ARTICLE INFO

AUTHOR'S AFFILIATIONS
Internal Medicine Department, Sebelas Maret University/ Dr. Moewardi General Hospital

CORRESPONDING AUTHOR
Agus Joko Susanto, Internal Medicine Department, Sebelas Maret University/ Dr. Moewardi General Hospital
E-mail:
agusjoko.susanto4@gmail.com

Article history

Received	27-11-2024
Revised	22-03-2025
Accepted	25-03-2025
Available online	31-03-2025

Please cite this article in APA 7th edition style as:
Susanto A. J., Sunggoro A. J., & Wati F. A. (2025). Correlation of Serum 25(OH) vitamin D levels with TNF-α and caspase levels in Sjögren's syndrome Patients. *Jurnal Ilmiah Kedokteran Wijaya Kusuma, 14 (1), 91-98*

http://dx.doi.org/10.30742/jikw.v14i1.4136

Correlation of Serum 25(OH) Vitamin D Levels With TNF-α and Caspase Levels in Sjögren's Syndrome Patients

Agus Joko Susanto, Agus Jati Sunggoro, Fatna Andika Wati*

Abstract

Background: Vitamin D deficiency is known to cause changes in disease pathogenesis in primary Sjögren's syndrome related to its immunological effects. **Objective:** This study aims to determine the correlation between serum 25(OH) vitamin D levels and TNF-α and caspase levels in Sjögren's syndrome patients. **Methods:** This study was a cross-sectional study involving 34 Sjögren's syndrome patients aged 18-59 years with vitamin D deficiency/insufficiency and measured levels of TNF-α and caspase. **Result:** The correlation between 25(OH) vitamin D levels and caspase levels obtained a value of r=-0.581, which means that there is a negative correlation in the moderate category (r=0.400-0.599) between 25(OH) vitamin D levels and caspase levels, and the p-value =<0.001 (p-value<0.05). The correlation between 25(OH) vitamin D levels and TNF-α levels obtained a value of r=-0.436, which means that there is a negative correlation in the moderate category (r=0.400-0.599) between 25(OH) vitamin D levels and a decrease in TNF-α, and p-value =<0.001 (p-value<0.05). **Conclusion:** There was a significant negative relationship between 25(OH) vitamin D levels and TNF-α and caspase levels.

Keywords: Caspase, Sjögren's syndrome, TNF-α, 25(OH) vitamin D

Original Research Article

INTRODUCTION

Patients with Sjögren's syndrome (SS), a systemic autoimmune disorder, experience xerostomia (dry mouth) and xerophthalmia (dry eyes) as a result of lymphocyte infiltration in the exocrine glands. Exocrine gland attacks by SS can result in extra glandular symptoms and systemic involvement. With a ratio of 9:1 to 19:1, SS is most common in women. According to Dumusc et al. (2022) and Radić et al. (2023), the prevalence is approximately 0.1-0.6%. Primary SS (pSS) occurs on its own, while secondary SS (sSS) occurs in conjunction with other autoimmune disorders such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA). With a female-to-male ratio ranging from 9:1 to 14:1, this crippling illness mainly affects women. With an estimated global frequency ranging from 0.1% to 4.8%, depending on the population under study and the diagnostic standards applied, SS is one of the most prevalent autoimmune illnesses (Dabravolski et al., 2024). Although SS illness has no known origin, several factors, including genetics, hormones, environmental factors, alterations in B lymphocytes, and innate immunity, are implicated. The development of SS is influenced by immune cell activation,

autoantibody synthesis, and some genetic variables (Espinoza-espinoza et al., 2019; Moreno-quispe and Moreno, 2020; Athanassiou and Mavragani, 2022).

The production of the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) rises in several inflammatory or autoimmune disorders. The salivary glands and saliva exhibit elevated TNF-α expression in Sjögren's syndrome, an autoimmune illness. Numerous cell types, such as the salivary gland epithelium, T helper 1 cells that invade salivary glands, and cytotoxic T cells 1, can release TNF-α in SS patients (Zhou et al., 2017; Tian et al., 2021).

Cholecalciferol, also known as vitamin D3, is produced in the skin (80%) by UVB sun, which converts 7-dehydrocholesterol into pre-vitamin D3 and initiates the hydroxylation process, or it can be absorbed by food (20%). Vitamin D is both calcemic and non-calcemic in the body. In its calcemic action, vitamin D mobilizes calcium from bones to maintain normal blood calcium concentrations and raises calcium concentrations by triggering proteins involved in phosphate and active intestine absorption. The vitamin D receptor (VDR), which is present in the parathyroid, pituitary, promyelocyte, lymphocyte, keratinocyte, ovary, and colon cells, is another way that vitamin D3 works. 1-α-hydroxylase is also present in vascular smooth muscle cells, macrophages, cancerous cells, and immune system cells in the colon, breast, and prostate, and it can generate $1,25(OH)_2D_3$ (also known as calcitriol, is the active form of vitamin D). This indicates that $1,25(OH)_2D_3$ affects particular immunological responses and functions as an immunomodulator of the innate and adaptive immune systems (Radić et al., 2023).

Immune responses, both innate and adaptive, are regulated by vitamin D3. It has a more comprehensive function in the adaptive immune response, particularly in modulating T cell responses. $1,25(OH)_2D_3$ prevents dendritic cells from maturing, which prevents them from activating T cells. Moreover, $1,25(OH)_2D_3$ suppresses the synthesis of cytokines. By inhibiting IL-12, $1,25(OH)_2D_3$ indirectly prevents Th1 lymphocyte response and development. As a result, IL-2, TNF-α, and IFN-γ are no longer produced. By controlling the activity of Th2 lymphocytes and regulatory T cells (Treg), $1,25(OH)_2D_3$ also contributes to the production of the anti-inflammatory cytokine IL-10. By inhibiting the synthesis of TNF-α and IL-23, $1,25(OH)_2D_3$ prevents Th17 cells from developing. Increases in Th17 or Th1 lymphocyte activity and quantity have been associated with a range of autoimmune disorders, including rheumatoid arthritis, multiple sclerosis, Graves' disease, SLE, type I diabetes mellitus, and connective tissue diseases (Radić et al., 2023).

The connection between vitamin D deficiency, vitamin D supplementation, and immune-mediated illnesses has long been researched. According to several research, 25(OH) vitamin D (also known as 25-hydroyvitamin D, the major circulating form of vitamin D in the serum) levels are lower in autoimmune disease patients than in healthy individuals (Radić et al., 2023).

Vitamin D contains anti-inflammatory properties, regulates the immune system, and is crucial for maintaining calcium and phosphorus balance. Lack of vitamin D is thought to trigger the body's inflammatory response to infections, which initiates numerous defense mechanisms, including the hemostatic system, leukocytes, and the cytokine network (Ashtari et al., 2022). When immune cells produce excessive amounts of pro-inflammatory cytokines, such as TNF-α, IL 1b, TNF-α, and IL 8, systemic inflammatory response syndrome (SIRS) may result (Aridan, 2021). Additionally, vitamin D can alter the immune system by influencing cytokines such as TNF-α. Sjogren's syndrome activity may be associated with low vitamin D levels (Wu et al., 2020). The strongest indicator of a person's vitamin D levels is their 25(OH) vitamin D level, which indicates how much vitamin D they obtain from their diet, sunlight, and vitamin D reserves in their liver. 25(OH) vitamin D levels of 20–30 ng/ml, 10–20 ng/ml, and less than 10 mg/ml were considered indicators of vitamin D insufficiency, deficiency, and severe deficiency (Zheng et al., 2021).

TNF-α antibody treatment was effective in rheumatoid arthritis patients with adequate blood vitamin D levels (Kim et al., 2020). These outcomes suggest that vitamin D insufficiency may be linked to elevated TNF-α levels and heightened disease activity (Ashtari et al., 2022). According to other studies, vitamin D has a negative link with TNF-α during the acute phase of the disease because it

regulates TNF-α. Because it does not particularly target the TNF-α receptor, vitamin D prevents negative effects on the anti-inflammatory functions of TNF-α1 by reducing the synthesis of TNF-α, which can minimize pro-inflammatory effects (Silberstein, 2021; Visser et al., 2022).

Vitamin D and pSS have a somewhat paradoxical relationship. Accordingly, some meta-analyses identified a correlation between low vitamin D levels and pSS, whereas other studies found no correlation. Furthermore, in Korean pSS patients, low serum calcifediol (25(OH)D3) levels were linked to tear breakup times, Schirmer I values, corneal staining scores, and conjunctival staining scores. Similarly, a Korean study found that in individuals with pSS, low blood levels of 25(OH)D3 were associated with the EULAR Sjogren's syndrome disease activity score. Patients with pSS in China and India, however, did not exhibit this correlation. These results strongly imply that additional studies involving larger populations are required to identify potential causal relationships and the biological mechanisms underlying them (Dabravolski et al., 2024). The purpose of this study is to ascertain whether 25(OH) vitamin D levels and TNF-α and caspase levels are correlated in patients with Sjogren's syndrome at Dr. Moewardi General Hospital. We anticipate that this study will provide a basis for the administration of vitamin D supplements to pSS patients who are vitamin D deficiency. Additionally, we intend to carry out this study in order to administer vitamin D supplements and track their effects on the activity of SS illness.

MATERIALS AND METHODS

The study carried out during the period from May, 2020 through June, 2024. Patients meeting the SS diagnosis criteria based on the American- European Consensus Group criteria (AECG) or ACR/EULAR, being between the ages of 18 and 59, being willing to participate in the study, and having vitamin D deficiency or insufficiency were the research subjects. Participants who declined to take part in the study, passed away during it, had retinitis or conjunctivitis, or had a significant disease were excluded. About 4 mL of blood was collected through the median cubital vein. 25(OH) vitamin D levels were measured from the serum of patients using Enzyme-Linked Fluorescent Assay (ELFA) method with MINI VIDAS. The levels of TNF-α and caspase were measured using enzyme-linked immunosorbent assay (ELISA) method with FineTest TNF-α ELISA Kit (Wuhan Fine Biotech, Wuhan, Hubei, China) and Caspase ELISA Kit (Wuhan Fine Biotech, Wuhan, Hubei, China), respectively. The measurement units of 25(OH) vitamin D, TNF-α, and caspase were ng/mL, pg/mL, and ng/mL, respectively. The measurement of TNF-α and 25(OH) vitamin D levels was conducted at Dr. Moewardi General Hospital, while caspase levels measurement was conducted at the Biomedical Laboratory, Faculty of Medicine, Gadjah Mada University, Yogyakarta.

Data analysis using the Pearson correlation test if the data was normally distributed and the Spearman rank correlation test if the data was not normally distributed. We performed a normality test using the Shapiro-Wilk test. A p-value of less than 0.05 was considered statistically significant. SPSS version 26 for Windows (IBM, New York, USA) was used for statistical analysis.

RESULTS

The number of samples in this study was 34 subjects. The baseline characteristics of the subjects in the study are shown in Table 1.

Table 1. Baseline characteristics of Sjögren's syndrome patients

Characteristic	n	%
Gender		
Male	4	11.8
Female	30	88.2
Age (y)		
≤64	22	64.7
≥65	12	35.3
Characteristic	n	%

Continue next page

Continued

Body weight (kg)	51.1	
Duration of Sjögren's syndrome (y)		
<1	7	20.6
1-4	24	70.6
5-9	3	8.8
Dry mouth	25	73.5
Dry eye	31	91.2
Locomotor system (Arthritis/arthralgia)	27	79.4
Ro-52 positivity	34	100

The following is the table of the TNF-α, caspase and 25(OH) vitamin D levels

Table 2. Description of TNF-α, Caspase and 25(OH) vitamin D levels

Variabel	Mean	±SD	Minimum	Maximum
TNF-α (pg/ml)	61.18	±2.02	56.63	64.29
Caspase	7.49	±0.08	7.31	7.62
25(OH) vitamin D (ng/ml)	20.06	±6.12	8.00	29.00

The following findings from a scatter plot of 25(OH) vitamin D and caspase levels provide an overview of the data on the link between the two variables.

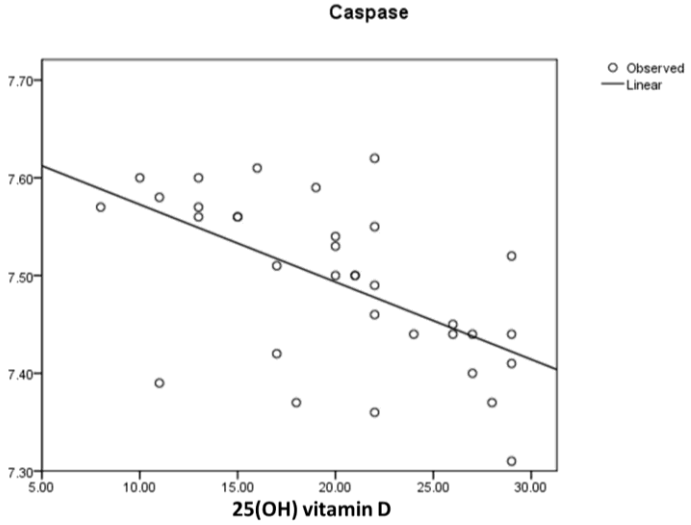

Figure 1. Scatterplot of the Relationship between 25(OH) vitamin D Levels and Caspase Levels

A straight line from upper left to lower right represents the scatterplot data distribution of the correlation between 25(OH) vitamin D levels and caspase levels, as seen in Figure 1. This implies that caspase levels decrease when 25(OH) vitamin D levels increase.

The results of statistical analysis of the correlation between 25(OH) vitamin D levels and caspase levels are as follows.

Table 3. Correlation between 25(OH) vitamin D levels and Caspase levels

Variable	Caspase Levels	
	r	*p-value*
25(OH) vitamin D	-0.581	<0.001*

Note: Pearson correlation test: *) significant at p<0.05

Table 3 indicates that there is a medium category negative relationship (r = 0.400-0.599) between vitamin 25(OH) vitamin D levels and caspase levels, with a correlation value of r = -0.581. The p-value is less than 0.001 (p-value < 0.05), indicating that the correlation is statistically significant.

Consequently, a strong negative correlation with a medium strength exists between vitamin D levels and caspase levels.

The average TNF-α level was 61.18 ± 2.02 pg/ml with a minimum of 56.63 pg/ml and a maximum of 64.29 pg/ml, the average level of caspase was 7.49 ± 0.08 pg/ml with a minimum of 7.31 pg/ml and a maximum of 7.62 pg/ml, and the average level of 25(OH) vitamin D was 20.06 ± 6.12 ng/ml with a minimum rate of 8.00 ng/ml and a maximum of 29.00 ng/ml.

A scatter plot between 25(OH) vitamin D levels and TNF-α levels provides an overview of the data on the link between the two, showing the following findings:

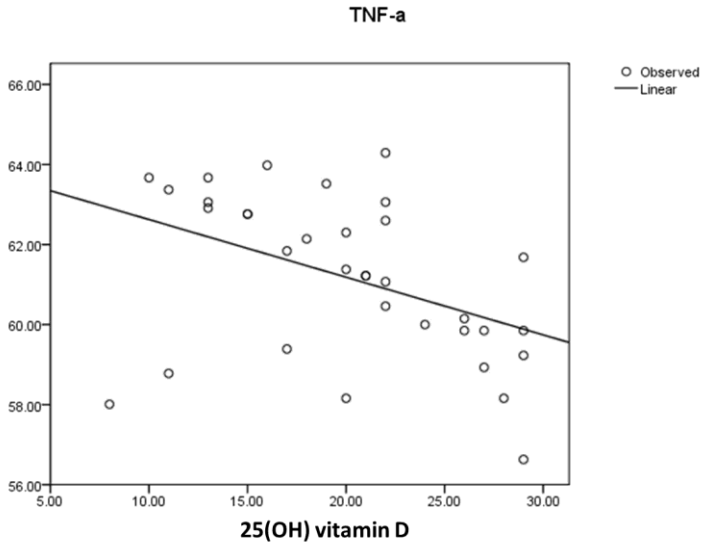

Figure 2. Scatterplot of the relationship between 25(OH) vitamin D levels and TNF-α levels

It is known from Figure 2 that the scatterplot data distribution on the relationship between TNF-α and 25(OH) vitamin D levels forms a linear line from top left to bottom right. This indicates that the lower the 25(OH) vitamin D levels, the higher the TNF-α levels. This suggests that TNF-α levels and 25(OH) vitamin D levels are negatively correlated.

The results of statistical analysis of the correlation between 25(OH) vitamin D levels and TNF-α levels are as follows.

Table 4. Correlation between 25(OH) vitamin D levels and TNF-α levels

Variable	TNF-a	
	r	*p-value*
25(OH) vitamin D levels	-0.436	<0.001*

Note: Pearson correlation test: *) significant at p<0.05

According to Table 4, there is a moderate negative correlation (r = 0.400–0.599) between 25(OH) vitamin D and TNF-α levels. The correlation is statistically significant with a p-value of 0.001 (p-value < 0.05). So, there is a moderately strong negative relationship between the levels of 25(OH) vitamin D in the blood and the levels of TNF-α.

DISCUSSION

Global epidemiological research has focused a lot of emphasis on the connection between vitamin D deficiency and autoimmune disorders. Low vitamin D levels have consistently been linked to an increased risk or severity of autoimmune diseases, according to numerous studies. For example, people with low vitamin D levels have greater rates of rheumatoid arthritis (RA) and disease activity. Among other conditions, similar correlations have been identified in inflammatory bowel disease (IBD),

multiple sclerosis (MS), and systemic lupus erythematosus (SLE) (Dabravolski et al., 2024; Dadaei et al., 2015). Our study's goal was to determine whether low vitamin D levels and elevated caspase and TNF-alpha levels were related in pSS patients receiving care at Dr. Moewardi General Hospital, Surakarta.

According to this study, 25(OH) vitamin D levels and caspase levels were found to be negatively correlated, the lower the 25(OH) vitamin D levels, the higher the caspase levels. By controlling cell death pathways and modifying immunological responses, the caspase family plays a crucial role in the pathogenesis of autoimmune disorders, highlighting its vital role in preserving immune homeostasis. Because of their dual involvement in cell death and non-cell death, caspases play a critical role in the onset and progression of autoimmune disorders (Zhang et al., 2025). According to Nakamura et al. (2018), caspase plays a part in the lacrimal gland apoptosis that occurs in Sjogren's syndrome. By causing the apoptosis of epithelial cells in the oral and ocular mucosa, elevated saliva levels of TNF-α and caspase-1 may contribute to the pathogenesis of pSS and reinforce the well-established function of innate immunity in mucosal inflammation of pSS (Karabulut et al., 2017).

Recent research indicates that the proteolytic maturation of inflammation involves a set of caspases, including human caspase-1, caspase-4, and caspase-5, as well as murine caspase-11 and caspase-12. These caspases are called "inflammatory caspases." It has been shown that the apoptotic pathway in pSS causes dysfunction in salivary gland endothelial cells, which is primarily characterized by downregulation of Bcl-2, apoptosis-related activation of caspase-3, and hyperexpression of several apoptotic proteins, including Fas, Fas-ligand, and Bax (Fasano et al., 2020). There is currently no research that examine the relationship between vitamin D deficiency or insufficiency and caspase levels in Sjogren's syndrome. Thus, this is the first study to look into the relationship between vitamin D deficiency or insufficiency and Sjogren's syndrome caspase levels. The results of the study showed a negative correlation between vitamin D levels and caspase levels in SS patients. This suggests that when vitamin D levels fall, caspase levels will rise. This supports vitamin D's role in regulating the immune system.

According to this study, 25(OH) vitamin D levels and TNF-α levels were also found to be negatively correlated, the lower the 25(OH) vitamin D levels, the higher the TNF-α levels. Studies have shown that vitamin D deficiency is associated with increased levels of inflammatory cytokines such as IL6, TNF-α, and interferon-gamma, which can worsen disease symptoms in autoimmune conditions. The results of various meta-analyses investigating the link between vitamin D deficiency and autoimmune disease activity are consistent in showing a significant association. A meta-analysis of studies on RA, MS, SLE, and T1D found that individuals with these conditions tend to have lower levels of vitamin D compared to healthy controls, with deficiency correlating with increased disease activity (Harris, 2024). However, until now there has been no research that has found a relationship between vitamin D levels and the degree of SS disease activity. Some studies even suggest that low vitamin D levels are associated with the development of lymphoma and peripheral neuropathy in SS patients (Radic et al, 2023).

According to earlier studies, the cytokines most frequently associated with pSS include interleukin (IL)-6 (50%), interferon (IFN)-γ (82%), tumor necrosis factor (TNF)-α (70%), and IL-2 (42.5%). Helper T (Th) 1 cells generate the pro-inflammatory cytokines IL-2, IFN-γ, and TNF-α, while Th2 cells produce the anti-inflammatory cytokines IL-4 and IL-10. B cells can also produce a variety of cytokines, such as the anti-inflammatory cytokine IL-10 and the pro-inflammatory cytokines IL-6 and TNF-α. A complicated signaling network made up of several cytokines controls the immunological response. Severe systemic disease, including pSS, can arise from the overexpression of pro-inflammatory cytokines and the lack or low levels of anti-inflammatory cytokines (Shang et al., 2023). T cells and macrophages are the primary producers of TNF-α, which comes in two forms: transmembrane TNF-α (Tm TNF-α) and soluble TNF-α (sTNF-α). sTNF-α is a powerful modulator of autoimmune disorders and inflammation. By activating the NF-kB and MAPK pathways, TNF-α can bind to either TNFR1 or TNFR2 and induce inflammation (Zhan et al., 2023). A class of cytokines known as the tumor necrosis factor

(TNF) family is responsible for apoptosis, or cell death. CD4+ T cells, monocytes, and epithelial cells secrete TNF-α, which plays a significant role in the pathophysiology of SS (An et al., 2022).

Resolving vitamin D insufficiency could lead to better health outcomes. Vitamin D supplementation has been linked to better joint function and a decrease in disease activity in RA. In a similar vein, MS patients who used vitamin D supplements showed slower disability progression and reduced recurrence rates. Vitamin D supplementation improved kidney function and decreased flare-ups in SLE. These results provide credence to the idea that vitamin D protects against autoimmune disorders by regulating inflammation and immunological function (Harris, 2024). These study results could be the basis for further research by providing vitamin D supplements to SS patients who have vitamin D deficiency or insufficiency.

CONCLUSION

Serum vitamin D levels are negatively correlated with TNF-α and caspase levels in SS patients receiving treatment at RSUD Dr. Moewardi Surakarta. This implies that the serum levels of TNF-α and caspase decrease with increasing vitamin D levels. This may suggest that among pSS patients receiving treatment at Dr. Moewardi General Hospital, vitamin D levels are correlated with the level of inflammatory activity. The connection between vitamin D supplementation and inflammatory indicators in patients with pSS who suffer from vitamin D deficiency or insufficiency requires more investigation. Giving vitamin D supplements to SS patients who aren't getting enough of it can be justified by this negative correlation. The idea is that as the patient's vitamin D levels increase, apoptosis and inflammatory indicators will decrease and they will feel better.

CONFLICT OF INTEREST

The authors report there are no competing interests to declare.

REFERENCES

An, Q., Zhao, J., Zhu, X., Yang, B., Wu, Z., Su, Y., Zhang, L., Xu, K., & Ma, D. (2022). Exploiting the role of T cells in the pathogenesis of Sjögren's syndrome for therapeutic treatment. *Frontiers in Immunology*, 13:1-15. https://doi.org/10.3389/fimmu.2022.995895

Aridan, A. (2021). Hubungan Antara Defisiensi Vitamin D Dengan Kadar Interleukin 6 Pada Anak Obes. Skripsi thsis. Fakultas Kedokteran Universitas Hasanuddin, Makssar

Ashtari, F., Madanian, R., Zarkesh, S.H., & Ghalamkari, A. (2022). Serum levels of interleukin-6 and Vitamin D at the onset of multiple sclerosis and neuromyelitis optica: A pilot study. *J Res Med Sci*, 27:67. https://doi.org/10.4103/jrms.jrms_796_21

Athanassiou, P., Mavragani, C., Athanassiou, L., Kostoglou-Athanassiou, I., & Koutsilieris, M. (2022). Vitamin D Deficiency in Primary Sjögren's Syndrome: Association with Clinical Manifestations and Immune Activation Markers. *Mediterr J Rheumatol*, *33*(1):106-8. https://doi.org/10.31138/mjr.33.1.106

Dabravolski, S. A., Churov, A. V., Starodubtseva, I.A., Beloyartsev, D.F., Kovyanova, T.I., Sukhorukov, V. N., & Orekhov, N.A. (2024). Vitamin D in Primary Sjogren's Syndrome (pSS) and the Identification of Novel Single-Nucleotide Polymorphisms Involved in the Development of pSS-Associated Diseases. *Diagnostics (Basel)*, *14*(18):2035. https://www.mdpi.com/2075-4418/14/18/2035

Dadaei, T., Safapoor, M.H., Asadzadeh Aghdaei, H., Balaii, H., Pourhoseingholi, M.A., Naderi, N., Zojaji, H., Azimzadeh, P., Mohammadi, P., & Zali, M.R. (2015). Effect of vitamin D3 supplementation on TNF-α serum level and disease activity index in Iranian IBD patients. *Gastroenterol Hepatol Bed Bench*, *8*(1):49-55. https://pmc.ncbi.nlm.nih.gov/articles/PMC4285932/

Dumusc, A., Rao, V., & Bowman, S.J. (2022). Sjögren's syndrome. *Medicine*, *50*(1):55-59. http://dx.doi.org/10.1016/j.mpmed.2021.10.009

Espinoza-Espinoza, L. A., Moreno-Quispe, L. A., & Moreno, R. M. (2019). Vitamins A , D , E in the Primary Sjögren Syndrome compared with Control Group. *Saudi Journal of Biomedical Sciences*, *4*(1):1-4. http://10.21276/sjbr.2019.4.1.1

Fasano, S., Mauro, D., Macaluso, F., Xiao, F., Zhao, Y., Lu, L., Guggino, G., & Ciccia, F. (2020). Pathogenesis of primary Sjögren's syndrome beyond B lymphocytes. *Clin Exp Rheumatol*, *126*(4):315-23. https://www.ncbi.nlm.nih.gov/pubmed/33095148

Harris, O. (2024). The Impact of Vitamin D Deficiency on Autoimmune Disease Activity: A Comprehensive Meta-Analysis. *International Journal of Clinical Rheumatology*. *19*(11):316-319. https://10.37532/1758-4272.2024

Karabulut, G., Kitapcioglu, Gİ., Özcaka, Ö., Alpöz, E., Nalbantsoy, A., Kocanaogullari, H., Gucenmez, S., Keser, G., & Kabasakal, Y. (2018). Saliva levels of caspase-1, TNF-Î±, and IFN-Î³ in primary Sjögren's syndrome: oralmucosal abnormalities revisited. *Turkish Journal of Medical Sciences*, *48*(3). https://doi.org/10.3906/sag-1710-31

Kim, H., Baek, S., Hong, S. M., Lee, J., Jung, S. M., Lee, J., Cho, M., Kwok, S. K., & Park, S. H. (2020). 1,25-dihydroxy Vitamin D3 and Interleukin-6 Blockade Synergistically Regulate Rheumatoid Arthritis by Suppressing Interleukin-17 Production and Osteoclastogenesis. *J Korean Med Sci*, *35*(6):e40. https://doi.org/10.3346/jkms.2020.35.e40

Moreno-Quispe, L.A., Serrano, J., Virto, L., Sanz, M., Ramírez, L., Fernández-Castro, M., Hernández, G., & López-Pintor, R.M. (2020). Association of salivary inflammatory biomarkers with primary Sjögren's syndrome. *J Oral Pathol Med*,*49*(9):940-47. https://doi.org/10.1111/jop.13070

Nakamura, H., Horai, Y., Shimizu, T., & Kawakami, A. (2018). Modulation of Apoptosis by Cytotoxic Mediators and Cell-Survival Molecules in Sjögren's Syndrome. *International Journal of Molecular Sciences*, *19*(8), 2369. https://doi.org/10.3390/ijms19082369

Radić, M., Kolak, E., Đogaš, H., Gelemanović, A., Bučan Nenadić, D., Vučković, M., & Radić, J. (2023). Vitamin D and Sjögren's Disease: Revealing the Connections-A Systematic Review and Meta-Analysis. *Nutrients*, *15*(3):497. https://doi.org/10.3390/nu15030497

Shang, L., He, L., & Li, M. (2023). What exactly is the relationship between plasma cytokines and the clinical phenotype of primary sjögren's syndrome? a single-centre retrospective study. *International Immunopharmacology*, 122:110567. https://doi.org/10.1016/j.intimp.2023.110567

Silberstein, M. (2021). COVID-19 and IL-6: Why vitamin D (probably) helps but tocilizumab might not. *Eur J Pharmacol*, 899:174031. https://pubmed.ncbi.nlm.nih.gov/33722593/

Tian, Y., Yang, H., Liu, N., Li, Y., & Chen, J. (2021). Advances in Pathogenesis of Sjögren's Syndrome. *J Immunol Res*, 5928232. https://doi.org/10.1155/2021/5928232

Visser, M. P. J., Dofferhoff, A. S. M., van den Ouweland, J. M. W., van Daal, H., Kramers, C., Schurgers, L.J., Janssen, R., & Walk, J (2022). Effects of Vitamin D and K on Interleukin-6 in COVID-19. *Front Nutr*, 8:761191. https://doi.org/10.3389/fnut.2021.761191

Wu, Y., Cai, Y., Liu, M., Zhu, D., & Guan, Y . (2020). The Potential Immunoregulatory Roles of Vitamin D in Neuromyelitis Optica Spectrum Disorder. *Multiple sclerosis and related disorders*, 43:102156. https://doi.org/10.1016/j.msard.2020.102156

Zhang, W., Wu, H., Liao, Y., Zhu, C., Zou, Z.(2025). Caspase family in autoimmune diseases. *Autoimmunity Reviews*. *24*(2):103714. https://doi.org/10.1016/j.autrev.2024.103714

Zheng, M., Zhu, S., li, Y., Chen, J., & Lai, W. (2021). Interferon alpha serum level association with low vitamin D levels in Chinese patients with primary Sjögren's syndrome. *European Journal of Inflammation*, 19:1-8. https://doi.org/10.1177/20587392211014053

Zhou, J., Kawai, T., & Yu, Q. (2017). Pathogenic role of endogenous TNF-α in the development of Sjögren's-like sialadenitis and secretory dysfunction in non- obese diabetic mice. *Physiology & behavior*, *176*(1): 139–48. https://doi.org/10.3390/ijms19082369