeh, Sardine, Frozen meat, Cashew nuts, Caramels, Maple syrup, Lemonade.
Food excluded from Table 2	Barley, Rice, Chayote (choko), Bamboo shoots, Brussel sprouts, Celery, Chives, Garlic, Leek, Shallot, Swede, Cheese (fresh), Cheese Emmental, Milk, Sour cream, Beans, Mung Bean sprouts, Soya beans, Beef, Lamb, Rabbit, Veal, Cooked egg (white), Yolk, Green tea,	Corn, Lime, Arugula, Radicchio, Truffles, Cheese Feta, Cheese Fontina, Cheese Muenster, Cheese Parmesan, Cheese Port-Salut, Canned anchovies, Prawns, Surimi, Chicken liver, Offal, Salami, Smoked meat, Hazelnut, Chocolate (milk), Fruit Jam, Orange juice,	Durian, Guava, Longan, Loquat, Lychee, Nectarine, Rambutan, Redcurrant, Starfruit, Watermelon, Artichoke, Beetroot, Bok choy, Capsicum, Endive, Fennel, Parsnip, Pumpkin, Radish, Water chestnut, Watercress, Cheese Gruyere,

Low content <5 mg/kg (green); moderate content 5–20 mg/kg (yellow); and high content >20 mg/kg (red).

nutrition facts label. These actions by manufacturers and policymakers will help patients limit their amines intake, will help providers to better instruct patients, and will help researchers to accurately assess dietary intake.[33]

Conclusion

A valid risk assessment requires data on exposure, and thus on the contents of contaminants in foods. However, these data are highly variable and may significantly differ even within narrowly confined regions. In this regard, more attention should be paid to the preparation, extension and maintenance of food composition databases.

Further studies are necessary to establish safety limits for bioactive amines in food, and the intolerance they may cause.

Ethical disclosures

Confidentiality of data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this investigation.

Conflicts of interest and source of funding

The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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REVIEW

Histamine, histamine intoxication and intolerance

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KEYWORDS
Histamine intolerance;
Histamine;
Scombroid poisoning;
Diamine oxidase

Abstract Excessive accumulation of histamine in the body leads to miscellaneous symptoms mediated by its bond to corresponding receptors (H_1–H_4). Increased concentration of histamine in blood can occur in healthy individuals after ingestion of foods with high contents of histamine, leading to histamine intoxication. In individuals with histamine intolerance (HIT) ingestion of food with normal contents of histamine causes histamine-mediated symptoms. HIT is a pathological process, in which the enzymatic activity of histamine-degrading enzymes is decreased or inhibited and they are insufficient to inactivate histamine from food and to prevent its passage to blood-stream. Diagnosis of HIT is difficult. Multi-faced, non-specific clinical symptoms provoked by certain kinds of foods, beverages and drugs are often attributed to different diseases, such as allergy and food intolerance, mastocytosis, psychosomatic diseases, anorexia nervosa or adverse drug reactions. Correct diagnosis of HIT followed by therapy based on histamine-free diet and supplementation of diamine oxidase can improve patient's quality of life.

Introduction

Adverse reactions of the organism to ingested food (Fig. 1) can be divided into toxic and non-toxic, caused by specific individual intolerance of food, which is generally tolerated in healthy individuals. Based on immunological mechanisms the allergic reactions occur. The most common and most severe food allergy is IgE-mediated food allergy, which occurs in predisposed individuals – atopics. Food intolerances occur in non-immune mechanisms. They can be a result of disturbance of enzymes of gastrointestinal system or as a result of pharmacologic effects of vasoactive amines present in food.[1] One of these food intolerances is histamine intolerance, which is analysed in this review article.

Histamine and it's role in organism

Biogenic ammine – histamine (2-[4-imidazolyl]ethylamine) has been known since 1910, when it was isolated for the first time from *Claviceps purpurea* by Sir Henry Dale and his colleagues from Wellcome Laboratories.[2] Today, we know that histamine plays an important role in many physiological and pathological processes. Histamine causes contraction of smooth muscle cells, particularly the bronchi and intestine, dilation of vessels and their increased

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