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Body Mass Index and skin reactivity to histamine and *Dermatophagoides pteronyssinus* in children and adolescents followed in a pediatric allergy service

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Summary
Rationale. *Recent data suggest that the nutritional status assessed by body mass index (BMI) is positively associated with skin reactivity to histamine in children.* ***Objective.*** *To study the relation between BMI and skin reactivity to histamine and* Dermatophagoides pteronyssinus *in allergic children and adolescents.* ***Methods.*** *The medical charts of patients attended in our outpatient clinic between 2013 and 2014 (n = 972) were evaluated. Only patients with asthma, allergic rhinitis or wheezing infants sensitized to at least one aeroallergen were selected: a total of 626 patients (6 months to 19 year-olds; 60.1% male) were enrolled. Weight (kg), height (m), BMI (weight/height^2), and the mean diameter of the wheals induced by histamine (10 mg/ml) and* Dermatophagoides pteronyssinus *in skin prick tests (SPT) were obtained. Skin index (SI; ratio of allergen-induced wheal diameter and corresponding histamine diameter) was also analyzed.* ***Results.*** *All patients had shown a mean wheal diameter of histamine greater than 1 mm. There was no increased skin reactivity to histamine with increasing BMI Z score (ZBMI). However, a significant correlation between BMI and the mean wheal of histamine was observed in patients < -1 ZBMI. Similar results were observed with* Dermatophagoides pteronyssinus*, (even considering the SI).* ***Conclusions.*** *We did not document interference of nutritional status (ZBMI) on the skin reactivity to histamine or* Dermatophagoiodes pteronyssinus *in atopic patients. Further investigation is required.*

Introduction

Skin prick test (SPT) is an important tool in the assessment of allergic sensitization and can be influenced by various factors: age, ethnicity, body site where the test is performed (1,2), exposure to smoking (3), use of certain drugs, type of devices used, etc. (1,2).
Association between asthma and/or allergic rhinitis with obesity is becoming more common. Considering that both diseases are associated with systemic inflammation (4), obesity could interfere with *in vivo* evaluation of allergic sensitization. Recently, the nutritional status assessed by body mass index (BMI) was documented to be associated in children (5) and adults (6) with increased skin reactivity to histamine. Although both studies evaluated histamine skin response in allergic patients, in none of them was analyzed the relationship between BMI and skin response to individual allergen (5,6).
Therefore, the scope of this study was to evaluate the relationship between BMI and the mean diameter of the wheal induced by histamine and *Dermatophagoides pteronyssinus* (Dp) in children and adolescents treated at an allergy service.

Materials and Methods

Demographic (gender, age, diagnosis, prescription) and clinical data (weight [kg], height [m]) from patients aged 6 months to

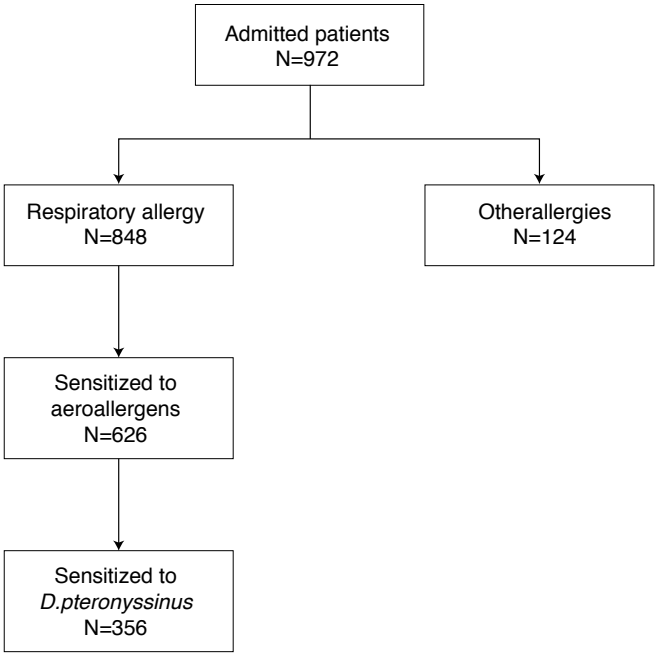
19 years admitted in our division (2013-14) due to wheezing episodes, asthma, allergic rhinitis and food/drug allergy, were obtained from the electronic medical records (n = 972).

The subjects underwent SPT (puncture) with standard battery of allergens, used routinely in our service, composed by: Dp, *Dermatophagoides farinae*, *Blomia tropicalis*, *Blattella germanica*, *Periplaneta americana*, dog dander, cat dander, fungi mixture, milk, egg, saline (negative control), and histamine (10 mg/mL, positive control) (IPI ASAC®, Brazil) (7). SPT were performed by trained personnel using metal lancet. Antihistamines were interrupted at least 10 days before SPT. Patients with both positive SPT to at least one aeroallergen (mean wheal equal to or greater than 3 mm) (8) and with a mean histamine-induced wheal diameter equal to or greater than 1 mm were included in the study (n = 626) (**figure 1**). Patients with negative results to histamine or with positive response to negative control were excluded from the study (1,2).

A total of 626 children (60.1% males) were enrolled and 356 had positive skin test result to Dp. The children's nutritional status was evaluated by body mass index (BMI, weight / height^2, Anthro OMS.22 Plus®), compared to the World Health Organization (WHO) reference, and expressed in BMI Z score (ZBMI) (9). For analysis purposes, the data referring to histamine and Dp reactions and skin index (SI; ratio of Dp-induced wheal diameter and corresponding histamine wheal diameter) were obtained (7). The study was approved by the Ethics and Research Committee of the Escola Paulista de Medicina of the Federal University of São Paulo, and all participants signed an Informed Consent.

According to the nature of variables studied parametric (Student t) and nonparametric (Kruskal-Wallis) tests were used. The relationship between nutritional status (ZBMI) and histamine- and Dp-induced mean wheal diameter were evaluated by the Spearman's correlation coefficient. In all tests the rejection level for the null hypothesis was set at 5%.

Figure 1 *- Flowchart of patients involved in the study.*



Results

During 2013-2014, 972 patients were admitted in our division, of which 87.2% had asthma and/or allergic rhinitis or were

Table 1 *- Histamine-induced mean wheal diameter (M ± SD) and Spearman's correlation coefficients (r) between nutritional status (BMI Z score) and histamine-induced mean wheal diameter of patients according to age range and interval of BMI Z scores.*

BMI Z score	0 to 2 yrs			2 to 5 yrs			5 to 10 yrs			> 10 yrs		
	N	Histamine (95% CI)	r (95% CI)	N	Histamine (95% CI)	r (95% CI)	N	Histamine (95% CI)	r (95% CI)	N	Histamine (95%CI)	r (95%CI)
< -1[(a)]	11	4.72 ± 1.30 (3.86-5.60)	0.41 (-0.28-0.82)	16	4.71 ± 1.00 (4.19-5.22)	-0.24 (-0.66-0.29)	16	5.75 ± 1.63 (4.88-6.62)	-0.28 (-0.69-0.27)	11	7.18±1.82* (5.96-8.41)	0.27 (-0.41-0.76)
-1 a +1[(b)]	36	4.64 ± 1.75 (4.05-5.23)	-0.13 (-0.45-0.22)	109	4.81 ± 1.76 (4.48-5.15)	-0.18 (-0.36-0.01)	102	5.70 ± 1.70 (5.37-6.04)	0.11 (-0.10-0.30)	88	5.65±1.56 (5.32-5.98)	-0.16 (-0.37-0.06)
+1 a +2[(c)]	20	4.58 ± 1.67 (3.79 -5.36)	0.52 (0.08-0.79)	43	5.40 ± 1.56 (4.92-5.87)	0.04 (-0.28-0.35)	38	5.91 ± 1.96 (5.25-6.56)	-0.05 (-0.38-0.29)	39	5.22±1.61 (4.70-5.74)	-0.13 (-0.44-0.20)
> +2[(d)]	10	4.0 ± 1.08 (3.23-4.77)	0.16 (0.08-0.40)	26	5.50 ± 1.85 (4.75-6.25)	0.42[1] (0.03-0.70)	36	6.18 ± 1.94 (5.53-6.82)	0.18 (-0.16-0.49)	25	6.06±1.89 (5.28-6.84)	0.04 (-0.37-0.44)

BMI Z score: Body mass index Z score; 95% CI: 95% Confidence interval IC 95%; Kruskal-Wallis: Histamine: 0-2 yrs, 2-5 yrs, 5-10 yrs: a = b = c = d. Older than 10 yrs: a > b, c; b = c = d

Spearman's correlation coefficient: [1]p < 0.05

wheezing infant, 73.9% were sensitized to at least one of the tested aeroallergens (n = 626) and were included in the study, and 56.7% (n = 356) of them were sensitized to *Dermatophagoides pteronyssinus* (**figure 1**). BMI ranged from 10.9 to 37.8 and ZBMI from -4.7 to 6.3, with the following distribution: 2.7% patients below -2 ZBMI, 53.4% in the normal range (-1 to +1 ZBMI), and 15.5% were considered obese (> +2 ZBMI).

Table 1 shows the histamine-induced mean wheal diameter of patients according to age range and ZBMI score. No significant differences of histamine-induced wheal diameter between the different ZBMI intervals were observed with respect to each age range. Spearman's correlation coefficient between histamine-induced mean wheal diameter and ZBMI was not significantly different, except for 2 to 5 years old age group and +1 to +2 ZBMI. Similar results were observed considering the Dp-induced mean wheal diameter (data not shown).

Table 2 summarizes the statistical analysis regardless of the age of the patients. In the whole group, there were no differences regarding age and mean histamine-induced wheal when considering the ZBMI groups; however, a significant correlation between ZBMI and histamine-induced wheal was observed among those subjects with BMI lower than -1 ZBMI (undernourished).

The evaluation of Dp-sensitized patients showed no significant differences with respect to the mean Dp-induced wheal. Nevertheless, a significant correlation was observed between ZBMI and Dp-induced wheal among those patients scored between +1 ZBMI and +2 ZBMI. Regarding SI (mean), there were no significant differences among ZBMI groups as well as no significant correlation between SI and ZMBI.

Discussion

When evaluating the skin response to histamine and/or allergens, it is important to be aware of when it is clinically present, which extracts and devices were applied, and the inter-individual variation in test run (1,2,9). Several studies have shown that, in the first month of life, the child's skin is able to express an age-dependent inflammatory response to histamine (10-12). There were no differences regarding age among the different ZBMI groups assessed.

In addition, when evaluating skin response to histamine and allergen extracts, it is important to point out that the mechanism involved in each one is partially different. Histamine acts directly on the subcutaneous inflammatory cells causing local release of inflammatory substances, including histamine itself, while allergen extracts must penetrate the skin, bind to a specific Immunoglobulin E (IgE) fixed to the surface of mast cells, release inflammatory mediators that contain histamine, and present a clinical expression of the inflammatory reaction (wheal and

Table 2 *- Age (M ± SD), histamine-induced mean wheal diameter (M ± SD), patients sensitized to* Dermatophagoiodes pteronyssinus *(+veSPT / total, %), Dp-induced mean wheal diameter (M ± SD), skin index (M ± SD) and Spearman correlation coefficients (r) of the patients according to the nutritional status (ZBMI).*

			Histamine		*Dermatophagoides pteronyssinus*			Skin index	
ZBMI	**N**	**Age (month) (95% CI)**	**M ± SD mm (95% CI)**	**r[e] (95% CI)**	**+ve SPT / Total (%)**	**M ± SD mm (95% CI)**	**r[f] (95% CI)**	**M ± SD (95% CI)**	**r[g] (95% CI)**
<-1[(a)]	54	78.3 ± 58.7 (63.2-95.3)	5.5 ± 1.7 (5.0-6.0)	0.42[1] (0.16-0.62)	29/54 (53.7)	4.8 ± 2.1 (4.0-5.6)	0.267 (-0.12-0.58)	0.84 ± 0.25 (0.75-0.94)	0.018 (-0.37-0.39)
-1 a +1[(b)]	335	86.0 ± 55.7 (80.1-92.0)	5.3 ± 1.7 (5.1-5.5)	-0.06 (-0.05-0.16)	197/335 (58.8)	5.0 ± 1.7 (4.8-5.3)	0.129 (-0.01-0.27)	0.95 ± 0.36 (0.90-1.00)	0.085 (-0.06-0.22)
+1 a +2[(c)]	140	84.2 ± 57.0 (74.8-93.7)	5.4 ± 1.7 (5.1-5.6)	-0.08 (-0.24-0.08)	70/140 (50.0)	5.2 ± 2.3 (4.7-5.8)	0.264[1] (0.02-0.48)	0.97 ± 0.40 (0.88-1.10)	0.166 (-0.08-0.39)
> +2[(d)]	97	86.9 ± 47.9 (77.2-96.6)	5.8 ± 1.9 (5.4-6.2)	0.19 (-0.01-0.38)	60/97 (61.9)	5.6 ± 2.1 (5.0-6.1)	0.036 (-0.23-0.29)	0.95 ± 0.41 (0.84-1.10)	-0.128 (-0.38-0.14)

M ± SD: mean ± standard deviation; ZBMI: Z body mass index score; 95% CI: 95% confidence interval; +ve SPT: *D. pteronyssinus* positive skin prick test; skin index: ratio between mean wheal diameter induced by *D. pteronyssinus* and the corresponding histamine mean wheal.

Histamine

Kruskal-Wallis: age and mean wheal diameter, a = b = c = d;

r[e]: Sperman correlation index between ZBMI and histamine; [1]$p < 0.05$.

+ve SPT to *D. pteronyssinus*

Kruskal-Wallis: age, mean wheal diameter and skin index, a = b = c = d;

r[f]: Spearman correlation index between ZBMI and *D. pteronyssinus*; [1]$p < 0.05$;

r[g]: Spearman correlation index between ZBMI and skin index.

flare). Therefore, a complementary evaluation of local release of endogenous histamine in the assessment of the response to Dp in Dp-sensitized patients was added to our study, and the results were similar to those observed with histamine. Even though a significant correlation has been found between histamine and BMI for those patients in the group that scored -1 ZBMI and Dp in the normal range group, these results are not sufficient to enable us to endorse an interference of nutritional status with the response to histamine and Dp as well as with SI. Reaction to Dp was chosen to evaluate the relationship between allergic sensitization and nutritional status because it is the most prevalent among Brazilian population (13,14).

BMI has been pointed as one of the main indexes for the diagnosis of nutritional status. However, the limits set to define different nutritional patterns vary according to gender and age. Thus, it has been recommended the use of ZBMI for this evaluation, especially if patients are of different age groups. Moreover, the ZBMI cut-offs used to classify nutritional status (overweight, obesity, etc.) vary by age and an individual can, therefore, be classified differently according to the defined ZBMI for a certain age. This is due to some inconsistencies in the growth curves obtained from WHO (7).

Despite this, even in isolated comparisons, we did not detect a universal significant relationship among BMI and the studied variables. The significant correlation between BMI and skin response to histamine previously observed in children should be due to the narrow age range of the children studied (5). Although it was not an objective of this study we cannot fail to stress on the possible interrelationship between vitamin D, nutritional status and allergic sensitization (15,16).

In conclusion, according to our data, the nutritional status assessed by BMI did not influence the skin response to histamine and to allergen in children treated in a specialized allergy service. Additional studies are needed to clarify this possible relationship more precisely.

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