The influence of food histamine intake on asthma activity

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Abstract

Background: Asthma is a complex chronic inflammatory disorder, with many factors influencing its prevalence. Diet's impact on the symptoms of the disease is still controversial, although various dietary patterns or specific nutrients have been studied. Objective: The objective of this crossover, randomised, two-period study was to examine the potential of controlling dietary histamine intake and, through this, alter asthma symptoms in children with mild intermittent asthma. Methods: Children with mild intermittent asthma were randomly assigned to either a high- (HH) or low- histamine (LH) diet, based on the Mediterranean pattern, for 4 weeks (t0). This was followed by a 2-week washout period (t1) before patients crossed to the alternative diet (t2) for an additional 4 weeks. Children were assessed at baseline and after the completion of each diet phase. They also recorded symptoms and peak flow throughout the intervention. Adherence to the dietary intervention was assessed via four random 24-hour recalls for each intervention period and comparison of selected qualitative and quantitative indices, i.e. histidine, food choices, energy, macro- and micronutrients intake. Results: Eighteen children (10 boys), with mean age 11,5±3,1years were recruited and completed the study. A trend for prolonged and more severe symptoms was observed during HH. There was good adherence to the diet during remission periods, but lower compliance during symptomatic periods, particularly for the HH group. The mean actual intake differed significantly between the two diets, not only in the histamine content but also in energy, sugar and various micronutrients, including sodium. Conclusions & Clinical Relevance: Diet may have an active and direct impact on asthma symptoms. A diet deviating from the Mediterranean standard in terms of high energy, histamine, and salt has been associated with asthma worsening. Dietary interventions in asthmatic patients should be prospectively evaluated for a longer period and with proper nutritional education.

Title Page

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To the editor

Food histamine due to its pharmacological action may be involved in provoking symptoms of wheeze and asthma [1]. The current study aimed to investigate whether controlling dietary histamine intake can interfere with respiratory symptoms in children with mild asthma.

Eighteen children (10 boys; mean age 11.5 ± 3.1 years), with mild asthma[2], were enrolled from an outpatient allergy unit of a tertiary pediatric hospital.

Exclusion criteria were the presence of other chronic or acute diseases (except rhinitis, allergic conjunctivitis or atopic dermatitis), need for current or previous systematic treatment for disorders other than asthma, and food allergy history. Parents provided informed consent and the local ethics committee approved the study.

A two-period, two-intervention, randomized crossover design was followed (Table 1). Participants were randomly assigned (computer-generated random numbers) to start with one out of the two offered diet patterns for four weeks and continue with the other for another four weeks, with a two-week washout period in between, in which they could consume their typical diet without any restriction. One diet was designed as low-histamine (LH) and the other as high-histamine (HH) in regard to the histamine content of the foods.

Foods from all groups (dairy, fruits, vegetables, starch, meat, fat) were ranked according to their histamine content into low or high histamine. A food list (Table 1), together with four model diet plans based on the Mediterranean diet prototype, one for each week of the 4-week intervention period, were prepared (online repository, Table 2). Patients and their parents were instructed and encouraged to follow these diet plans or modify according to the LH or HH respective food list and alter food portion sizes *ad libitum* to avoid weight changes.

Before randomization (t0), participants were evaluated to confirm mild asthma according to GINA [3] and controlled with low inhaled corticosteroids (fluticasone propionate pMDI 100μg bid). Basic anthropometric measurements (weight and height) were recorded.

Daily symptom scores [4] were recorded on diary cards throughout the study. Upper airway symptoms included blocked/stuffy nose, runny nose, sneezing/itchy nose, itchy/sore/watery eyes, hoarse voice, and sore throat. Lower airway symptoms included cough and wheezing/noisy breathing during the day, the night and during exercise. Each symptom was scored from 0 (no symptom) to 3 (severely troublesome). A sum of at least 3 score units for either the upper or the lower respiratory symptomatology was considered as a "*higher score* " day. The quantitative association of symptoms and the comparison between the different dietary intervention periods and the recorded symptom score (upper, lower or total) were evaluated and analyzed.

After the end of the first (t1) and second (t2) intervention period, asthma symptom records were re-assessed on-site, and weights were measured. At t1 guidance for the cross-arm diet plan was provided, for patients to proceed to the second intervention stage after the two weeks washout period. During the intervention periods, four 24hour recalls were recorded by phone randomly during each diet intervention, to assess compliance and provide assistance for better diet implementation. Histidine intake, which is metabolized to histamine, together with the overall energy, macronutrients and micronutrients were further determined via the 24-diet recalls with the Food-Processor Nutrition Analysis Software [5]. A post-hoc analysis of food choices during the intervention period was performed to evaluate preference changes depending on the provided food lists and symptoms fluctuation.

The distributions of all recorded parameters were assessed with the Shapiro-Wilk test. Descriptive statistics are presented as median (inter-quartile range) for non-normally distributed variables and means ± standard deviation for normally distributed parameters. The Wilcoxon rank-sum test and Kruskal Wallis tests were used to compare continuous variables and the Pearson's X^2 test to compare categorical variables among studied groups. The Wilcoxon matched-pairs rank-sum test was used to compare continuous variables within the same individual between the multiple measurements. All reported p-values are based on 2-sided tests and compared with a significance level of 5%. Stata 9.1 for Windows (Stata Corp LP, College Station, TX) was used for all statistical calculations and plots.

No loss of asthma control was recorded during the study period. Both upper and lower respiratory symptom scores were lower during the LH period, but the relevant statistical comparisons were not significant. The median number of symptom-free days was higher during the LH diet period as compared to the HH (5.5 days vs 9.5), but again non-significant (p-value=0.753) (Table 3).

Histidine intake was found to be higher in the HH diet (online supplementary, Table 5). Food choices varied among the LH and HH periods as expected. During the HH diet, milk, junk food, juices and vegetables intake was higher at symptom-free days than during the LH diet. At higher score days intake of oils and butter, fish, chocolate, egg and junk food was higher in HH diet than in LH. Fish consumption with the anti-inflammatory n-3 PUFA [6] was generally low, but increased during days with higher symptom scores independently of the diet assigned, possibly due to caregivers' belief that is a "healthy" choice to relieve symptoms.

Moreover, symptoms fluctuation affected food choices within the same intervention period. In the symptom-free days during the HH diet, children consumed more starchy foods, olive oil, chocolate, bacon, ham or sausages and junk food, than within days with higher symptoms where they included more fish and butter. Respectively, in the LH symptom-free days, they selected more starchy products, juices from permitted fruit and permitted ham. On the contrary, at higher symptoms days during the LH diet, they consumed more olive oil and fresh fish.

In terms of micronutrients, inadequate intake of vitamin D, correlated previously to pulmonary dysfunction in childhood [7], potassium, and manganese were noted at all stages of intervention.

Marginally lower intake of calcium and folate compared to the Dietary Reference Intakes (DRIs) [8] were noted

during LH. On the other hand, LH diet was superior in beta-carotene, which is an important antioxidant suggested to be directly involved in asthma pathogenesis [7], as well as in fluoride and vitamin K intake in comparison to HH (online repository, Table 5).

A trend towards lower symptoms and more symptom-free days during the LH diet periods revealed. Lack of statistical significance could be explained by the short intervention period, the small sample of participants, the mild symptomatology or the trend for a more "healthy diet" (Table 4) during symptom deterioration periods.

Furthermore, as elucidated from our results, a diet intervention aiming to control a single nutrient's intake may not be feasible unless, as elsewhere shown, this is based on a food supplement or ready-prepared meals to control overall intake [9]. Both these strategies, though, do not reflect the ability of patients to adapt to the proposed changes of eating habits, nor provide the long-term effect of dietary changes. Anyhow, such change is generally difficult to adopt and maintain unless proper therapeutic techniques from medical nutrition therapy are incorporated [10].

Eating behaviors change in asthmatics during days with symptoms. Whether such change affects clinical outcomes requires further exploration with long-term dietary interventions.

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Impact statement:

Food choice is affected and/or may affect symptoms in children with mild asthma. Diet intervention is promising yet challenging, for asthma control.

Signature

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Table 1: Food ranking in low and high histamine content

Food group/ Type of diet	**Low Histamine**
Dairy products	Plain milk without additives (cow's or goat's), butter, plain yogurt, ricotta cheese, cottage c
Fruit	Apple, apricot, peach, pear, melon
Vegetables	Asparagus, cabbage, lettuce, green beans, onion, pepper, radish, turnip
Legumes	Peas, lentils, chickpeas
Starchy products/grains	Bread with natural yeast without preservatives, oat cereals, pure corn flakes, potato, sweet
Nuts	Chestnut, sunflower seeds, pine nuts, pistachios, almonds, coconuts, currants, red currants,
Spices	Herbs, spices except for anise, red pepper, curry (ready-made spicy products not allowed)
Meat/poultry/fish	Beef, chicken without skin, turkey without skin, fresh fish, lamb, rabbit, veal, cooked eggs, l
Fats/ oils	All vegetable oils, homemade sauces prepared with permitted ingredients
Beverages	homemade lemonade
Sweets/sweeteners	Sugar, homemade jams, homemade sweets with permitted ingredients

Table 3 Comparisons between the median number of days with symptoms and median symptom score during the two intervention periods.

Data are presented as median (interquartile range).

		Type of diet	**Type of diet**	
		Low Histamine	High Histamine	p-values
Symptoms duration in days	**Symptoms duration in days**	5.5 (8)	9.5 (4)	0.753
Respiratory Symptoms	Upper*	4.67 (11.5)	12.5 (5.83)	0.780
	Lower*	4.25 (13.1)	14 (12.45)	0.727
	Total*	11.33 (53.5)	30.17 (21.42)	0.889

* units in symptom score scale

** comparisons between different types of diets (Wilcoxon matched-pairs sign test)

Table 4 Food choices according to symptoms fluctuation during and among the two intervention periods

	LH period	**LH period**		**HH period**	**HH period**		**HH vs LH**	**HH vs LH**
	Remission	Episode	p-value[1]	Remission	Episode	p-value[1]	Remission p-value[2]	Episode p-value[3]
Milk	1.74 (±1.38)	2.69 (±1.21)	0.064	2.69 (±1.98)	3.77 (±1.35)	0.133	**0.004**	0.107
Starchy food	3.65 (2.94)	6.04 (2.72)	**0.021**	4.61 (3.28)	6.27 (±1.85)	**0.046**	0.972	0.141
Meat	4.01 (±2.91)	5.19 (±2.32)	0.382	3.25 (±2.05)	4.4 (±1.78)	0.133	0.196	0.207
Olive oil	3.24 (±3.12)	0.26 (±0.44)	**0.014**	0.28 (±0.44)	4.23 (±3.16)	**0.002**	**0.002**	**0.007**
Butter	0.318 (±0.83)	0.05 (±0.14)	0.299	2.56 (±2.62)	0.46 (±0.5)	**0.043**	**0.014**	**0.007**
Fish	0.51 (±0.89)	0.75 (±0.59)	0.184	3.7 (±2.93)	0.29 (±0.47)	**0.003**	0.059	**0.003**
Chocolate	0.268 (±0.7)	0.28 (±0.45)	0.657	0.9 (±0.74)	3.33 (±3.06)	**0.007**	**0.002**	**0.015**
Egg	0.05 (±0.15)	0.04 (±0.08)	0.809	0.89 (±1.47)	0.18 (±0.34)	0.053	**0.027**	**0.006**
Sweats	0.74 (±0.8)	1.12 (±1.1)	0.328	1.55 (±1.34)	1.46 (±1.08)	0.861	0.463	0.123
Nuts	0.67 (±1.3)	0.4 (±0.42)	0.528	0.61 (±1.39)	0.09 (±0.19)	0.426	**0.035**	0.514
Bacon or sausages or ham	0.11 (±0.18)	5.08 (±3.21)	**0.002**	0.31 (±1.11)	0.71 (±0.46)	**0.030**	**0.002**	0.242
Junk food	1.01 (±1.27)	0.89 (±1.15)	0.889	0.12 (±0.3)	2.03 (±1.41)	**0.002**	0.055	**0.017**
Fried oil	0.79 (±1.25)	0.14 (±0.13)	0.726	1.23 (±1.59)	1.26 (±0.94)	0.917	**0.003**	0.105
Juices	0	0.8 (0.76)	**0.004**	0.15 (0.56)	0.12 (0.2)	0.155	**0.016**	0.317
Fruit	0.29 (±0.37)	0.82 (±0.61)	0.546	1.27 (±2.35)	0.59 (±0.49)	0.726	0.221	0.302
Vegetables	0.66 (±1.02)	0.1 (±0.23)	0.052	0.4 (±0.51)	0.95 (±0.79)	0.028	**0.002**	0.806

Values are presented in mean (±standard deviation)

Comparisons (Wilcoxon matched-pairs rank-sum test) of food choices

[1] during episodes vs. remission periods within the same intervention period

[2] during remission between the two intervention periods

[3] during episodes between the two intervention periods

ONLINE REPOSITORY

Table 2: Model weekly diet plan provided to the patients for the LH and HH period of the dietary intervention

Low Histamine	*Low Histamine*	*Low Histamine*
Breakfast	1 cup of whole fat milk+ 2whole wheat homemade chocolate biscuits	1 cup whole milk+ 1slice of whole
Snack	1 cup melon	1 cup of fresh mixed apple-pear
Lunch	1 portion green fresh beans+ 1 slice of whole wheat bread+ potatoes	1 portion stuffed zucchini or peppe
Snack	Oven-baked apple with egg and breadcrumbs, sugar and cinnamon	1 milkshake with whole fat milk, v
Dinner	Caesars Chicken salad with lettuce, boiled corn, cucumber, olive oil	1 chicken burger with whole wheat

High Histamine	*High Histamine*	*High Histamine*	*High Histamine*	*High Histamine*	*High Histamine*	*High Histamine*
Breakfast	1 cup of whole fat milk+ 2whole wheat homemade chocolate biscuits	1 cup whole milk+ 1slice of whole wheat bread+ 1tsp Nutella	1 cup of milk choco-late+ 2 homemade vanilla biscuits	1 cup of milk+ 1 whole wheat bread+ 1tsp honey	1 whole fat yogurt with fruit	1 whole fat milk+ $\frac{1}{2}$ cup corn flakes	1 whole fat milk+ 2 slices of toasted bread+ 2tsp straw-berry jam
Snack	1 cup of fresh orange juice	1 cup of mixed fresh fruit juice	1 banana	1 cup anana juice	1 banana	1 kiwi fruit	1 cup of fresh orange-anana juice
Lunch	1 portion of lentils+ mature yellow cheese (Cretian graviera)+ 1slice of wholewheat bread	1 portion stuffed tomatoes with rice and mince meat+ 1slice of wholewheat bread+ feta cheese	1 portion of fish sticks+ 1boiled potato+ cauliflower or broccoli	1 portion "tourlou" vegetables (aubergine, carrots, cucumber, tomato, olive oil, potatoes)+ 1 slice whole wheat bread	1 portion pasta with tomato sauce and mush-rooms+ parmesan cheece+ Tomato salad	4-5 fried meatballs+ 15-20 slices of fried potatoes+ broccoli or cauliflower	1 portion spinach with rice and tomato+ feta cheese+ 1 slice of whole wheat bread
Snack	1 yogurt with chocolate slices	Homemade Banana milkshake (banana, whole milk, honey)	Fruit salad: grapes, orange, banana	1 cup strawber-ries or grapes	chocolate ice cream	50gr milk or back chocolate	Lemon or straw-berry Sorbet

High Histamine	*High Histamine*	*High Histamine*	*High Histamine*	*High Histamine*	*High Histamine*	*High Histamine*	*High Histamine*
Dinner	1 piece of ham and cheese pie	1 burger with pork mince neat_-tomato salad	1 hot dog: whole wheat bread, 1 sausage stuffed with cheese, 1tsp mustard, 1tsp ketchup	1 souvlaki with pork meat and whole wheat pita bread, fried potatoes, tomato	Chef salad: Roquefort cheese, salami, cedar, boiled egg, tomato, lettuce, olive il	1 slice of spinach pie	Baked pork meat with Greek salad

Table 5. Comparison of micronutrient intake (mean values) with Dietary Reference Intake (DRI).

Type of diet	**Sodium (mg)**	**Potassium (mg)**	**Calcium (mg)**	**Iron (mg)**	**Phosphorus (mg)**	**Magnes**
High Histamine	**3200**	2922	1365	14.5	1603	280
Low Histamine	1808	2557	807	12	1208	240
DRI	1500	4500	1300	8	1250	240

	Vitamin A (RE)	**Vitamin C (mg)**	**Vitamin D (ug)**	**Vitamin E (IU)**	**Thiamin (mg)**
High Histamine	737	84	**4.5**	11.6	2
Low Histamine	627	46	**4.46**	10.4	1.26
DRI	600	45	**15**	11	0.9

Deficient intake in specific nutrients is marked in bold letters.