Observational Study

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Association between food allergy and ankylosing spondylitis

An observational study

Qian Niu, MD[a], Wei Wei, MM[b], Zhuochun Huang, MD, PhD[a], Junlong Zhang, MD[a], Bin Yang, MD, PhD[a,*], Lanlan Wang, MD[a]

Abstract

Food allergies can alter the gut microbiome composition, increasing the risk of conditions such as ankylosing spondylitis (AS).

To identify the association between specific allergens and AS, we investigated the differences in the serum levels of 14 food antigen-specific immunoglobulin (Ig) G between AS patients and healthy participants. The association between the levels of these antibodies and disease activity was assessed by measuring the inflammatory marker C-reactive protein (CRP).

We enrolled 75 AS patients and 78 healthy controls who had undergone antigen-specific IgG tests in West China Hospital between January 2015 and October 2017, and performed enzyme-linked immunosorbent assays for specific IgG against 14 food allergens: rice, egg, mushroom, milk, pork, chicken, beef, crab, codfish, corn, soybean, tomato, shrimp, and wheat. The following tests were used to analyze differences between AS patients and healthy controls: χ^2 test for sex, and a 2-tailed Student *t*-test or Mann–Whitney *U* test based on the results of Levene test for age and IgG levels. Correlations between IgG and CRP levels were calculated using a Spearman's correlation.

AS patients had significantly higher serum levels of beef-, crab-, and pork-specific IgG than did healthy participants. In addition, the serum levels of pork-specific IgG were significantly and positively correlated with CRP.

These results suggest that α-Gal, the predominant natural antigen in mammalian red meat, might play a potential role in the pathogenesis of AS, and therefore, AS patients should exclude such allergenic foods, including beef, crab and pork, from their daily diet.

Abbreviations: α-Gal = galactose-α-1,3-galactose, AS = ankylosing spondylitis, CRP = C-reactive protein, IFN-γ = interferon-gamma, Ig = immunoglobulin, IL = interleukin, TNF-α = tumor necrosis factor-alpha.

Keywords: allergens, ankylosing spondylitis, food allergy, gut microbiome, IgG

1. Introduction

Food allergy has emerged as an unanticipated "second wave" of the allergy epidemic,[1] dramatically increasing the burden of allergic diseases.[2] In some highly industrialized regions, the prevalence of food allergy in infants has reached 10%,[3] and there are reports that rates of food allergy are now increasing in parallel to the steep gradient of economic transition in rapidly developing countries.[4,5] In addition, a study revealed that approximately 20% of the global population is sensitive to food extracts.[6] Allergens from foods such as crab, cow's milk, or eggs can cause skin rash, vomiting, or even death in susceptible individuals.[7,8] In addition, allergic reactions can also cause nonsymptomatic changes such as chronic inflammation in the intestinal mucosa.[9] Kimura et al[10] reported elevation of serum levels of interleukin (IL)-2, IL-5, IL-6, IL-8, C-reactive protein (CRP), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) in patients with food protein-induced enterocolitis syndrome after an oral food challenge. Chen et al[11] found that the serum level of the inhibitory cytokine IL-10 was significantly lower in patients with food allergy. Kawaguchi et al[12] demonstrated that food antigens associated with high serum IgG levels caused intestinal inflammation by inducing the production of IFN-γ and IL-17 by $CD4^+$ T cells; this inflammation was ameliorated by the elimination of these food antigens. Moreover, another study showed that dysregulation of IL-6, IL-10, IL-17, TNF-α, and IFN-γ contributed to the pathogenesis and progression of ankylosing spondylitis (AS).[13]

AS is a chronic autoimmune disease characterized by axial skeleton arthritis and enthesitis.[14,15] Although the pathogenesis of AS is not yet fully elucidated, an increasing number of studies have revealed an association between AS and the gut microbiome,[16,17] which plays an important role in the development of

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[a] Department of Laboratory Medicine, West China Hospital, [b] West China Medical School, Sichuan University, Chengdu, China.

[*] Correspondence: Bin Yang, Department of Laboratory Medicine, West China Hospital, Sichuan University, Chengdu 610041, China (e-mail: yangbinhx@scu.edu.cn).

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the immune system.[18,19] Several recent studies have also indicated a close relationship between food allergy and the intestinal microbiome.[20] A study by Ling et al[21] revealed that the composition of the intestinal microbiome in infants with food allergy was different from that in healthy controls, and that levels of *Clostridium sensu stricto* were correlated with serum IgE levels. Hua et al[22] reported that American adults with allergies, especially to nuts and seasonal pollen, have low diversity, reduced *Clostridiales*, and increased *Bacteroidales* in their gut microbiota. In addition to its involvement in food allergy, the intestinal microbiome has an important role in the pathogenesis and progression of several autoimmune diseases because it is involved in how the immune system functions.[23,24] Dysfunction of the host–microbiota relationship may be a central event in the pathogenesis of spondyloarthropathy.[25] Alteration of the gut microbial population disrupts the gut barrier, leading to mucosal inflammation and increased serum levels of pro-inflammatory cytokines, which contribute to the development of AS.[26] Food allergy is one of the most common reasons for mucosal inflammation.[9,27] As both food allergy and autoimmune disease are closely linked to the intestinal microbiome, it is a reasonable hypothesis that food allergy plays a role in the development of autoimmune diseases such as AS.

Several recent studies have indicated the existence of an association between food allergy and rheumatoid diseases. A study by Li et al[28] revealed that the pathogenesis of rheumatoid arthritis is closely correlated with increased levels of egg- or milk-specific antibodies. Cai et al[29] found that patients with ulcerative colitis and inflammatory bowel diseases had higher sensitivity to food allergens. However, to the best of our knowledge, no studies have investigated the involvement of food allergy in the development of AS.

Traditionally, researchers used to focus on the presence of serous IgE antibodies as an indicator of food intolerance, but such characteristically immediate allergic reactions are quite rare in some conditions. By contrast, circulating IgG antibodies reflect a more delayed or even asymptomatic response following exposure to a unique food antigen.[29] In this study, we investigated the differences in the serum levels of 14 food antigen-specific IgG between AS patients and healthy participants in order to identify specific allergens that are associated with AS. In addition, we further analyzed the correlations between serum levels of antigen-specific IgG and CRP, a typical inflammatory biomarker used as an indicator for AS disease activity, to explore the association between allergen-specific IgG and disease activity in AS patients.

2. Methods

This study was approved by the Institutional Review Board of Sichuan University. All participants provided written informed consent to participate in this study.

2.1. Participants

We enrolled 78 healthy volunteers (48 men and 30 women) and 75 patients with AS (46 men and 29 women) who underwent specific IgG tests in the West China Hospital between January 2015 and October 2017. Patients and healthy controls were matched according to both age and sex. AS was diagnosed by rheumatologists according to New York clinical criteria.[30] CRP levels were measured when patients were recruited. The characteristics of the patients and healthy controls are shown in Table 1.

Table 1

Characteristics of patients with AS and healthy controls.

Characteristics	Patients with AS (n = 75)	Healthy controls (n = 78)
Age in years, mean (SD)	35.0 (9.3)	36.1 (10.4)
Sex, n (%)		
Male	46 (61.3)	48 (61.5)
Female	29 (38.7)	30 (38.5)
Cases of positive HLA-B27, n (%)	61 (81.3)	ND
Serum IgG in g/L, mean (standard deviation)	17.6 (7.3)	ND
Serum IgA in mg/L, mean (standard deviation)	2997.5 (1412.9)	ND
Serum IgM in mg/L, mean (standard deviation)	1171.5 (426.0)	ND
Serum IgE in mg/L, mean (standard deviation)	181.8 (92.9)	ND
Serum CRP in mg/L, median (IQR)	11.80 (3.05–26.40)	ND

AS = ankylosing spondylitis, CRP = C-reactive protein, HLA-B27 = human leukocyte antigen-B27, IQR = interquartile range, ND = not determined, SD = standard deviation.

2.2. Blood samples

All participants provided a 3-mL fasting blood sample, which was collected into a BD Vacutainer tube (BD Biosciences, San Diego, CA) containing sodium heparin. Plasma was obtained after centrifugation and stored at 2–8°C until testing. Before testing, all samples were incubated at room temperature (18–25°C) for 30 minutes.

2.3. Serum antigen-specific IgG analysis

An enzyme-linked immunosorbent assay was used to detect the serum antigen-specific IgG level according to the operation manual (Biomerica Inc., Newport Beach, CA). Levels of specific IgGs for the following 14 food allergens were measured: rice, egg, mushroom, milk, pork, chicken, beef, crab, codfish, corn, soybean, tomato, shrimp, and wheat.

2.4. Statistical analysis

The following summary statistics are used to describe the participants' baseline characteristics: mean (standard deviation), median (interquartile range), or number (percentage). Numerical results are expressed as median and interquartile range, and were analyzed using IBM SPSS software (version 20.0; IBM Corp., Armonk, NY). The χ^2 test was used to analyze the difference in sex between patients with AS and healthy controls. A 2-tailed Student *t*-test or a Mann–Whitney *U* test based on the results of Levene test was used to evaluate differences in age and IgG levels between AS patients and healthy controls. A Spearman's correlation was performed to detect correlations between the IgG and CRP levels. The Bonferroni method was used to correct the significance levels, which were set at 0.003 for all statistical tests.

3. Results

3.1. Differences in serum levels of antigen-specific IgG between patients with AS and healthy controls

As shown in Table 2, beef-, pork-, and crab-specific IgG levels were significantly higher in patients with AS than in healthy controls (all *P*-values <0.003, Table 2 and Fig. 1).

Table 2

Differences in serum levels of antigen-specific IgG between patients with AS and healthy controls.

Food allergen	Serum levels of specific IgG (U/μL) Mean (IQR)		*P* value
	Patients with AS	Healthy Controls	
Beef†	18.83 (4.94–23.35)	6.63 (3.88–12.57)	**2.13E-10**
Chicken	17.10 (5.02–21.23)	16.08 (7.33–22.36)	.514
Codfish	19.91 (12.46–24.40)	7.23 (3.12–20.55)	.061
Corn	17.44 (10.78–23.46)	8.56 (5.46–16.71)	.303
Crab†	30.80 (16.08–52.34)	11.06 (9.02–19.28)	**8.02E-08**
Egg, white/yolk	33.59 (8.04–63.88)	20.75 (7.00–155.70)	.595
Mushroom	10.33 (8.23–13.74)	3.05 (1.68–3.71)	.011
Cow's milk	14.36 (12.09–21.84)	64.52 (24.01–99.40)	.126
Pork†	16.04 (12.46–20.60)	4.83 (2.75–6.95)	**1.22E-07**
Rice	18.49 (15.34–30.68)	10.12 (5.71–24.29)	.116
Shrimp	18.26 (13.60–22.27)	5.38 (2.65–11.06)	.031
Soybean†	18.26 (15.83–24.00)	17.17 (9.71–32.13)	.581
Tomato†	12.48 (8.47–18.37)	7.62 (2.92–15.40)	.016
Wheat	10.87 (7.86–16.98)	16.29 (8.67–30.03)	.212

† Mann–Whitney *U* test was performed according to the Levene test results. A *P*-value < 0.003 was considered significant.
Significant *P*-values are presented in bold font.
AS = ankylosing spondylitis, IQR = interquartile range.

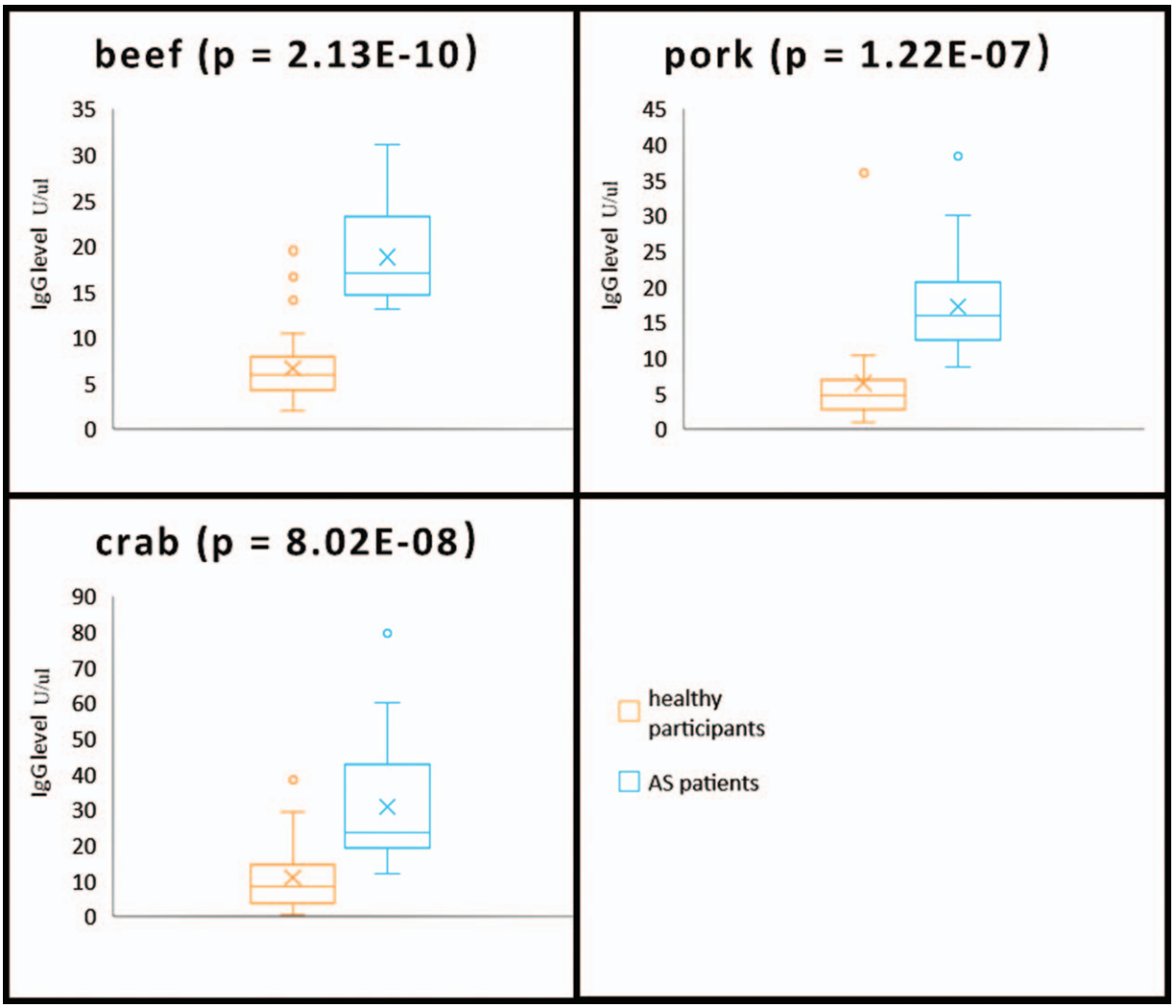

Figure 1. Differences in serum beef-, pork-, and crab-specific IgG levels between AS patients and healthy controls. AS = ankylosing spondylitis.

Table 3

Correlations between serum levels of antigen-specific IgG and CRP.

Food allergen	*r*	*P* value
Beef	0.121	.523
Chicken	0.391	.33
Codfish	−0.037	.848
Corn	−0.078	.684
Crab	0.079	.593
Egg, white/yolk	−0.102	.593
Mushroom	0.067	.724
Cow's milk	−0.128	.502
Pork	0.597	**4.98E-04**
Rice	0.241	.199
Shrimp	0.006	.974
Soybean	0.044	.817
Tomato	0.003	.895
Wheat	0.33	.075

Significant *P* values are presented in bold font.
CRP = C-reactive protein.

3.2. Correlations between serum levels of antigen-specific IgG and CRP

A statistically significant positive correlation was found between serum levels of pork-specific IgG and CRP ($r = 0.597$, P-value = 4.98E−04), whereas serum levels of all other antigen-specific IgG did not show any significant correlation with the CRP level (all P-values > 0.003, Table 3).

4. Discussion

The inverse correlation between the onset of allergic disorders and the incidence of infections has been demonstrated,[31,32] but the relationship between allergy and AS is still unclear. In this study, patients with AS had significantly higher serum levels of beef- and pork-specific IgG than healthy controls did. Both beef and pork are types of red meat that contain galactose-α-1,3-galactose (α-Gal) as the primary allergen.[33] α-Gal is the most abundant natural antigen in all mammals except Old World monkeys and humans.[34] The anti-Gal antibody is involved in several immunological pathogeneses, including allergy to red meat and cetuximab—a monoclonal antibody used in cancer therapy.[35] A study by Wigglesworth et al revealed that binding of α-Gal and anti-Gal antibodies could activate the complement system, resulting in the recruitment and activation of macrophages, which then infiltrate the wound and induce tissue regeneration.[36] This pro-inflammatory effect indicates that binding of α-Gal and anti-Gal antibodies might contribute to the pathogenesis and progression of AS. In addition, a positive correlation between serum levels of pork-specific IgG and CRP was found in the present study, which suggests that pork-related food allergy (α-Gal) plays a potential role in AS development.

Crabs and shrimp are types of shellfish, and shellfish antigens have a high level of cross-reactivity.[37] We found higher serum levels of crab-specific IgG in patients with AS than in healthy controls; however, a similar difference was not detected for shrimp-specific IgG. This suggested that patients with AS are more sensitive to the unique crab antigens, but not to similar antigens found in shellfish. Although reports of a correlation between crab or shellfish antigens and autoimmune diseases are rare, our finding might be useful for managing the diet of patients with AS.

Our study has some limitations. The sample size was small, which could lead to inaccurate results. In addition, we only measured CRP levels in this study; levels of several inflammatory cytokines such as interleukins, IFN-γ, and TNF-α should be investigated in future studies.

5. Conclusions

Serum levels of beef-, crab-, and pork-specific IgG differed significantly between patients with AS and healthy participants. These findings suggest that the predominant natural antigen in mammalian meat, α-Gal, might play a role in the pathogenesis of AS; this potential role and the underlying mechanism should be explored in future studies. Our findings indicate that patients with AS should avoid allergenic foods such as beef, crab, and especially pork in their diet.

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Author contributions

Conceptualization: Qian Niu, LanLan Wang.
Data curation: Wei Wei.
Formal analysis: Wei Wei.
Funding acquisition: Qian Niu, Junlong Zhang, Bin Yang.
Investigation: Qian Niu.
Methodology: Qian Niu, Zhuochun Huang, Junlong Zhang.
Project administration: LanLan Wang.
Software: Wei Wei, Zhuochun Huang.
Supervision: LanLan Wang.
Validation: Bin Yang.
Writing – original draft: Qian Niu.
Writing – review & editing: Bin Yang, LanLan Wang.

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