Interferon alpha serum level association with low vitamin D levels in Chinese patients with primary Sjögren’s syndrome

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Abstract
The purpose of this retrospective cross-sectional study was to explore the clinical and pathogenic significance of vitamin D and its relationship with interferon-α (IFN-α) in Chinese patients with primary Sjögren’s syndrome (pSS). In our study, 32 pSS patients and 50 healthy controls were included. Serum vitamin D and IFN-α concentrations were determined by enzyme-linked immunosorbent assay (ELISA) and analyzed with the correlations of EULAR Sjögren’s Syndrome Disease Activity Index (ESSDAI). The multiple linear regression analysis of 25-OH vitamin D3 level with ESSDAI scores in pSS patients was also investigated. Serum 25-OH vitamin D3 significantly correlated in an inverse manner with ESSDAI scores (p < 0.001, r = −0.781) and IgG (p < 0.001, r = −0.64). Serum 25-OH vitamin D3 were only related to peripheral nervous system (PNS) domain deficiency. Further, serum IFN-α was positively correlated with ESSDAI, but negatively correlated with serum 25-OH vitamin D3. These results suggest an important role of vitamin D regulating disease activity in pSS patients and value of supplement vitamin D in pSS treatment.

Keywords
Chinese population, disease activity, interferon alpha, primary Sjögren’s Syndrome, vitamin D

Introduction
Primary Sjögren’s syndrome (pSS), a systemic autoimmune disease with prevalence rate approximately 61 cases per 100,000 inhabitants, presents with a wide spectrum of clinical manifestations and autoantibodies.1,2 The histological hallmark is a focal infiltration of exocrine glands by lymphocytes, confirmed by minor labial salivary gland biopsy. The therapeutic management of pSS is still based on symptomatic treatment of sicca symptomatology and broad-spectrum immunosuppression,1 indicating further investigation is needed.

Type I interferon (IFN) constitute critical elements of innate immune system in response to viral infections. The initial evidence regarding the role of IFN-α in pSS was reported that a patient with hepatitis C treated with IFN-α developed pSS.3

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This finding was observed in labial salivary gland biopsies and serum in pSS patients.\textsuperscript{4,5} An activated type I IFN system known as the IFN signature with gene expression profiling up-regulation by type I IFN, plays an important role in pSS.\textsuperscript{6} This IFN signature was observed not only in salivary glands, but also in plasmacytoid dendritic cells (pDCs) presenting in the peripheral blood, which are the major source of IFN-\(\alpha\). Moreover, IFN signature was specifically enhanced in anti-SSA and/or anti-SSB positive pSS patients, indicating a relationship between upregulation of IFN-\(\alpha\) and autoreactive B-cells.\textsuperscript{4}

The classical functions of vitamin D are to regulate calcium/phosphorus homeostasis and control bone metabolism. However, vitamin D deficiency was observed in several autoimmune disorders, as systemic lupus erythematosus and rheumatoid arthritis.\textsuperscript{7,8} However, the level of vitamin D in pSS is still controversial.\textsuperscript{9,10} Vitamin D receptors were found in both innate and adaptive immune cells, including macrophages, dendritic cells (DCs), B cells, and T cells.\textsuperscript{11} The overall effects of vitamin D on the adaptive immune system were mostly through DCs. In vitro assessment, DCs would be induced to a “tolerogenic state" by vitamin D, characterized by low levels of inflammatory cytokines, such as interleukin-12 (IL-12) and tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), with increased levels of the anti-inflammatory IL-10. These cells induce the differentiation of regulatory T (Treg) cells and the apoptosis in the autoreactive T cells.\textsuperscript{7} Evidences supporting the interaction between vitamin D and IFN-\(\alpha\) have come from studies on hepatitis C patients and systemic lupus erythematosus (SLE) patients. Vitamin D has a direct antiviral effect against hepatitis C virus. A mechanistic study suggested that ligand-unbound vitamin D receptor (VDR) may sequester STAT1, a key transcription factor in type I IFN signaling. Thus, low-level of vitamin D contribute to defective IFN-mediated antiviral response due to higher levels of unbound VDR.\textsuperscript{12} This synergistic effect in antiviral progress was not seen in SLE. Vitamin D deficiency was associated with a trend toward increased IFN-\(\alpha\) and interferon-sensitive genes expression in both animal model and SLE patients.\textsuperscript{8,13,14} However, there have been no reports to detect the relationship between vitamin D and IFN-\(\alpha\) in pSS patients.

In this present work, we tried to determine the level of vitamin D in Chinese patients with pSS. Also, the effects of both vitamin D and IFN-\(\alpha\) through their relationship with disease activity were explored.

**Materials and methods**

**Patients**

Thirty-two (28 females and 4 males) Chinese patients with pSS were consecutive enrolled in this retrospective cross-sectional study at the Division of Rheumatology Nanfang Hospital, Southern Medical University, during the period from December 2018 to December 2019. The diagnosis of pSS was established according to the revised European-American consensus criteria.\textsuperscript{15} Blood samples from age and sex matched healthy controls (HC) were obtained from the Medical Examination Center of Nanfang Hospital, Southern Medical University. The criteria for exclusion included vitamin D supplement therapy 800 IU once daily within 3 months of screening, hypercalcemia (serum calcium level >10.4 mg/dl), hypercalciuria (urinary calcium-to-creatinine ratio >0.8), a history of lithangiuria, or hyperparathyroidism, selected laboratory abnormalities, active tuberculosis, and recent clinically serious infections. The study was approved by the Ethics Committee of Nanfang Hospital, Southern Medical University (NFEC-2019-240) and all participants provided written informed consent prior to study enrollment. All research work with human subjects was in compliance with the Helsinki Declaration.

**Measurement of serum vitamin D and IFN-\(\alpha\) concentrations**

Serum 25-OH vitamin D3 level is the best indicator of overall vitamin D status, because it reflects total vitamin D from dietary intake, sunlight exposure, as well as the conversion of vitamin D from stores in the liver.\textsuperscript{16} Therefore, serum 25-OH vitamin D3 levels were measured in duplicated way by ELISA (Immunodiagnostic Systems Inc, Fountain Hills, AZ, USA). Vitamin D insufficiency, deficiency and severe deficiency was defined as a 25(OH)D3 level of 20–30 ng/ml, 10–20 ng/ml, and <10 mg/ml.\textsuperscript{17}
Serum levels of IFN-\(\alpha\) were measured using a human IFN-\(\alpha\) kit (Bender MedSystems Inc, Burlingame, CA, USA) according to the manufacturer’s instructions. All blood samples were collected at 9 am.

**Statistical analysis**

All calculations were performed by using SPSS program, version 20 (SPSS, Chicago, IL, USA, 2012) for Windows Vista. A two-tailed \(p\) value <0.05 was considered statistically significant. Unless otherwise stated, continuous variables are in the form of mean ± standard deviations (SD). Categorical variables are compared as number and percentage. Based on the results of the normality test, the association of 25-OH vitamin D3 and IFN-\(\alpha\) with measures of disease activity and severity was analyzed by analysis of Kruskal-Wallis test followed by an appropriate posttest.

**Results**

**Patients**

Total 32 well-characterized patients with pSS and 50 healthy volunteers were enrolled. Patients’ clinical and serologic features are listed in Table 1. The pSS cases had an average age of 43 years (±14) and 88% of them are women. The subjects with pSS had a mean disease duration of 80 months (±48) with increased serum IgG (22.5 ± 7.4 g/l). Approximately 88% and 62% of the pSS patients were seropositive for Ro/SSA and La/SSB autoantibodies. The average ESSDAI of pSS patients were 12.2 ± 4.2. Over half of patients were affected in pulmonary domain (81%), biological domain (69%), and glandular domain (62%). None of them were affected in lymphadenopathy domain.

### Decreased serum 25-OH vitamin D3 levels in pSS patients were negatively correlated with disease activity

The mean level of serum 25-OH vitamin D3 was 25.1 ± 11.3 ng/ml in all of our pSS patients, which was significantly lower than health controls (35.8 ± 5.5, \(p < 0.001\)) (Figure 1(a)). The distributions of vitamin D insufficiency, deficiency, and severe deficiency were 28%, 28%, and 9%. To explore whether the level of 25-OH vitamin D3 exhibited some clinical significances in pSS, the relationships between 25-OH vitamin D3 and ESSDAI, as well as serum IgG levels were evaluated. Our data showed that the levels of 25-OH vitamin D3 were negatively correlated with ESSDAI \((r = -0.781, p < 0.001)\) and serum IgG \((r = -0.64, p < 0.01)\) (Figure 1(b) and (c)). Meanwhile, the levels of 25-OH vitamin D3 were only related to peripheral nervous system (PNS) domain deficiency (Table 2), suggesting insufficient vitamin D may participate in pSS PNS disorders.

### Table 1. Characteristics of 32 patients with primary Sjögren’s syndrome (pSS) and 50 healthy controls (HC).

| Variable                  | pSS (n=32) | HC (n=50) |
|---------------------------|------------|-----------|
| Age, years (mean ± SD)    | 43 ± 14    | 40 ± 12   |
| Female, n (%)             | 28 (88)    | 45 (90)   |
| Dry eye, n (%)            | 14 (44)    |           |
| Dry mouth, n (%)          | 18 (56)    |           |
| IgG, g/l (mean ± SD)      | 22.5 ± 7.4 |           |
| CRP, mg/l (mean ± SD)     | 11.4 ± 6.7 |           |
| Anti-Ro/SSA positive, n (%)| 28 (88)    |           |
| Anti-La/SSB positive, n (%)| 20 (62)    |           |
| RF positive, n (%)         | 9 (28)     |           |
| ANA positive, n (%)       | 22 (69)    |           |
| SWS, ml/min (mean ± SD)   | 0.35 ± 0.36|           |
| ESSDAI                    | 12.2 ± 4.2 |           |

**Table 1.** Characteristics of 32 patients with primary Sjögren’s syndrome (pSS) and 50 healthy controls (HC).

- CRP: C-reactive protein; RF: rheumatoid factors; ANA: anti-nuclear antibodies; SWS: stimulated whole salivary flow; ESSDAI: EULAR Sjögren’s syndrome disease activity index; CNS: central nervous system; PNS: peripheral nervous system.
- *Number (%) of patients having any degree of activity per ESSDAI domain (score of at least 1).
Increased serum IFN-α expression was positively correlated with pSS disease activity

Serum IFN-α levels were increased in pSS patients (961.7 ± 467.9 vs 240.7 ± 83.5 pg/ml, p < 0.001), suggesting IFN-α may contribute to the pathogenesis of pSS (Figure 2(a)). Meanwhile, serum IFN-α showed a highly significant positive correlation with ESSDAI scores (r = 0.905, p < 0.001) (Figure 2(b)).

Serum IFN-α was negatively correlated with serum 25-OH vitamin D3

The facts that both serum 25-OH vitamin D3 and serum IFN-α levels were significantly correlated with ESSDAI encouraged us to evaluate the correlation between serum IFN-α and serum 25-OH vitamin D3. Our data showed that serum IFN-α was negatively correlated with serum 25-OH vitamin D3 (r = −0.753, p < 0.001) (Figure 3), indicating crosstalk between 25-OH vitamin D3 and IFN-α may exist in pSS pathogenesis.

Discussion

The role of vitamin D in autoimmune disorders has been the subject of several studies with regard to its importance as an immune regulator. This is the first study from China to demonstrate an association between vitamin D and pSS, highlighting its significant inverse correlation with ESSDAI scores.
Zheng et al. and IFN-α. Moreover, vitamin D deficiency contributed to PNS disorder in pSS patients.

Vitamin D activating enzyme 1α-hydroxylase (CYP27B1) and VDR are present in many cell types including various immune cells such as antigen-presenting cells, T cells, B cells and monocytes. In vitro data show that, in addition to modulating innate immune cells, vitamin D also promotes a more tolerogenic immunological status.20 The extra-renal synthesis of the active metabolite calcitriol—1,25(OH)2D—by immune cells and peripheral tissues has been proposed to have immunomodulatory properties similar to locally active cytokines.21,22 However, the association between the level of vitamin D and pSS remains controversial. Vitamin D enters the body through dietary intake (~20% of vitamin D3 is assumed with diet) or is synthetized by the skin (~80%) from 7-dihydrocholesterol following UVB exposure.7 A meta-analysis, including nine studies, showed that four of the nine studies reported significantly lower vitamin D level in pSS patients than in healthy controls, while the other five did not. But latitude differences could not explain why different levels of vitamin D from different studies, which are most from temperate countries.10 Besides, the exclusion criteria are variable, just two studies mentioned vitamin D supplements should be excluded.17,23 Another explanation for the decreased levels of 25-OH vitamin D3 in pSS patients could be extrarenal 1α-hydroxylation. In humans evidence for extrarenal 1α-hydroxylation activity has been reported in sarcoidosis and arthritis.24

Figure 2. Correlations of serum IFN-α levels and disease activity in pSS patients: (a) serum IFN-α levels in patients with pSS and healthy controls and (b) correlations of serum IFN-α levels and ESSDAI. The data represent the mean ± SD. pSS: primary Sjögren’s syndrome; ESSDAI: EULAR Sjögren’s syndrome disease activity index.

Figure 3. Correlations of serum IFN-α levels and 25-OH vitamin D3 levels in pSS patients. The data represent the mean ± SD. pSS: primary Sjögren’s syndrome.

Among the extraglandular manifestations of pSS, the occurrence of PNS involvement is reported with the frequency of 10%–46%.25,26 According to our results, vitamin D levels of patients with pSS are inversely correlated with PNS domain. This finding is supported by one previous study, suggesting decreasing vitamin D levels maybe associated with neuropathy among pSS patients.27 In PNS, Schwann cells are glial cells that are in intimate contact with axons throughout development. Schwann cells generate the insulating myelin sheath and provide vital trophic support to the neurons that they ensheath.28 Evidences supported that high local concentration of vitamin D could increase nerve growth factor (NGF) in Schwann cells through VDR, indicating vitamin D may have
Vitamin D deficiency in the pathogenesis of neuropathy disorders have been demonstrated, like multiple sclerosis (MS). 25-OH vitamin D3 is synthesized by neurons and microglia and neural cells express the VDR. Recently vitamin D shows the ability of modulation of T cell trafficking into nervous system. Inhibition of Th1 cells and its stimulation of IL-10 production have been observed in MS animal model. Moreover, 25-OH vitamin D3 induces indoleamine 2,3-dioxygenase-positive tolerogenic dendrocytes and regulatory T cells in the periphery and concomitantly reduces the number of autoreactive T cells in nervous system (Figure 4). Not only MS, it has been reported that vitamin D deficiency was associated with peripheral neuropathies (PN) in various ways. Vitamin D deficiency was reported in patients with type 2 diabetes who had clinically diagnosed PN, painful sensorial PN, and primary dysimmune PN. And vitamin D deficiency was an independent risk factor of PN in type 2 diabetes. However, the evidence of vitamin D role in patients with pSS PN related pathological mechanisms is still very limited.

As mentioned above, IFN signature was specifically enhanced in anti-SSA and/or anti-SSB positive pSS patients. Our data showed over 80% patients with pSS were anti-SSA(+) or anti-SSB(+). As has been expected, IFN-α levels were elevated. Interestingly, our study revealed a negative correlation of vitamin D with IFN-α ($p < 0.001$, $r=-0.753$). There are no reports assessing the association between IFN-α and vitamin D in pSS patients. Moreover, we also investigated the association between vitamin D and IgG level, which was strong negative correlation. The inverse correlation between vitamin D and autoantibodies (rheumatoid factor) was also observed in Indian patients with pSS. It is still uncertain whether the negative association between IFN-α and vitamin D is a mere coincidence or a real relationship in pSS.

There are limitations in this study. We have excluded patients who were prescribed high dose vitamin D supplementation. However, due to the natural of vitamin D generation, different season and latitude impacts are still the confounding factors. Regarding to no biologics approved for pSS indication in China, all the enrolled patients were treated by conventional synthetic DMARDs (csDMARDs). So, the differences of treatment responses and vitamin D levels between the patients who taking biologics and csDMARDs cannot be evaluated. Contradictory and very limited vitamin D data in pSS patients make key components for sample size calculation, like minimal clinically relevant difference, the variability of the outcome measure, hard to determine. Most of the associations seen in the study need to be interpreted with caution in view of small numbers and retrospective nature of this study. Further large sample size and longitudinal studies are required to understand causality.

**Conclusion**

Our findings suggested that vitamin D deficiency may aggravate pSS, especially in PNS domain. The significant inverse correlation of vitamin D with ESSDAI scores, Ig G and IFN-α highlights its immune-modulatory role contribute to disease outcomes. Therefore, vitamin D supplements may serve as a valuable drug in the treatment of patients with pSS.

**Author contributions**

MZ, SZ, YL, and WL all contributed to conception, drafting, writing, and final approval of the manuscript. JC contributed to case collection. MZ and SZ wrote the manuscript. WL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
**Ethics approval**
Ethical approval for this study was obtained from Bioethics Committee of Nanfang Hospital (NFEC-2019-240).

**Declaration of conflicting interests**
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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**Informed consent**
Written informed consent was obtained from all subjects before the study.

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**Availability of data and materials**
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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