Serum IgG4 elevation in SAPHO syndrome: does it unmask a disease activity marker?

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Abstract

Objective

SAPHO syndrome is a rare inflammatory disorder with multiple phenotypes, including synovitis, acne, pustulosis, hyperostosis, and osteitis. IgG4 is a subclass of immunoglobulin G, and the elevation of IgG4 has been found in different autoimmune diseases. In the present study, we explored the clinical significance of serum IgG4 levels in patients with SAPHO syndrome.

Methods

Fifty-two patients who met the classification criteria of SAPHO syndrome were included in this study. Clinical data and disease activity markers were collected including erythrocyte sedimentation rate (ESR), high sensitivity C-reactive protein (hsCRP), pain visual analogue scale (VAS), Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Ankylosing Spondylitis Disease Activity Score (ASDAS). Serum immunoglobin (IgA, IgM, and IgG) and IgG subclass (IgG1, IgG2, IgG3, and IgG4) levels were determined using the immunonephelometric assay.

Results

Raised serum IgG4 levels (>1400 mg/dL) were detected in 23% (12/52) of patients. Patients with elevated sIgG4 levels had significantly higher pain VAS (5.42±2.76 vs. 3.08±1.78, p=0.02), BASMI (1.80±1.64 vs. 0.38±0.94, p=0.03) and ASDAS (3.20±0.65 vs. 1.74±0.58, p<0.001) levels compared with patients with normal sIgG4 levels. This difference was also observed for ESR (38.2 vs. 22.2 mm/h, p=0.01) and serum CRP (21.0 vs. 2.2 mg/L, p=0.04) levels, which also positively correlated with sIgG4 levels. We also included 4 patients whose IgG4 levels decreased and correlated with the decrease in hsCRP and ESR levels after treatment.

Conclusion

Elevated sIgG4 levels are common in patients with SAPHO syndrome and are associated with high disease activity. Further investigations are needed for this phenomenon.

Key words

SAPHO syndrome, IgG4, visual analogue scores

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Introduction

SAPHO syndrome is a rare autoinflammatory disorder, composed of synovitis, acne, pustulosis, hyperostosis, and osteitis. Our previous results showed palmoplantar pustulosis and anterior chest wall pain are common in Chinese SAPHO syndrome patients (1). Because of the high heterogeneity of the phenotypes, the validation of diagnosis is still difficult. Based on clinical features and radiological and histological tests, no standard criteria for SAPHO syndrome are universally accepted (2). While spontaneous remission happens in some patients, the prognosis remains uncertain within patients who suffer from severe clinical features. Additionally, the responses to treatments, for example diphosphonate (3, 4), are still controversial. The ability to define the subtypes of SAPHO syndrome is of great importance to treat patients and predict the prognosis. Commonly used disease activity markers are visual analogue scale (VAS) and inflammatory indicators. Our previous study indicated that patients with spinal or sacroiliac involvement had significant higher hsCRP and ESR levels (5). VAS is often treated as pain measurement, but was reported to be "not very accurate" and "almost guesswork" because of its subjectivity (6). A plasma protein called high sensitivity C-reactive protein (hsCRP), known for its rapid increased expression as part of the acute phase reaction, was reported to be influenced by gene and environmental conditions (7). In ankylosing spondylitis patients, hsCRP did not correlate with disease activity (8). As a result, recent studies tried to find new markers to accurately measure the disease activity. In terms of radiographic examinations, CT scan of SAPHO syndrome patients marked the disease activities (9). Previous studies indicated that tracer uptake was observed in bone scintigraphy in the anterior chest wall in most SAPHO patients which may function in disease activity marker (10). Whether PET/CT imaging could act as disease activity marker to classify subtypes of SAPHO syndrome is still controversial (11, 12).

Previous studies indicated that compared with normal patients, serum levels of proinflammatory and anti-inflammatory cytokines and receptor activator of nuclear factor-κB ligand/osteoclastogenesis inhibitory factor (RANKL/OPG) differ in SAPHO syndrome patients, and active SAPHO patients have anomaly balances of these biomarkers (13). Serum biomarkers could serve as potential markers to define SAPHO syndrome subtypes.

IgG4 is a subclass of immunoglobulin G, which recently received attention because of the recognition of IgG4-related diseases (14). The elevation of IgG4 has been found in various kinds of diseases, such as autoimmune diseases, lymphoma, chronic infections, etc. (15). It was reported that new phenotypes could be defined by IgG4 level. For example, elevated serum IgG4 defines a specific clinical phenotype of rheumatoid arthritis (16). IgG4 elevation, as a characteristic in IgG4-related diseases, functions in differentiating IgG4-related diseases with other autoimmune diseases, such as Mikulicz's disease from Sjögren's syndrome (17), and type I autoimmune pancreatitis from autoimmune pancreatitis (18). Elevated IgG4 levels have been reported in SAPHO patients (19). However, no studies have explored the clinical significance of serum IgG4 levels.

In this study, we present sIgG4 as disease activity marker and predictor for treatment response in patients with SAPHO syndrome.

Materials and methods

Patients

Fifty-two patients who fulfilled the classification criteria for SAPHO (proposed by Kahn MF (20)) were recruited from March 2015 to April 2018 at Peking Union Medical College Hospital, Beijing. Patients who had IgG subclass measurements and disease assessment data were included in this study. Patients who did not have clinical assessments at the same time as the IgG4 subclass measurement were excluded from this study. In addition, patients with the following diseases were excluded from this study: allergic disorders, Castleman disease, Churg-Strauss syndrome and IgG4-RD. Five included patients were naïve on therapy, and other pa-

tients have been treated by nonsteroidal anti-inflammatory drugs (NSAIDs), methotrexate (MTX), bisphosphonate, biological agents, etc. The study was approved by the Peking Union Medical College Hospital Ethics Committee as ZS-944. Written informed consent was obtained from each patient.

Clinical assessments

Clinical data included the following variables: age, sex, skin lesions (psoriasis vulgaris (PV) and palmoplantar pustulosis (PPP)), type of joint involvement (chest wall, axis, and peripheral involvement), hsCRP, ESR, interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), tumour necrosis factor-α (TNF-α), and immunoglobin (IgA, IgM, IgG, IgG1, IgG2, IgG3, and IgG4) were collected before treatments. The severity of symptoms were assessed by the VAS, BASDAI, BASFI, BASMI and ASDAS.

Statistical analysis

Clinical characteristics were compared using the chi-squared test or the Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. Mann-Whitney U-test was used to compare variables with a skewed distribution. Spearman's rank order correlation test was used to assess the correlation between two variables. $p<0.05$ was considered statistically significant unless stated otherwise.

Table I. Baseline demographic characteristics.

Factor	Elevated IgG4 n=12	Normal IgG4 n=40	*p*-value
Sex (male)	4	10	0.57
Age (years)	38.4	40.0	0.74
PV	1	8	0.30
PPP	8	22	0.62
Chest wall involvement	9	30	0.59
Axis involvement	8	22	0.79
Peripheral involvement	6	20	0.97
hsCRP, mg/L	21	2.2	0.04*
ESR, mm/h	38.2	21.2	0.01*
IL-6, pg/mL	14.1	5.7	0.32
IL-8, pg/mL	86.0	222.0	0.14
IL-10, pg/mL	5.01	5.0	0.08
TNF-α, fmol/L	60.2	29.2	0.46
IgA, mg/mL	3.7	2.8	0.07
IgG, mg/mL	16.3	13.1	0.04*
IgM, mg/mL	1.1	1.0	0.69
IgG1, mg/L	8728.2	7516.4	0.20
IgG2, mg/L	6874.5	4768.1	0.04*
IgG3, mg/L	221.0	240.0	0.34
IgG4, mg/L	1450.0	367.0	<0.001***
IgG1/IgG, %	49.4	57.1	0.02*
IgG2/IgG, %	37.1	36.7	0.90
IgG3/IgG, %	1.1	2.6	0.50
IgG4/IgG, %	9.8	3.6	<0.001***
Naïve on therapy	1	5	0.69

PV: psoriasis vulgaris; PPP: palmoplantar pustulosis; hsCRP: high sensitivity C reactive protein; ESR: erythrocyte sedimentation rate; IL-6: interleukin-6; IL-8: interleukin-8; IL-10: interleukin-10; TNF-α: tumour necrosis factor-α; Ig: immunoglobin
*$p<0.05$; **$p<0.01$; ***$p<0.001$.

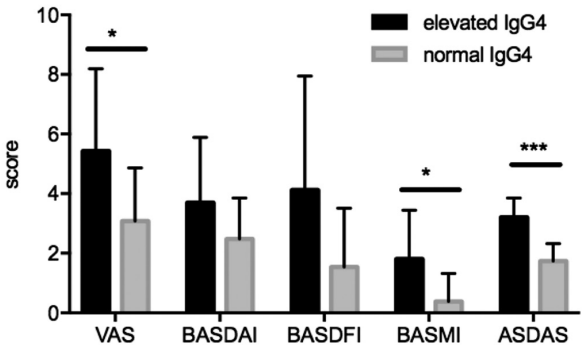

Fig. 1. Relationship between serum IgG4 levels and patients' measurement scores. Patients with elevated levels of IgG4 had higher VAS, BASDAI, BASDFI, BASMI, and ASDAS scores.

*$p<0.05$; **$p<0.01$; ***$p<0.001$.

Results

Clinical manifestations of 52 SAPHO syndrome patients

The cut-off for IgG4 elevation is 1400 mg/L (the upper limit for normal serum IgG4 at Peking Union Medical College Hospital). Twelve among 52 recruited patients (23.0%) showed an elevated serum IgG4 level.

Table I presents the general characteristics of SAPHO patients with elevated (n=12) and normal (n=40) IgG4 levels. The IgG4 level for all patients was 839±857.34 mg/L. The mean IgG4 level in normal IgG4 patients was 453.0 mg/L, which was significantly less than that in the elevated IgG4 group (2209.2 mg/L). There were no significant differences of disease involvement between the elevated and normal IgG4 groups. The mean IgG4/IgG ratio in the elevated IgG4 group was 9.8%, which was significantly higher than that in the normal IgG4 group (3.6%). Patients with elevated IgG4 serum levels were characterised by increasing hsCRP (21 *vs*. 2.2 mg/L; $p=0.04$) ESR (38.2 *vs*. 21.2 mm/h; $p=0.01$) and IgG2 (6874.5 *vs*. 4768.1 mg/L; $p=0.04$) levels.

IgG4 and clinical disease activity

VAS, BASDAI, BASFI, BASMI, and ASDAS were used to evaluate the disease activity of SAPHO patients. Patients with elevated serum IgG4 levels had significantly higher VAS, BASMI, and ASDAS levels than patients with the normal serum IgG4 levels (VAS, 5.42±2.76 *vs*. 3.08±1.78, $p=0.02$; BASMI, 1.80±1.64 versus 0.38±0.94, $p=0.03$; ASDAS, 3.20±0.65 *vs*. 1.74±0.58, $p<0.001$). Close to significance, BASDAI and BASFI were higher in the elevated IgG4 group than the normal IgG4 group (BASDAI, 3.69±2.20 *vs*. 2.48±1.37; BASFI, 2.20±3.93 *vs*. 1.10±1.80) (Fig. 1).

Patient's ESR (38.2 *vs*. 21.2 mm/h, $p=0.01$) and hsCRP (21.0 *vs*. 2.2

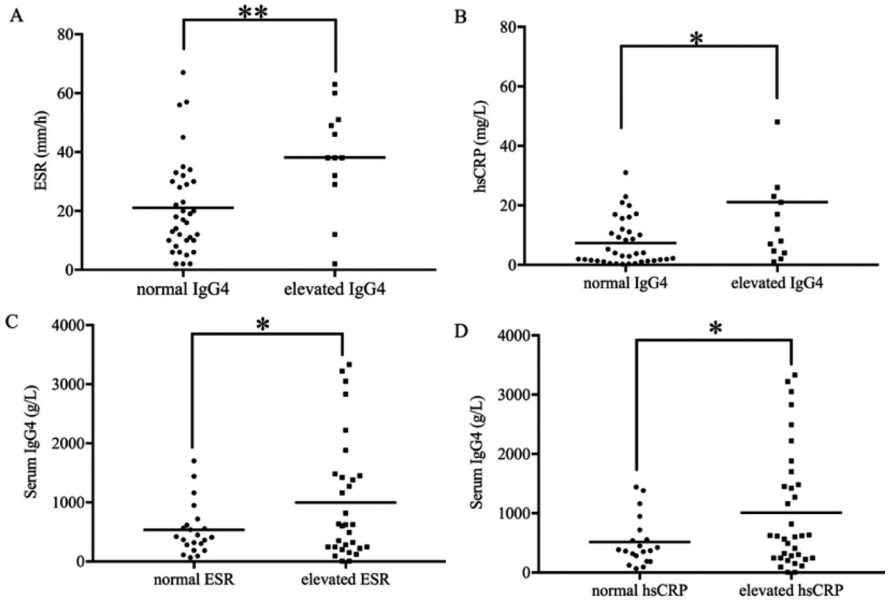

Fig. 2. Relationship between disease activity and serum IgG4 levels.
A: ESR levels were higher in the elevated IgG4 group. **B**: hsCRP levels were higher in the elevated IgG4 group. **C**: Serum IgG4 levels were higher in the elevated ESR group. **D**: Serum IgG4 levels were higher in the elevated hsCRP group.
*p<0.05; **p<0.01; ***p<0.001.

Table II. Correlation analysis between IgG4 and hsCRP, ESR, ASDAS.

IgG4	r-value	p-value
hsCRP	0.363	0.009**
ESR	0.301	0.035*
ASDAS	0.608	<0.001***

*p<0.05; **p<0.01; ***p<0.001.

mg/L, p=0.04) levels in the elevated IgG4 group were significantly higher than those of the normal IgG4 group (Fig. 2A-B). Of the total 52 patients, 55.1% had an elevated ESR level (ESR >20 mm/h); the median IgG4 levels of patients in elevated and normal ESR were 622.0±1236 mm/h and 259.5±382 mm/h (p=0.034) (Fig. 2C), respectively, and showed a significant difference between these two groups. High hsCRP levels were seen in 60.8% of patients (hsCRP>3 mg/L). The median IgG4 levels in elevated and normal hsCRP were 615.0±1456 mg/L and 376.5±465.5 mg/L, respectively, and revealed a statistical significance (p=0.03) (Fig. 2D).

Serum IgG4 levels correlated positively with hsCRP (r=0.363, p=0.009), ESR (r=0.301, p=0.035) and ASDAS (r=0.678, p<0.001). Data are shown in Table II. Figure 3 shows the graphical representation of these correlations.

Serum IgG4/IgG in the elevated hsCRP group (4.33%±7.29%) showed no differences with the normal hsCRP group (3.52%±4.22%), and no significances were revealed in the elevated ESR group (4.19%±7.23%) and the normal ESR group (3.95%±3.3%). Correlation analysis showed no correlations between IgG4/IgG and ESR or hsCRP.

Treatment in elevated IgG4 patients

Among 12 patients with elevated IgG4 levels, 4 patients had evaluated serum IgG4 levels more than once. Patient A's initial IgG4 level was 2490 mg/L. After the treatment of tocilizumab injection once and methotrexate and tripterygium glycoside orally for one month, the serum IgG4 level decreased to 1950 mg/L and was accompanied with a decrease of hsCRP and ESR levels from 13.3 mg/L to 1 mg/L and 62 mm/h to 19 mm/h, respectively. Then, celecoxib was added to the therapy. One month later, the serum IgG4 of this patient dropped to a normal level (1150 mg/L). In addition, hsCRP and ESR levels decreased to 0.12 mg/L and 7 mm/h, respectively. The serum IgG4 levels were tested during the treatment for other three patients, and their disease activity were marked by hsCRP and ESR. Although different treatments were given to these four patients, we can clearly see from Figure 4 that hsCRP, ESR and serum IgG4 levels had the same tendency through the whole treatment period.

Discussion

According to our findings, 12/52 of SAPHO patients had increased IgG4 serum levels >1400 mg/L, which is the upper limit for normal serum IgG4 at Peking Union Medical College Hospital. IgG4-RD is a newly recognised disease characterised by active lesions, lymphoplasmacytic infiltrated IgG+ plasma cells, storiform fibrosis and often elevated serum IgG4 (21). SAPHO syndrome, usually without involvement of pancreatic glands, salivary glands, and lacrimal glands, has seldom evidence in relation with the IgG4-RD (22). Elevation of serum IgG4 is one of the diagnostic criteria of IgG4-RD; however, its specificity is low, and elevated serum IgG4 levels has been reported in many other diseases in addition to IgG4-RD. These diseases include autoimmune diseases, malignancies, chronic infections, Rosai-Dorfman disease, Castleman disease, etc. In the present study, 25% of patients who suffered from SAPHO syndrome had elevated serum IgG4 levels, which was even higher than 13.6% indicated by Ebbo *et al*. (15). Zhang *et al*. (23) investigated IgG subclasses in autoimmune diseases and found that IgG4 levels were significantly higher in pSS and SSc patients than in healthy controls. However, the sample size of the present study is small, which means the proportion of elevated serum IgG4 should be tested in future research studies. In the present study, the IgG4 level was 839 mg/L. Although IgG4 levels from healthy controls were not included in the study, this level of IgG4 is higher than the data from healthy controls in Zhang's study, indicating an elevation

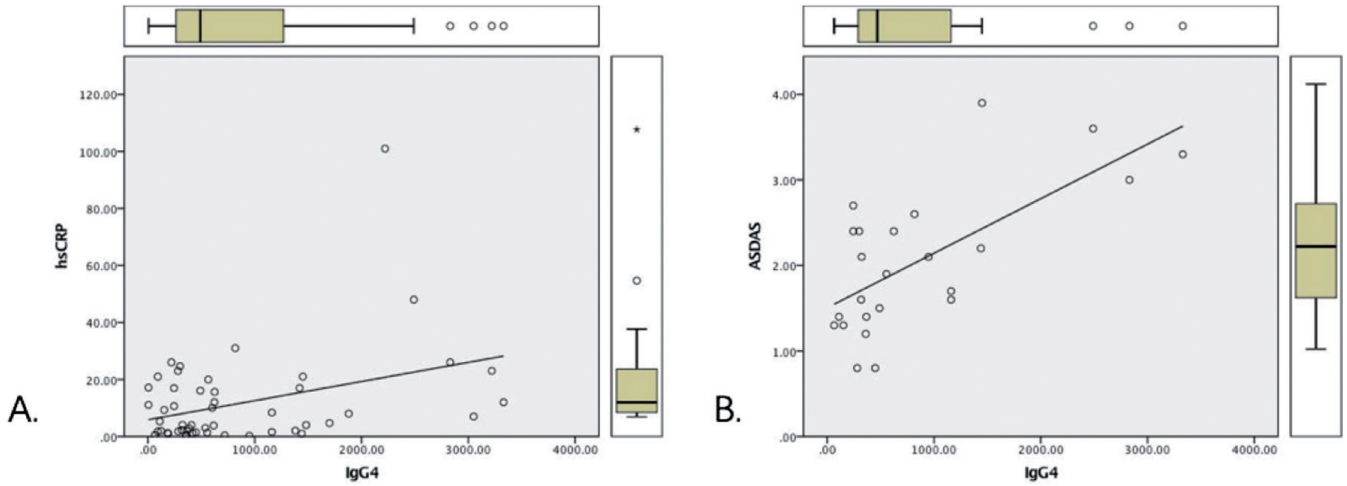

Fig. 3. Correlation graphical presentation. HsCRP (**A**) and ASDAS (**B**) showed linear correlation with IgG4.

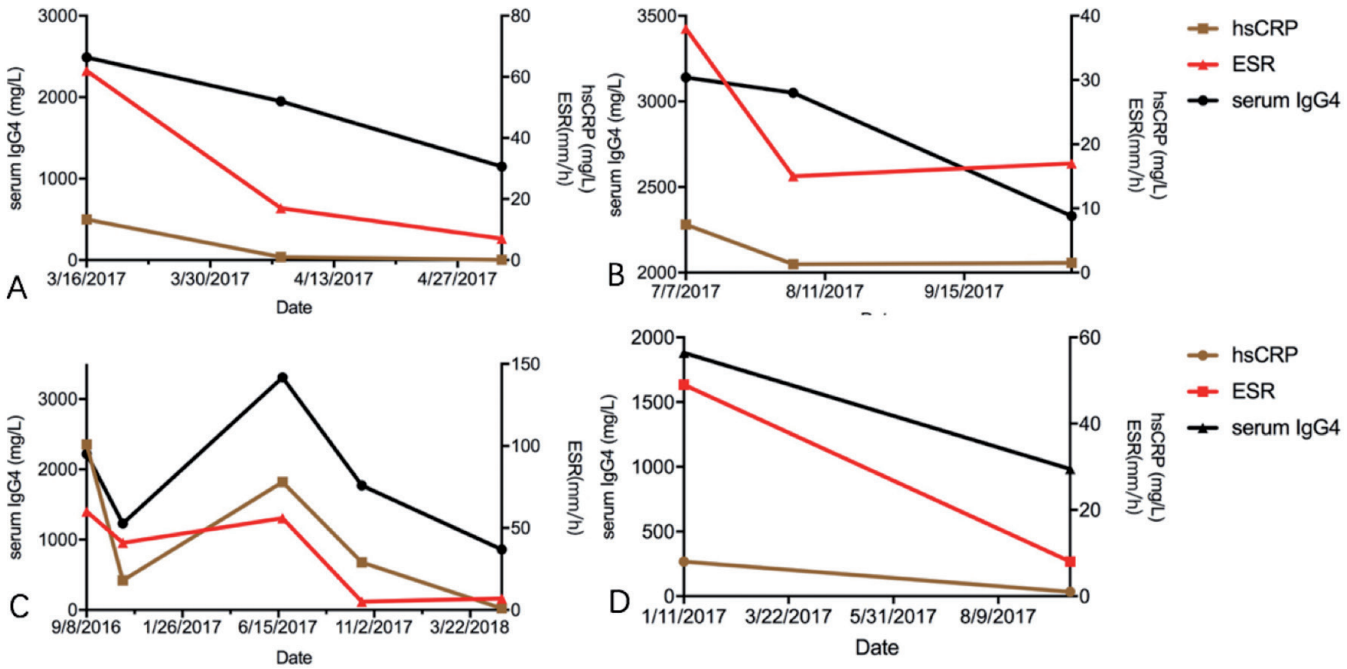

Fig. 4. Serum IgG4, hsCRP, ESR levels after treatment. Serum IgG4, hsCRP, ESR changed with the same trends in four patients.

of serum IgG4 levels in SAPHO syndrome.

The mechanism of IgG4 elevation in SAPHO syndrome seems to be unclear. A previous study showed that IL-6 could stimulate IgG4 production in vitro through B cell differentiation by increasing Th17 expression (24). Patients with RA and AS have been reported to have higher IL-6 levels than healthy controls (25). Multicentric Castleman disease occurs with abundant IgG4-positive cells and elevated IgG4 levels, as well as higher IL-6 levels (26). After the treatment with IL-6 receptor antibody and tocilizumab, IgG4 levels decreased in most RA patients (27). This study suggested that IL-6 may play an important role in the elevation of IgG4 levels. However, Xu *et al*. indicated that SAPHO patients had lower NK cells and Th17 cells compared with healthy controls, which may suggest the decreasing of IL-6 in SAPHO syndrome patients (28). In the present study, we found the elevated IgG4 group had higher levels of IL-6, although without significance. To date, the IL-6 and IgG4 relationship in SAPHO syndrome has not been researched and needs more future studies. On the other hand, IL-8 was reported to inhibit IgG4 production (29). However, no further evidence was found about the mechanism of this inhibition. Although, in the present study, the IL-8 level was lower in the IgG4 elevation group, no significance was achieved. Whether the elevation of IgG4 originated from the suppression of IL-8 remains unclear. It was reported that RA patients with elevated IgG4 levels had significantly higher RF and anti-CCP antibodies, which highly reduced after tocilizumab treatment (16, 27). These studies showed that elevated RF-IgG4 or anti-CCP IgG4 were the reason for the elevation of IgG4 levels in RA patients. However, although 22%

of SAPHO patients had increased autoantibodies (30), no specific patterns, for example, IgG4-type autoantibodies, were detected (31).

The aim of the present study was to determine whether IgG4 levels in SAPHO patients associated with distinct clinical and serologic features. Serum IgG4 was shown to correlate with disease activity in patients with RA (16); similarly, we found that SAPHO disease activity was higher in patients with increased serum IgG4 levels. Our results indicated that the elevated IgG4 groups had higher hsCRP, ESR, BASMI, and ASDAS. Additionally, for patients with higher ESR and hsCRP levels, IgG4 levels were significantly elevated. Further correlation analysis suggested that IgG4 was correlated with hsCRP, ESR and ASDAS. In terms of clinical features, there were no relationships between IgG4 levels and clinical features, such as PV, PPP, chest wall involvement, axis involvement and peripheral involvement, which indicated that the elevation of IgG4 was not associated with a specific clinical characteristic.

Our study primarily explored the correlation of IgG4 levels and treatments. Our results included 4 patients with high IgG4 levels. There are no specific drug treatments or standard treatment protocols for SAPHO. NSAIDs in the case celecoxib, and disease-modifying anti-rheumatic drugs (DMARDs), focus on the relieving the patient's pain and modifying the inflammation. Tripterygium glycoside, a Chinese medicine extracted from tripterygiumwilfordii, was indicated to have the best remission rate than other treatments in SAPHO patients (32). Bisphosphonate, for example zoledronic acid, aimed at inhibiting bone resorption and suppressing IL-1β, IL-6 and TNF-α secretion, which may be used in patients who are refractory to NSAIDs, corticosteroids and DMARDs. Additionally, biological agents, for example tumour necrosis factor inhibitors and IL-6 receptor antibody, could be used for refractory patients (29). The IL-6 receptor antibody, tocilizumab, is commonly used in patients with RA. It was reported that decreased IgG4-specific anti-CCP antibodies were achieved after tocilizumab treatment. In the present study, tocilizumab was also used in one SAPHO patient. Tocilizumab injection, accompanied with methotrexate and tripterygium glycoside treatment for 2 months, led to disease remission, including IgG4 level decreasing from 2490 mg/L to normal level and significantly decreasing hsCRP and ESR levels. For patients with high levels of serum IgG4, our results showed potential high IL-6 levels, despite having no significance.

In the present study, patients in the elevated IgG4 group had higher levels of IgG. The increasing IgG levels could be the result of IgG4 or IgG2 elevation. Through correlation analysis, no correlations were found between IgG4/IgG and hsCRP, ESR or other disease activity scores; in contrast to IgG-RD patients, IgG4/IgG is not a good disease marker compared to IgG4 in SAPHO patients. Our study indicated serum IgG2 levels were significantly higher in the IgG4 elevated group, although no differences were found for IgG2/IgG. IgG2 autoantibodies are stimulated by carbohydrate antigens (T cell-independent antigens), while most autoantigens are derived from proteins (T cell-dependent antigens), which stimulate IgG1 and IgG3 autoantibodies (33). Zhang *et al*. found that serum IgG2 and IgG4 levels were significantly lower in pSS and SSc patients compared with healthy controls; while in PBC patients, higher IgG2 and IgG2/IgG levels were indicated (34). However, higher levels of IgG2 were observed in pSS and SLE patients in another research study (35, 36). No consensus has been reached for the serum IgG2 level in autoimmune diseases, and no studies have revealed the reason of this difference in IgG2 levels; further research is needed to resolve this problem. As a result, IgG2 elevation associated with IgG4 elevation should be further studied in the future.

The present study has some limitations. First, the sample size is small, which lead to some critical clinic data showing trends without significance. On the other hand, clinical assessments were not complete, which gives rise to low credibility. Additionally, the present study explored the correlation between serum IgG4 and patients' clinical characteristics; molecular mechanisms (*i.e*. what triggers the elevation of IgG4 in SAPHO syndrome patients) should be studied in future studies. Despite the small sample size, the present study indicated that IgG4 could be a potential disease activity marker. High levels of serum IgG4 may suggest a specific response to certain treatments and should be studied in future carefully.

Conclusion

Elevated sIgG4 levels are common in patients with SAPHO syndrome and is associated with high disease activity. Further investigations are needed for this phenomenon.

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