ORIGINAL ARTICLE

Increased Total and Mite-Specific Immunoglobulin E in Patients With Aspirin-Induced Urticaria and Angioedema

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■ Abstract

Background: An increased prevalence of atopy has been observed in patients with intolerance of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs).
Objective: To investigate total and mite-specific immunoglobulin (Ig) E in serum from patients with hypersensitivity to NSAIDs and healthy controls.
Methods: Patients who reacted to 2 or more chemically unrelated NSAIDs with urticaria and angioedema, confirmed by a double-blinded provocation test with aspirin, were skin tested with inhalant allergens. Total and specific IgE to *Dermatophagoides pteronyssinus* (Dp) and *Blomia tropicalis* (Bt) in the serum was quantified by enzyme-linked immunosorbent assay (ELISA) in patients and a control group of healthy blood donors.
Results: One-hundred-and-fourteen patients and 74 controls were studied. Skin tests were positive in 95 patients (83.3%). Total mean IgE levels were 107.1 (91.3) IU/mL in controls and 161.0 (150.8) IU/mL in patients (P=.006). Mean (SD) levels of IgE to Dp were 0.210 (0.17) optical density (OD) units in controls and 0.473 (0.65) OD units in patients (P=.001). Levels of specific IgE to Bt were 0.230 (0.20) OD units in controls and 0.522 (0.8) OD units in patients (P=.0001). Positive ELISA results for IgE to Dp were found for 29.6% of controls and 70.4% of patients (P=.0001); the corresponding percentages for Bt were 32.4% of controls and 67.6 % of patients (P=.0001).
Conclusions: Cross-reactive patients with NSAID-induced urticaria and angioedema exhibit an increased prevalence of sensitization to Dp and Bt and increased total serum IgE. Further research is necessary to determine the reasons for this association.

Key words: Angioedema. Aspirin. Asthma. Atopy. IgE. NSAID hypersensitivity. Rhinitis. Urticaria.

■ Resumen

Antecedentes: Se ha observado un aumento de la prevalencia de atopía en pacientes con intolerancia al ácido acetilsalicílico y a los antiinflamatorios no esteroideos (AINE).
Objetivo: Investigar la inmunoglobulina (Ig) E total y específica contra ácaros en suero de pacientes con hipersensibilidad a AINE y de controles sanos.
Métodos: Los pacientes que presentaron una reacción a dos o más AINE no relacionados químicamente con urticaria y angioedema, confirmados mediante una prueba de provocación con doble ciego con ácido acetilsalicílico, fueron sometidos a una prueba cutánea con alérgenos inhalados. Se cuantificó la IgE sérica total y específica contra *Dermatophagoides pteronyssinus* (Dp) y *Blomia tropicalis* (Bt) mediante enzimoinmunoanálisis de adsorción (ELISA) en los pacientes y en un grupo control de donantes de sangre sanos.
Resultados: Se estudiaron 114 pacientes y 74 controles. Las pruebas cutáneas dieron positivo en 95 pacientes (83,3%). Los niveles medios de IgE total fueron de 107,1 (91,3) UI/ml para los controles y de 161,0 (150,8) UI/ml para los pacientes (p=0,006). Los niveles medios (DE) de IgE contra Dp fueron de 0,210 (0,17) unidades de densidad óptica (DO) para los controles y de 0,473 (0,65) unidades de DO para los pacientes (p=0,001). Los niveles de IgE específica contra Bt fueron de 0,230 (0,20) unidades de DO para los controles y de 0,522

(0,8) unidades de DO para los pacientes (*p*=0,0001). Se hallaron resultados positivos de ELISA para IgE contra Dp en el 29,6% de los controles y en el 70,4% de los pacientes (*p*=0,0001); los porcentajes correspondientes para Bt fueron de 32,4% para los controles y de 67,6 % para los pacientes (*p*=0,0001).

Conclusiones: Los pacientes que muestran reacción cruzada con urticaria y angioedema inducidos por AINE presentan una mayor prevalencia de sensibilización a Dp y a Bt, y un aumento de la IgE sérica total. Es necesario realizar más estudios a fin de determinar los motivos de esta asociación.

Palabras clave: Angioedema. Ácido acetilsalicílico. Asma. Atopía. IgE. Hipersensibilidad a AINE. Rinitis. Urticaria.

Introduction

Hypersensitivity reactions to aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are relatively frequent, occurring in 0.1% to 0.3% of the general population [1]. Four clinical patterns of reactions have been proposed, namely respiratory reactions (aspirin-exacerbated respiratory disease or aspirin-intolerant asthma), cutaneous reactions (urticaria and angioedema), mixed reactions (urticaria and angioedema plus upper respiratory tract and ocular manifestations), and systemic reactions (anaphylaxis) [2].

A number of years ago, we observed an increased prevalence of the atopic trait in patients with NSAID hypersensitivity, mostly of the cutaneous pattern [3], a finding that has been constantly present in subsequent studies by our group. Summarizing the data from those studies, 360 (90.4%) of 398 NSAID-sensitive patients were found to have a personal history of atopic diseases and positive immediate-type skin tests to inhalant allergens.

An association between atopy and NSAID hypersensitivity has also been reported by other groups for cutaneous [4-6], respiratory [7,8], and systemic reactions [9]. Since immunoglobulin (Ig) E–mediated allergy does not seem to be involved in the majority of NSAID-induced reactions [10], these observations are intriguing. Nevertheless, it must be mentioned that there exist isolated case reports where IgE mediation has been thought to be responsible for reactions to pyrazolones [11], acetaminophen [12], and acetylsalicylic acid [13]. In order to explore in more detail the relationship between atopy and NSAID hypersensitivity, we carried out a case-control study in which we investigated levels of total and mite-specific IgE in a group of NSAID-sensitive patients with cutaneous reactions.

Methods

Study Population

Patients with a clinical history of cross-reactive acetylsalicylic acid/NSAID-induced urticaria and/or angioedema were prospectively recruited from an outpatient allergy clinic in Caracas, Venezuela, between 2003 and 2007. Seventy-four randomly selected healthy controls were also recruited from the blood bank at Hospital Universitario de Caracas in Caracas. The study was approved by the institutional review boards of Hospital Universitario de Caracas and Clínica El Avila. A full explanation of the investigation was given and written informed consent was obtained from all participants.

Patients referred to the allergy clinics with suspected NSAID intolerance, of any age or gender, were submitted to double-blinded placebo-controlled oral provocation tests with acetylsalicylic acid. Briefly, incremental doses of acetylsalicylic acid from 25 to 500 mg or placebo, given on different days, were concealed in identical opaque capsules and administered 1 hour apart, with 4 hours of hospital observation and telephone recall 24 hours later. Vital signs and pulmonary function (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], forced expiratory flow at 25%-75% of FVC [FEF_{25-75}], and peak expiratory flow [PEF]) were monitored at baseline and hourly for 4 hours, and the skin, nose, eyes, and thorax were examined at the same intervals. The presence of breathlessness, cough, wheezing, dysphonia, nasal or ocular itching, sneezing, rhinorrhea, nasal obstruction, and conjunctival erythema was specifically investigated. Test results were regarded as positive for urticaria or angioedema if involvement of 20% or more of the body surface area was present. Antihistamines and leukotriene receptor antagonists were withheld for at least 96 hours before testing.

Only patients who reacted to at least 2 chemically unrelated NSAIDs (cross-reactors) were included in the investigation. Patients with other phenotypes of NSAID hypersensitivity such as reactions to a single NSAID, aspirin-exacerbated respiratory disease, chronic idiopathic urticaria, and anaphylaxis induced by NSAIDs were excluded, as were pregnant women. Per protocol it was decided to only include NSAID cross-reactive patients as they are relatively common in our patient population and represent a real challenge for clinicians. Also, the finding of new biomarkers might contribute to a better diagnosis of this condition. Single reactors, in contrast, are seen less frequently and their management is relatively easy (avoidance of offending NSAID and chemically related drugs).

High-risk patients were defined as NSAID-sensitive individuals who reacted to weak cyclooxygenase (COX) inhibitors (acetaminophen) or COX-2 inhibitors (nimesulide, meloxicam, celecoxib, rofecoxib), as proposed by Matucci et al [14].

The clinical pattern of the reactions was classified as cutaneous (urticaria and angioedema) or mixed (urticaria and/or angioedema plus upper respiratory tract and/or ocular symptoms), as previously described [2]. Data from clinical records obtained during the inclusion visit were collected; these included age, sex, drugs involved in previous reactions, and past or present history of allergic diseases.

Skin Tests

Immediate-type hypersensitivity skin tests were done using the prick method, with reading after 15 minutes of application. The following inhalant allergens were tested: *Dermatophagoides pteronyssinus* (Dp), *Blomia tropicalis* (Bt) (CBF Leti, Madrid, Spain), American cockroach, cat, dog, feather mix, *Penicillium, Aspergillus, Cladosporium, Alternaria, Cynodon dactylon, rye grass*, red top grass, Johnson grass, *Ambrosia artemisiifolia*, pigweed, lambsquarter, *Artemisa vulgaris, Pinus radiata*, sycamore, cypress, *Acacia*, cedar, and eucalyptus (ALK Abelló, Madrid, Spain). A wheal size of 3 mm or greater than the negative control was considered positive and atopy was defined as a positive reaction to at least 1 allergen and the presence of a medical history of atopic disease (asthma, allergic rhinitis, and eczema). Histamine phosphate 1 mg/mL (ALK Abelló) was used as a positive control and glycerol-saline solution as a negative control. Antihistamines were omitted at least 96 hours before skin testing.

Quantification of Total and Specific Immunoglobulin E

Blood from patients and controls was drawn from the antecubital veins after which clotting serum was collected and stored at -70°C. Total IgE was determined by enzyme-linked immunosorbent assay (ELISA) using a commercial kit (Ridascreen; R-Biopharm AG, Darmstadt, Germany) according to the manufacturer's instructions. Since Bt and Dp are the main source of sensitization in tropical environments [15-17] and the prevalence of IgE sensitization to these allergens is frequent in allergic patients from Venezuela (91.6% and 97.2 %, respectively [18,19]), specific IgE against these 2 mites was determined by indirect ELISA, as described previously [20]. Absorbance was measured at 405 nm using a spectrophotometer (Spectra MAX 250; Molecular Devices, Sunnyvale, California, USA) and expressed as optical density (OD) units. Samples were assayed in duplicate and levels of specific IgE above 0.142 OD (mean [SD] OD of 5 [3] nonatopic subjects) were considered positive.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences software (SPSS version 16 for Windows; SPSS Inc., Chicago, Illinois, USA). Comparisons of demographic characteristics between patient and control groups were made using $\chi2$ tests and the t test as needed. Since levels of total and mite-specific IgE did not show a normal distribution, analyses were performed by means of the nonparametric Mann-Whitney U test and analysis of variance (ANOVA) through logarithmic transformation of individual values. Correlations between levels of Dp- and Bt-specific IgE and between total and mite-specific IgE were studied by means of the nonparametric Spearman test. Frequencies of mite sensitization between healthy controls and NSAID-sensitive patients were compared by the Fisher exact test. A P value of .05 or less was considered statistically significant.

Results

Demographic and Clinical Data

Table 1 presents the demographic and clinical information of the patients included in the study (n=114). The group included 77 women and 37 men with a mean (SD) age of 31.4 (12.1) years. Fifty-seven percent had rhinitis and 19.2% had rhinitis and asthma. The control group (n=74) consisted of 38 women and 36 men, with a mean age of 34.9 (10.1) years.

The clinical pattern was exclusively cutaneous in 52 patients and mixed in 62. Skin prick tests with airborne allergens were positive in 95 patients. The allergens that induced positive skin tests are shown in Table 2.

Table 3 shows the NSAIDs responsible for reactions, as ascertained from patient questioning and a close review of medical records. All the patients had a history of reactions to more than 1 chemically unrelated NSAID.

Total Serum Immunoglobulin E

Total mean (SD) IgE levels in the serum were 107.1 (91.3) IU/mL in controls and 161.0 (150.8) IU/mL in NSAID-sensitive patients (ANOVA, P=.006). This finding remained significant when log10-transformed total IgE levels were compared between controls and patients (1.84 [0.43] vs 2.03 [0.40]; ANOVA, P=.003), and also when the Mann-Whitney U test was used (P=.008) (Figure 1). There were no significant differences in total IgE according to the clinical pattern of reactions, (cutaneous or mixed; data not shown).

Table 1. Demographic and Clinical Data for 114 NSAID-Sensitive Patients[a] With Cross-Reacting Urticaria and Angioedema

	No. of Patients	% of Patients
Women	77	67.5
Men	37	32.4
Atopic disease		
Any	90	78.9
Rhinitis	66	57.8
Rhinitis and asthma	22	19.2
Rhinitis and atopic dermatitis	1	0.87
Asthma	1	0.87
None	24	21.0
High risk	44	38.5
Clinical pattern		
Mixed reaction	62	54.3
Cutaneous reaction	52	45.6
Positive immediate-type skin hypersensitivity test	95	83.3

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.
[a]Mean (SD) age, 31.4 (12.1) y (range, 11-65 y).

Table 2. Results of Prick Tests With Inhalant Allergens

Allergen	No. of Patients With Positive Results	% of Total Patients (n=114)
Dermatophagoides pteronyssinus	95	83.3
Blomia tropicalis	87	76.3
Cat dander	33	28.9
Dog dander	29	25.4
Feathers	19	16.6
American cockroach	16	14.0
Rye grass	14	12.2
Penicillium	12	10.5
Aspergillus	11	9.6
Lambs quarter	11	9.6
Ambrosia artemisiifolia	10	8.7
Sycamore	8	7.0
Cynodon dactylon	6	5.2
Artemisa vulgaris	6	5.2
Cladosporium	5	4.3
Johnson grass	5	4.3
Red top grass	4	3.5
Pinus radiata	4	3.5
Eucalyptus	4	3.5
Acacia	4	3.5
Pigweed	4	3.5
Alternaria	3	2.6
Cedar	3	2.6
Cupressus	2	1.7

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

Table 3. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Incriminated in Reactions[a]

Drug	No. of Patients
Ibuprofen	69
Aspirin	63
Pyrazolone	40
Paracetamol	31
Diclofenac	29
Ketoprofen	21
Nimesulide	12
Meloxicam	7
Mefenamic acid	4
Rofecoxib	4
Ketorolac	3
Naproxen	2
Celecoxib	2
Piroxicam	1
Etoricoxib	1

[a]From medical records. All the patients reacted to more than 1 unrelated NSAID.

Mite-Specific Immunoglobulin E

Mean (SD) levels of specific IgE to Dp were 0.210 (0.17) OD units in controls and 0.473 (0.65) OD units in patients (ANOVA, P=.001). Mean Bt-specific IgE levels were 0.230 (0.20) OD units in controls and 0.522 (0.58) OD units in patients (ANOVA, P=.0001) (Figure 3). These results were also observed when mite-specific IgE levels were compared using the Mann-Whitney U test (Figures 2 and 3). When specific IgE sensitization was analyzed as a dichotomous variable, the percentage of individuals with positive ELISA results for Dp-specific IgE (OD ≥0.142) was 29.6% in controls and 70.4% in patients (P=.0001). The percentage of individuals with positive ELISA results for Bt-specific IgE was 32.4% in controls and 67.6% in patients (P=.0001). In the group of NSAID-sensitive patients, IgE levels to Bt were higher than IgE levels to Dp (P<.0001). There was a statistically significant correlation between levels of Bt-specific IgE in vitro and the diameters of wheals induced by Bt extract during prick testing (r=0.218, P<.05). No significant correlation between Dp-specific IgE and skin test diameters was present (P=.11).
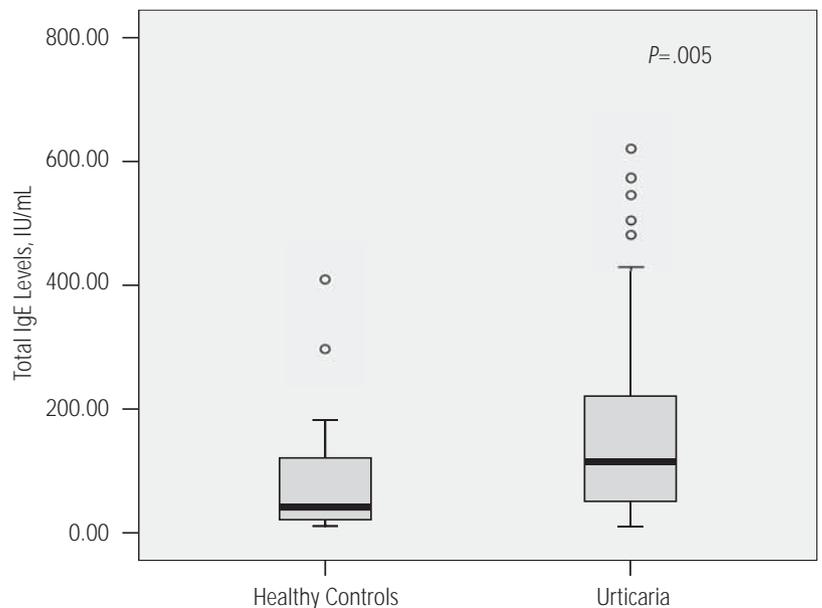

Figure 1. Levels of serum total immunoglobulin (Ig) E in healthy controls and NSAID-sensitive patients with urticaria and angioedema (P=.008). The box plot displays the median and interquartile range (IQR). The result was 81 (27.7-158.8) IU/mL for controls and 116 (50.8-214.7) IU/mL for NSAID-sensitive patients. NSAID indicates nonsteroidal anti-inflammatory drugs.
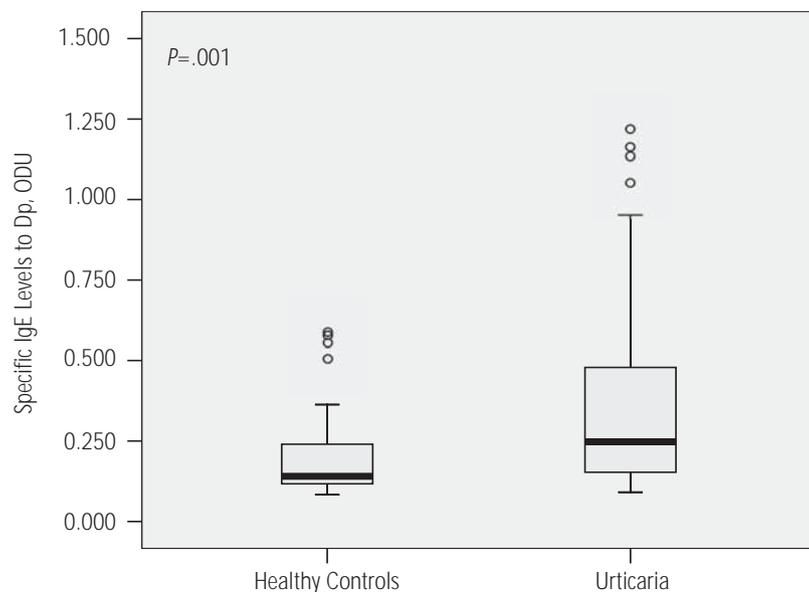
Figure 2. Levels of specific immunoglobulin (Ig) E to Dermatophagoides pteronyssinus (Dp) in healthy controls and patients sensitive to nonsteroidal anti-inflammatory drugs with urticaria and angioedema (median, 0.140 and interquartile range [IQR], 0.116-0.240 IU/mL vs median, 0.249 and IQR, 0.157-0.490, IU/mL respectively; P<.0001). ODU indicates optical density units.
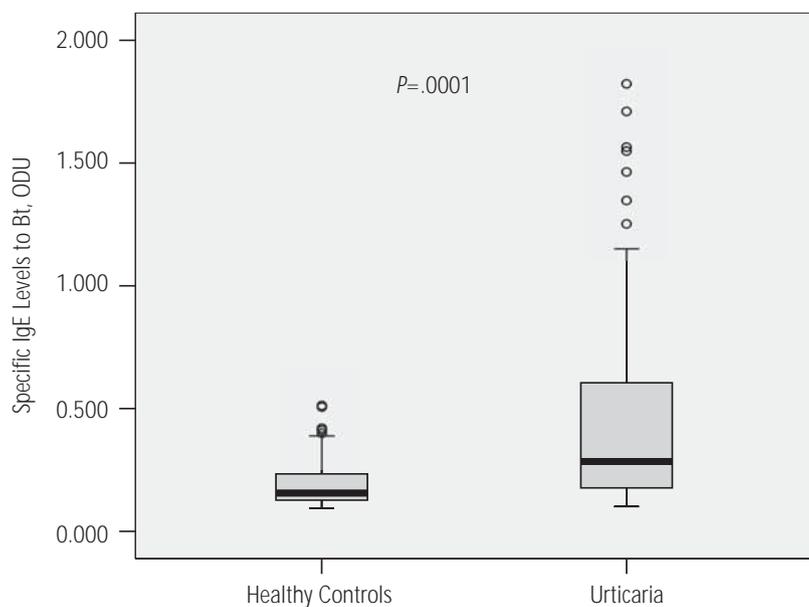

Figure 3. Levels of specific immunoglobulin (Ig) E to Blomia tropicalis (Bt) in healthy controls and patients sensitive to nonsteroidal anti-inflammatory drugs with urticaria and angioedema (median 0.155 and interquartile range [IQR], 0.126- 0.234 IU/mL vs 0.283 and IQR, 0.174-0.617 IU/mL respectively; P<.0001). ODU indicates optical density units.

Levels of Dp-specific IgE correlated with Bt-specific IgE (r=0.76, P<.0001) (Figure 4), and IgE levels to both, Dp and Bt, correlated with total serum IgE (r=0.5, P<.0001).

Discussion

Cutaneous reactions to NSAIDs have distinct mechanisms of production that are different from those responsible for common allergic (atopic) respiratory diseases due to environmental allergens such as rhinitis and asthma; hence, the increased prevalence of atopic conditions in patients with urticaria and angioedema due to NSAIDs is puzzling. In our study we observed increased levels of total IgE as well as mite-specific IgE in patients with urticaria and angioedema induced by NSAIDs. These results confirm our previous observations of an increased prevalence of atopic diseases and positive immediate-type hypersensitivity skin tests in such patient populations [3].

In tropical countries, total serum IgE measurements for the diagnosis of atopy have been traditionally limited because of the high prevalence of helminthic infestations, which induce the production of increased amounts of polyclonal and parasite-specific IgE. Although we did not perform coprologic examination for parasites in our study participants, both controls and patients belonged to the same socioeconomic strata and it is likely that the effects of parasitic infestation would be distributed equally in both groups. Total levels of IgE in the serum of NSAID-sensitive patients were significantly higher than those in healthy controls (Figure 1).

This observation was further supported by measurements of mite-specific IgE, since patient sera contained increased amounts of IgE antibodies to both, Dp and Bt (Figures 2 and 3). These results confirm the hypothesis that the prevalence of IgE-mediated allergic responses is increased in patients with NSAID hypersensitivity. Since mite allergy is so frequent in Venezuelan patients with respiratory allergy [18,19], our present data do not allow us to determine if those responses are exclusively limited to mite allergens or if they encompass a wider range of airborne allergens.

It is noteworthy that, in agreement with our results, Kim et al [20] recently observed that Korean patients with aspirin-intolerant acute and chronic urticaria exhibited an increased prevalence of atopy and total serum IgE.

In a recent study we observed that patients with NSAID-induced urticaria and angioedema had significantly larger wheals when skin was tested with Bt rather than Dp extract [21]. Those results have been confirmed in the present study where significantly increased levels of serum Bt-specific IgE were present. The reasons for this difference are not presently known, but they could be related to environmental sensitization to both cross-reactive and non-cross-reactive allergens also present in the Bt extract.

Since hypersensitivity to NSAIDs is probably determined by genetically determined disturbances of leukotriene synthesis, it is important to mention that various lines of evidence have suggested an interaction between IgE-specific immune responses and the leukotriene pathway. Atopic genes implicated in IgE-mediated allergic inflammation, including those regulating interleukin (IL) 4, IL-5, and IL-13 production, are localized in the 5q22-q35 chromosomal region of human chromosome 5, close to the LTC4 synthase (*LTC4S*) gene, the main locus that regulates cysteinyl leukotriene synthesis. This co-localization could explain the association between atopy and NSAID hypersensitivity. In this regard, it is important to mention that Acevedo et al [22] recently described an association between the *A-444C* allele of the *LTC4S* gene and low levels of IgE antibodies to Dp, low total IgE, and monosensitization, and suggested that *LTC4S* might be involved in the regulation of IgE response to mite allergens.

It has been demonstrated that cysteinyl leukotrienes can enhance the production of IgE and IgG by human B cells [23]. Furthermore, *LTC4S* knockout mice have markedly reduced antigen-induced type 2 helper (T_H2) pulmonary inflammation [24] and various investigators have reported that acetylsalicylic acid facilitates both food-dependent and food-dependent exercise-induced anaphylaxis [25-31]. In experimental animals, it has been observed that acetylsalicylic acid increases the permeability of the gastric mucosa to proteins and the development of anaphylaxis [32]. Additionally, an increased prevalence of NSAID cutaneous hypersensitivity has been reported in patients who develop oral mite anaphylaxis (pancake syndrome), an acute systemic allergic condition induced by the ingestion of mite-contaminated foods [33-35].

In conclusion, patients with cutaneous hypersensitivity to aspirin and NSAIDs have an increased prevalence of atopic diseases and increased levels of total and mite-specific serum IgE. NSAIDs, through their effects on the arachidonic acid metabolism, might modulate allergic responses. The possible effects of NSAIDs on the clinical response to leukotriene modifiers should be investigated further.
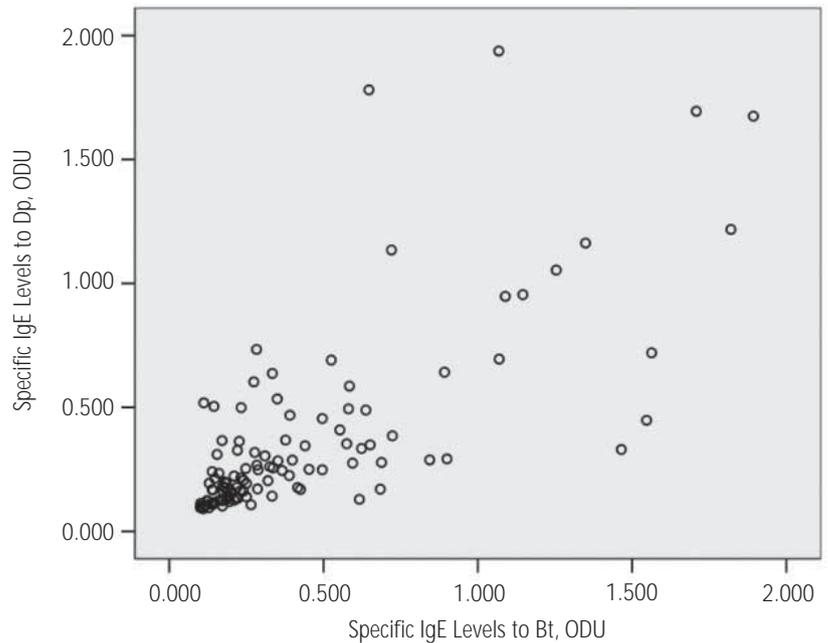

Figure 4. Correlation between serum Dermatophagoides pteronyssinus (Dp)–specific immunoglobulin (Ig) E and Blomia tropicalis (Bt)–specific IgE in patients with urticaria and angioedema induced by non-steroidal anti-inflammatory drugs (r=0.76, P<.0001, Spearman test). ODU indicates optical density units.

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