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Musculoskeletal Manifestations in Sjogren's Syndrome

Ridvan İşik and Ferhat Ege

Abstract

Sjögren's syndrome (SS) is a chronic, autoimmune, inflammatory disease characterized by lymphocytic infiltration, destruction and dysfunction of the exocrine glands. Sjögren's syndrome can be described as primary or secondary, depending on whether it occurs alone or in association with other systemic autoimmune diseases. Systemic manifestations of SS involve the musculoskeletal system. SS can be seen in association with both joint and muscle manifestations, including arthralgia and arthritis, as well as myopathy, which is usually asymptomatic. Besides, it may include bone metabolic disorders, fatigue and fibromyalgia. The diagnosis of Sjögren's syndrome is based on characteristic clinical signs and symptoms. The etiology and pathogenesis of SS is elusive and has not yet been clarified. There is no curative treatment for SS, thus the aim in the treatment of SS is to alleviate the symptoms.

Keywords: musculoskeletal, joints, fibromyalgia, fatigue, bones

1. Introduction

Sjögren's syndrome (SS) is a chronic, autoimmune, systemic, inflammatory disease that develops as a result of lymphocytic infiltration, destruction and dysfunction of the exocrine glands, and the lacrimal and salivary glands in particular. In 1933, Swedish ophthalmologist Henrik Sjögren described the clinical and histological findings associated with SS in 19 patients with rheumatoid arthritis, 13 of whom had dry mouth and dry eye symptoms [1]. SS predominantly affects middle-aged women who are within the fourth to sixth decade of their lives. The male/female ratio in patients with SS is approximately 6:1 to 9:1. SS is usually diagnosed in the fifth decade of life, but the first symptoms may appear years before diagnosis [2]. The incidence and prevalence rates of SS were estimated approximately as 6.92 cases per 100.000 persons/year and as 60.82 cases per 100.000 persons, respectively [3]. Geographical location and ethnicity have a strong influence on the biological and clinical phenotype of the disease. The onset of diagnosis of Sjogren syndrome and the gender preference may be affected by racial variation: the diagnosis can be accomplished up to 7 years earlier in patients of black/African American origins compared to Caucasians. Furthermore, the female to male ratio might reach 27:1 in patients of Asian descent [4]. There are two types of SS; first type, that is the primary SS, is the type without any concomitant connective tissue disorder, whereas the second type, that is the secondary SS, is the type observed together with other autoimmune diseases such as systemic lupus erythematosus (SLE),

rheumatoid arthritis (RA) or systemic sclerosis (SSc). SS is characterized by a wide spectrum of signs and symptoms, ranging from glandular involvement, structural symptoms, extraglandular manifestations and systemic autoimmune features. SS can be seen in association with both joint and muscle manifestations, including arthralgia and arthritis, as well as myopathy, which is usually asymptomatic. SS mostly involves the bone, the synovium and the cartilage tissue [5].

2. Pathogenesis

The etiology and pathogenesis of SS has not been clarified, as is the case with other autoimmune diseases [6]. Until now, it has been widely accepted that environmental factors play a role in the pathogenesis of SS [7]. Nevertheless, a thorough review of the recently published studies available in the literature revealed that the complex interaction between epithelial cells and targets of the autoimmune response and genetic and epigenetic changes also play a role in the pathogenesis of SS, in addition to the activated innate and adaptive immune system [8, 9].

The genetic component of SS are yet to shed light on. However, recent studies have begun to elucidate the familial links of the disease, identify specific risk alleles, and even classify patients according to their global gene expression levels. In these studies, many risk alleles for SS have been highlighted. Identification of these risk alleles helps in early diagnosis and choice of treatment options. Patients with extra-glandular manifestations (EGM) were found to have higher expression of genes involved in innate (apoptosis, TLR and interferon signaling) and adaptive (T and B cell activation) immune responses that play a key role in SS. On the other hand, patients with glandular features (GF) and diffuse pain (WP) were found to have the highest differential gene expression related to sensory perception and pain [10]. In complex diseases such as SS, the on and off signals of gene expression related to inflammatory pathways are managed by epigenetic mechanisms. Several epigenetic mechanisms, i.e., DNA methylation, miRNAs, and lncRNAs, contribute to turning on and off the expression of genes involved in inflammatory pathways and may target amelioration of SS therapy [11].

Considerable efforts have been made to elucidate the role of the innate immune system in the pathogenesis of SS. Plasmacytoid dendritic cells (pDC) are the pre-dominant type I interferon (IFN) producing cells. The transcriptional profile of SS plasmacytoid dendritic cells (pDCs) has been investigated and interestingly, it was found to be associated with enhanced cytokine production of pDCs. TLR7 dominant innate immunity may be associated with the development of sialadenitis in SS. Additionally, the few evidence supporting the role of TLR7-dominant innate immunity in the development of sialadenitis in SS [12].

The role of B and T cell subsets, particularly, of T follicular helper cells (Tfh) and of their regular counterparts, that is the T follicular regulatory cells (Tfr) cells, has been extensively investigated. The recent data on the subject revealed an increase in the proportion of Tfr and Tfh cells in SS patients as compared to the healthy control subjects, and an imbalance between proinflammatory and immune regulatory pathways in SS. Tertiary or ectopic lymphoid structures (TLS) are lymphoid clusters of T and B cells that form in non-lymphoid organs in response to chronic inflammation. TLS form in the target organ of autoimmune diseases, including SS, and is generally associated with worse disease progression. New insights into TLS formation and care are paving the way for new therapeutic approaches to SS [13].

3. Articular involvement

Most SS patients exhibit musculoskeletal symptoms such as arthralgia, myalgia, and morning stiffness. SS directly affects the peripheral joints, causing arthralgia in approximately 90% of the patients. Up to 17% arthritis incidence has been reported in SS patients [14, 15]. Arthritis is often symmetrical, intermittent, non-erosive and does not leave deformity. SS mainly affects the metacarpophalangeal joints located in the upper extremity, particularly the metacarpophalangeal joints with non-erosive synovitis, but also affects the wrists, knees, shoulders, and metatarsophalangeal joints [16]. Clinical symptoms of SS are similar to those of rheumatoid arthritis (RA), with the exception of bone erosion, which is very rare in SS [17]. Joint symptoms associated with primary Sjögren's syndrome (pSS) were reported as synovitis, which can mimic rheumatoid arthritis but were distinguished based on the absence of structural damage [18]. Joint involvement may precede the onset of SS in 10–20% of patients, but in a large amount of SS patients (40–50% of the cases) its onset is concurrent with the onset of sicca symptoms [19]. Ultrasonographic US imaging has proven to be of great value in identification of inflammatory synovitis and detection of erosions. Patients with SS were evaluated by ultrasonography (US), the prevalences of synovitis and erosion were found as 21.7% and 34.8%, respectively [20]. The incidence of synovitis in the metacarpophalangeal joints was found as 41.6% [21]. Additionally, a significant correlation was found between the ESSDAI scores of the SS patients whose disease activities were determined according to European League Against Rheumatism (EULAR) Sjogren's Syndrome Disease Activity Index (ESSDAI) and the frequency of synovitis and tenosynovitis detected by US. Based on these findings, it has been suggested that US is a useful method in the evaluation of joint involvement in SS [22]. SS is a complex and heterogeneous disease and has pleomorphic symptoms that can manifest in many different ways [23]. Joint involvement was present in 31.4% of the diagnosed patients, and was manifested as the first symptom in 17% of the patients [24]. Joint involvement is also associated with the presence of many serological markers such as cryoglobulins characterized by extraglandular manifestations, hypergammaglobulinemia, rheumatoid factor (RF) and anti-Sjögren's-syndrome-related antigen A (anti-SSA/Ro) or anti-Sjögren's-syndrome-related antigen B (anti-SSB/La) antibodies [25]. Apart from RA, the highest percentage of RF positivity is seen in SS patients. Approximately 40% of the SS patients, and even a higher percentage if only the SS patients with joint involvement were considered, were found to have RF positivity [25]. Another serological marker associated with arthritic manifestations is anti-citrullinated protein antibodies (ACPAs). ACPAs were found in 5–10% of the SS patients. SS patients with ACPAs were found to have a higher incidence of arthritis than those without ACPAs (43.7% vs. 12.2%). In addition, during a follow-up period of 5–10 years, 43.8% of the SS patients with ACPAs were found to have developed RA [26]. SS patients with ACPAs had a higher tendency to have arthritis and were at a higher risk of developing RA [27]. Joint involvement such as arthralgia and arthritis negatively affects the quality of life in patients with SS [28], creating the need for pharmacological treatment or surgical intervention [29]. It has been emphasized that SS causes higher disease activity scores, which are expressed using scoring systems such as ESSDAI, due to joint involvement, and that joint involvements an important clinical feature in predicting long-term disease outcome in SS [30]. Arthritic manifestations of the SS are mild, but course of SS in association with other diseases varies greatly. However, it is still unclear whether this variation is due to any change directly associated with SS or the combined effect of the disorders

accompanying SS. Findings that prove the association of SS with other autoimmune diseases have been demonstrated by epidemiological and genetic studies. SS was accompanied by RA and SLE in 19.5% and 13.6% of the patients, respectively [31]. There are also studies that revealed an epigenetic relationship linking such diseases. In one of these studies, a gene-expression meta-analysis study in respect of RA, SLE and SS, a common gene-expression was identified for these diseases [32]. It is a common concern that such disease combinations will worsen joint problems and adversely affect the course of the disease. The frequency of RA and SS association and the effects of this association on the course of the disease and comorbid conditions, it was found that 31.2% of the RA patients were also diagnosed with SS, and that the coexistence of these two diseases led to higher disease burden, higher disease activity, higher number of comorbidities (hypertension, cardiovascular diseases, malignancy and infections) and a higher degree of erosive changes [33]. Therefore, type of SS, whether it is primary or secondary SS, should be carefully considered and it should be kept in mind that other autoimmune diseases, including RA, can accompany SS during the course of the disease. Thus, the attending clinician should be able to also characterize these other patient populations.

4. Muscles

Muscle pain has been reported in approximately 45–50% of the patients with SS [34]. A thorough literature review reveals that a mild inflammatory myopathy with subclinical or insidious onset has been observed in SS. Generally, this condition manifests itself as muscle pain and proximal muscle weakness. Histopathological examination was performed in SS patients with muscle pain, inflammation was found in 72% of the patients, and signs of degeneration/regeneration (i.e., histological findings of myositis) were found in 47% of the patients along with inflammation [35]. In that regard, it has been shown that although rare, inflammatory muscle diseases (particularly, inclusion body myositis and polymyositis) may be associated with SS. Accordingly, patients with more insidious onset muscle weakness and low muscle enzyme elevations in particular should be suspected of inflammatory muscle diseases. There are case reports, which argued that inflammatory muscle diseases and SS can progress together in patients with SS, and that the possible cause of the co-existence of these diseases is a common autoimmune pathway [36, 37]. Additionally, it was reported that cytosolic 5'-nucleotidase 1A, which is a specific marker for inclusion body myositis, can be detected in approximately 30% of the patients with SS [38]. Given this finding, SS patients with muscle weakness should also be screened for inflammatory muscle diseases.

5. Fibromyalgia and fatigue

Fibromyalgia (FM) is a common disease characterized by widespread chronic body pain, sleep disturbance, weakness, and mood disorders. One of the hypotheses put forward in respect of the formation of FM disease is chronic inflammation. It was reported in many studies that pro-inflammatory cytokines and mediators are higher in patients with FM than in general population [39]. Frequency of FM is high in rheumatic diseases such as ankylosing spondylitis and rheumatoid arthritis. One-third of FM patients (about 33%) with sicca syndrome and/or xerostomia tested

positive for Sjögren's syndrome biomarkers [40]. In parallel, association of FM with these autoimmune diseases is common. To give an example, in a recent study, in which the frequency of FM was investigated in patients with inflammatory arthritis (IA), it was found that frequency of FM in IA patients was found to be 15–20% more than the frequency of FM in general population [41]. When it comes to FM and SS, it is seen that these two diseases share common symptoms such as muscle aches, fatigue, and dry mouth and eyes, and there are many studies available in the literature that investigated the relationship between the two. In one of these studies, in which SS-related auto-antibodies in FM patients presented with dry mouth and/or dry eye complaints were investigated, SS biomarkers were found to be positive in 32% of the FM patients. It was suggested by the authors of the study that SS may play a role in the pathophysiology of FM [40]. The comorbidities and clinical symptoms of the two diseases largely overlap. To give a few examples; in a cross-sectional study conducted by Choi et al., which investigated the frequency and clinical effect of FM on patients with SS, as well as FM frequency, disease activity scales such as Eular Sjogren's Syndrome Patient Reported Index (ESSPRI) and Eular Sjogren Syndrome Disease Activity Index (ESSDAI), and depression in patients with pSS, FM was detected in 31% of the SS patients, and both ESSPRI and ESSDAI scores and depression scores were found to be higher in patients who have both SS with FM, as compared to patients without FM [42]; and in a very recent population-based retrospective-cohort study conducted with 149,706 participants, in which the future risk of developing SS in patients with FM was investigated, patients with FM were found to have a higher risk of developing SS as compared to the control subjects without FM [43]. Given the results of these studies, which suggest that the relationship between SS and FM affects the disease activity and diagnosis, clinicians should consider the two-way relationship between SS and FM in the management of SS or FM. Fatigue is one of the most common symptoms of both SS and FM. The pathophysiology in SS is not fully understood. Patients with SS suffer from sleep disorders as they feel the urge to drink excess water due to dry mouth resulting in sleep disruptions. Fatigue in patients with SS has been associated with the coexistence of sleep disorders and FM. The pathophysiology in SS is not fully understood. Patients with SS suffer from sleep disorders, since they feel the urge to drink excess water due to dry mouth. Fatigue in patients with SS has been associated in the literature with the coexistence of sleep disorders and FM. To give an example; in a large cohort study conducted with 437 patients with pSS, it was found that patients with both FM and pSS manifested significantly more structural, fatigue, and arthralgia symptoms than patients with only pSS [44]. The presence of such symptoms substantially impairs the quality of life in patients with SS. As a matter of fact, it was concluded as a result of a cross-sectional study conducted using questionnaires to measure quality of life of patients with SS that the main determinants of the poor quality of life in patients with SS were pain and fatigue, and that disease activity scores were higher in patients with a high incidence of the said symptoms [45]. For this reason, sleep quality of SS patients should be improved against the symptom of fatigue, which is very common in patients with SS. In addition, in the event that SS accompanied by FM, disease management should be adjusted accordingly.

6. Bones

SS impairs the bone metabolism not just because it is a systemic autoimmune disease, but also because of some other factors associated with SS such as interstitial

nephritis, renal tubular acidosis, steroid use, coexistence with other autoimmune diseases, and low vitamin D levels. As is the case with other autoimmune diseases, SS also causes osteoporosis (OP) and osteomalacia (OM). SS plays a role in metabolic bone diseases by causing variations in the signaling pathways of the Wingless-type (Wnt) and Nf- κ B receptor activating factor (RANK), its ligand (RANKL) and osteoprotegerin (OPG) [46]. It has been reported in the pathophysiological studies conducted on the aforementioned signaling pathways that autoimmune diseases such as SS inhibits bone formation, since it reduces the levels of DKK1 (Dickkopf-related protein 1), a protein which is involved in the Wnt pathway and plays a role in bone formation. In addition, it has been shown that the RANKL/RANK/OPG signaling pathway, which features the main osteogenic factors and plays an important role in bone homeostasis, is activated in many autoimmune diseases, and it has been suggested that this leads to bone destruction [47, 48]. Furthermore, the Wnt/b-catenin signaling pathway plays a key role also in the development and regulation of the immune system, in addition to organogenesis and morphogenesis of the exocrine gland. In that regard, it was found in a study by Fernandez-Torres et al. on the genetic polymorphisms of the Wnt/b-catenin signaling pathway in SS patients that some genes associated with the Wnt/b-catenin signaling pathway, such as LRP5 (low-density lipoprotein receptor-related protein 5), FRZB (frizzled related protein), and ADIPOQ (adiponectin), significantly increase the risk of developing SS [49]. In another study, in which impaired bone metabolism in SS was investigated, osteoporosis/osteopenia was detected in $\frac{2}{3}$ (two-thirds) of the SS patients. In the same study, it has been shown that DKK1, one of the Wnt signal mediators, was low in SS patients and that this low level is associated with a decrease in bone mineral density, suggesting that Wnt signaling mediators are potentially involved in the pathogenesis of SS [50]. In a case-control study conducted by Pasoto et al. with 71 SS patients and 71 healthy control subjects of matching age, sex, and race, study participants were screened for bone mineral density (BMD), vertebral fracture (VF), and bone microarchitecture (by means of high-resolution peripheral quantitative computer tomography (HR-pQCT)). Consequentially, as compared to the healthy control subjects, it was found that patients with SS had lower mean BMD values in both hip and lumbar vertebrae, and less cortical bone thickness, and that a higher frequency of SS patients (approximately 20% of the SS patients) had VF and significantly impaired bone microarchitecture [51]. Additionally, in the same study, HR-pQCT revealed significant cortical deterioration in SS patients. However, the final assessment on the primary causative factor for osteoporosis (OP) could not be made, due to the fact that all SS patients were on corticosteroid therapy at the time of the study. There is a significant relationship between corticosteroid use and the development of OP. In a recent large-scale cross-sectional study, in which the frequency of OP, risk factors and fragility fractures were investigated in relation to SS, a significant correlation was found between the development of OP and factors such as age, duration of disease, corticosteroid use, presence of anti-La antibodies and ESSDAI scores in patients with SS. Up to 8.5% of the patients with SS were found to have fragility fractures, and a significant correlation was observed between the SS disease duration and age, ESSDAI scores and fragility fracture [52]. Osteomalacia (OM) is a disease characterized by impaired bone mineralization. The development of OM in SS patients has been associated with tubulointerstitial nephritis (TIN) or distal renal tubular acidosis (dRTA). There are several studies available in the literature to that effect that highlight the effect of TIN and dRTA in patients with SS and its contribution to the development of osteomalacia [53, 54]. Patients with OM are susceptible to pseudo-fractures.

Therefore, diagnosis of OM in patients with SS is very important. It is not yet known whether these findings can be directly attributed to the relationship between SS, OP and OM, pathophysiologically. Nevertheless, the direct clinical relevance between these conditions should not be overlooked. The exact mechanism of the effect of SS on bone metabolism has not been determined, but it is obvious that there is a relationship, albeit an indirect one. The part which is not yet clear is whether it is the SS itself or the drugs used for the treatment of SS or the target organs affected in relation thereto are the main factors creating the said effect.

7. Available therapeutic options with possible benefit in musculoskeletal disease

There is no curative treatment for SS, thus the aim in the treatment of SS is to alleviate the symptoms of exocrinopathy and also to get the extraglandular manifestations of the disease under control. Management of SS patients requires a multidisciplinary approach involving collaboration with specialist doctors from different specializations, such as clinical immunologists, rheumatologists, ophthalmologists, otolaryngologists and/or dentists. Centers such as The Sjögren's Foundation, The British Society for Rheumatology, and EULAR publish guidelines for the management of SS [55–57]. Nevertheless, no specific therapeutic goal other than symptomatic relief has been put forward in these guidelines. Fatigue, one of the major symptoms targeted to be relieved by the treatment modalities used for the treatment of SS, is a symptom that significantly impairs quality of life in patients with SS. However, the effectiveness of the current medical treatments used to contain this symptom is still not up to the level. Available guidelines suggest regular physical activity as the best approach to improve fatigue [56, 57]. Hydroxychloroquine (HCQ) is usually recommended as the first-line treatment for musculoskeletal pain relief. On the other hand, methotrexate (MTX) is recommended to be used as a stand-alone medication or in combination with HCQ in patients who do not respond to HCQ, and particularly in those with severe inflammatory arthritis [56]. In cases where the combination of HCQ and MTX has proven ineffective in the treatment of inflammatory musculoskeletal symptoms, alternative options such as use of corticosteroids, leflunomide, sulfasalazine, azathioprine, cyclosporine, or biologic drugs may be considered [55, 57].

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References

- [1] Henrik S. Zur Kenntnis der keratoconjunctivitis sicca. Keratitis filiformis bei Hypofunktion der Tränendrüsen [On knowledge of keratoconjunctivitis sicca. Keratitis filiformis due to lacrimal gland hypofunction]. *Acta Ophthalmologica*. 1933;2:1-151
- [2] Brito-Zeron P, Theander E, Baldini C, et al. Early diagnosis of primary Sjögren's syndrome: EULAR-SS task force clinical recommendations. *Expert Review of Clinical Immunology*. 2016;12(2): 137-156
- [3] Qin B, Wang J, Yang Z, Yang M, Ma N, Huang F, et al. Epidemiology of primary Sjögren's syndrome: A systematic review and meta-analysis. *Annals of the Rheumatic Diseases*. 2015;74(11):1983
- [4] Brito-Zeron P, Acar-Denizli N, Zehner M, et al. Influence of geolocation and ethnicity on the phenotypic expression of primary Sjögren's syndrome at diagnosis in 8310 patients: A cross-sectional study from the big data Sjögren project consortium. *Annals of the Rheumatic Diseases*. 2017;76(6): 1042-1050
- [5] Saraux A, Pers JO, Devauchelle-Pensec V. Treatment of primary Sjögren syndrome. *Nature Reviews Rheumatology*. 2016;12:456-471
- [6] Shimizu T, Nakamura H, Kawakami A. Role of the innate immunity signaling pathway in the pathogenesis of Sjögren's syndrome. *International Journal of Molecular Sciences*. 2021;22(6):3090
- [7] Brito-Zeron P, Baldini C, Bootsma H, et al. Sjögren syndrome. *Nature Reviews Disease Primers*. 2016;2:16047
- [8] Bombardieri M, Argyropoulou OD, Ferro F, et al. One year in review 2020: Pathogenesis of primary Sjögren's syndrome. *Clinical and Experimental Rheumatology*. 2020;126(4):3-9
- [9] Chivasso C, Sarraud J, Perret J, Delporte C, Soyfoo MS. The involvement of innate and adaptive immunity in the initiation and perpetuation of Sjögren's syndrome. *International Journal of Molecular Sciences*. 2021;22(2):658
- [10] Vitali C, Dolcino M, Del Papa N, et al. Gene expression profiles in primary Sjögren's syndrome with and without systemic manifestations. *ACR Open Rheumatology*. 2019;1:603-613
- [11] Imgenberg-kreuz J, Almlöf JC, Leonard D, et al. Shared and unique patterns of DNA methylation in systemic lupus erythematosus and primary Sjögren's syndrome. *Frontiers in Immunology*. 2019;10:1686
- [12] Davies R, Sarkar I, Hammenfors D, et al. Single cell based phosphorylation profiling identifies alterations in toll-like receptor 7 and 9 signaling in patients with primary Sjögren's syndrome. *Frontiers in Immunology*. 2019;10:281
- [13] Luo S, Zhu R, Yu T, et al. Chronic inflammation: A common promoter in tertiary lymphoid organ neogenesis. *Frontiers in Immunology*. 2019;10:2938
- [14] Baldini C, Pepe P, Quartuccio L, et al. Primary Sjögren's syndrome as a multi-organ disease: Impact of the serological profile on the clinical presentation of the disease in a large cohort of Italian patients. *Rheumatology (Oxford, England)*. 2014;53(5):839-844
- [15] Ramos-Casals M, Brito-Zerón P, Solans R, et al. Systemic involvement in

- primary Sjogren's syndrome evaluated by the EULAR-SS disease activity index: Analysis of 921 Spanish patients (GEAS-SS Registry). *Rheumatology* (Oxford, England). 2014;**53**(2):321-331
- [16] Amezcua-Guerra LM, Hofmann F, Vargas A, et al. Joint involvement in primary Sjögren's syndrome: An ultrasound "target area approach to arthritis". *BioMed Research International*. 2013;**2013**:640265
- [17] Jacques T, Sudoł-Szopińska I, Larkman N, O'Connor P, Cotten A. Musculoskeletal manifestations of non-RA connective tissue diseases: Scleroderma, systemic lupus erythematosus, Still's disease, dermatomyositis/polymyositis, sjögren's syndrome, and mixed connective tissue disease. *Seminars in Musculoskeletal Radiology*. 2018;**22**(2):166-179
- [18] Mirouse A, Seror R, Vicaut E, et al. Arthritis in primary Sjögren's syndrome: Characteristics, outcome and treatment from French multicenter retrospective study. *Autoimmunity Reviews*. 2019;**18**(1):9-14
- [19] Vitali C, Del Papa N. Pain in primary Sjögren's syndrome. *Best Practice & Research. Clinical Rheumatology*. 2015;**29**(1):63-70
- [20] Lei L, Morgan S, Ntatsaki E, Ciurtin C. Comparative assessment of hand joint ultrasound findings in symptomatic patients with systemic lupus erythematosus and Sjögren's syndrome: A pilot study. *Ultrasound in Medicine & Biology*. 2019;**45**(2):452-460
- [21] Riente L, Scirè CA, Delle Sedie A, et al. Ultrasound imaging for the rheumatologist. XXIII. Sonographic evaluation of hand joint involvement in primary Sjögren's syndrome. *Clinical and Experimental Rheumatology*. 2009;**27**(5):747-750
- [22] Guedes LKN, Leon EP, Bocate TS, Bonfigliolli KR, Lourenço SV, Bonfa E, et al. Characterizing hand and wrist ultrasound pattern in primary Sjögren's syndrome: A case-control study. *Clinical Rheumatology*. 2020;**39**(6):1907-1918
- [23] Leone MC, Alunno A, Cafaro G, et al. The clinical spectrum of primary Sjögren's syndrome: Beyond exocrine glands. *Reumatismo*. 2017;**69**(3):93-100
- [24] Fauchais AL, Ouattara B, Gondran G, et al. Articular manifestations in primary Sjögren's syndrome: Clinical significance and prognosis of 188 patients. *Rheumatology* (Oxford, England). 2010;**49**(6):1164-1172
- [25] García-Carrasco M, Ramos-Casals M, Rosas J, et al. Primary Sjögren syndrome: Clinical and immunologic disease patterns in a cohort of 400 patients. *Medicine (Baltimore)*. 2002;**81**(4):270-280
- [26] Payet J, Belkhir R, Gottenberg JE, et al. ACPA-positive primary Sjögren's syndrome: True primary or rheumatoid arthritis-associated Sjögren's syndrome? *RMD Open*. 2015;**1**(1):26-44
- [27] Molano-González N, Olivares-Martínez E, Anaya JM, Hernández-Molina G. Anti-citrullinated protein antibodies and arthritis in Sjögren's syndrome: A systematic review and meta-analysis. *Scandinavian Journal of Rheumatology*. 2019;**48**(2):157-163
- [28] Cornec D, Devauchelle-Pensec V, Mariette X, et al. Severe health-related quality of life impairment in active primary Sjögren's syndrome and patient-reported outcomes: Data from a large therapeutic trial. *Arthritis Care & Research*. 2017;**69**(4):528-535
- [29] Chu LL, Cui K, Pope JE. Meta-analysis of treatment for primary

Sjögren's syndrome. *Arthritis Care & Research*. 2020;**72**(7):1011-1021

[30] Quartuccio L, Gandolfo S, Zabotti A, Zandonella Callegger S, Fabro C, De Vita S. Articular and peripheral nervous system involvement are linked to the long-term outcome in primary Sjögren's syndrome: The relevance of single organ manifestations rather than a composite score as predictors. *Frontiers in Immunology*. 2019;**10**:1527

[31] Alani H, Henty JR, Thompson NL, Jury E, Ciurtin C. Systematic review and meta-analysis of the epidemiology of polyautoimmunity in Sjögren's syndrome (secondary Sjögren's syndrome) focusing on autoimmune rheumatic diseases. *Scandinavian Journal of Rheumatology*. 2018;**47**(2):141-154

[32] Toro-Domínguez D, Carmona-Sáez P, Alarcón-Riquelme ME. Shared signatures between rheumatoid arthritis, systemic lupus erythematosus and Sjögren's syndrome uncovered through gene expression meta-analysis. *Arthritis Research & Therapy*. 2014;**16**(6):489

[33] Harrold LR, Shan Y, Rebello S, et al. Prevalence of Sjögren's syndrome associated with rheumatoid arthritis in the USA: An observational study from the Corrona registry. *Clinical Rheumatology*. 2020;**39**(6):1899-1905

[34] Tishler M, Barak Y, Paran D, Yaron M. Sleep disturbances, fibromyalgia and primary Sjögren's syndrome. *Clinical and Experimental Rheumatology*. 1997;**15**:71-74

[35] Lindvall B, Bengtsson A, Ernerudh J, Eriksson P. Subclinical myositis is common in primary Sjögren's syndrome and is not related to muscle pain. *The Journal of Rheumatology*. 2002;**29**(4):717-725

[36] Kanellopoulos P, Baltoyiannis C, Tzioufas AG. Primary Sjögren's syndrome

associated with inclusion body myositis. *Rheumatology (Oxford, England)*. 2002;**41**(4):440-444

[37] Migkos MP, Sarmas I, Somarakis GA, Voulgari PV, Tsamis KI, Drosos AA. Sjögren syndrome associated with inflammatory muscle diseases. *Mediterranean Journal of Rheumatology*. 2018;**29**(2):92-96

[38] Rietveld A, van den Hoogen LL, Bizzaro N, et al. Autoantibodies to cytosolic 5'-nucleotidase 1A in primary Sjögren's syndrome and systemic lupus erythematosus. *Frontiers in Immunology*. 2018;**9**:1200

[39] Mendieta D, De la Cruz-Aguilera DL, Barrera-Villalpando MI, et al. IL-8 and IL-6 primarily mediate the inflammatory response in fibromyalgia patients. *Journal of Neuroimmunology*. 2016;**290**:22-25

[40] Applbaum E, Lichtbroun A. Novel Sjögren's autoantibodies found in fibromyalgia patients with sicca and/or xerostomia. *Autoimmunity Reviews*. 2019;**18**(2):199-202

[41] Zhao SS, Duffield SJ, Goodson NJ. The prevalence and impact of comorbid fibromyalgia in inflammatory arthritis. *Best Practice & Research. Clinical Rheumatology*. 2019;**33**(3):101423

[42] Choi BY, Oh HJ, Lee YJ, Song YW. Prevalence and clinical impact of fibromyalgia in patients with primary Sjögren's syndrome. *Clinical and Experimental Rheumatology*. 2016;**34** (2 Suppl 96):S9-S13. Epub 2015 Aug 27

[43] Gau SY, Leong PY, Lin CL, Tsou HK, Wei JC. Higher risk for Sjögren's syndrome in patients with fibromyalgia: A nationwide population-based Cohort study. *Frontiers in Immunology*. 2021;**12**:640618

- [44] Torrente-Segarra V, Corominas H, Sánchez-Piedra C, et al. Fibromyalgia prevalence and associated factors in primary Sjögren's syndrome patients in a large cohort from the Spanish Society of Rheumatology registry (SJOGRENSER). *Clinical and Experimental Rheumatology*. 2017;**35**
- [45] Dias LH, Miyamoto ST, Giovelli RA, de Magalhães CIM, Valim V. Pain and fatigue are predictors of quality of life in primary Sjögren's syndrome. *Advances in Rheumatology*. 2021;**61**(1):28
- [46] Skarlis C, Palli E, Nezos A, Koutsilieris M, Mavragani CP. Study of the incidence of osteoporosis in patients with Sjögren's syndrome (pSS) and investigation of activation of the RANKL/RANK and osteoprotegerin (OPG) system. *Mediterranean Journal of Rheumatology*. 2018;**29**(4):224-227
- [47] Baron R, Kneissel M. WNT signaling in bone homeostasis and disease: From human mutations to treatments. *Nature Medicine*. 2013;**19**(2):179-192
- [48] Leibbrandt A, Penninger JM. RANK/RANKL: Regulators of immune responses and bone physiology. *Annals of the New York Academy of Sciences*. 2008;**1143**:123-150
- [49] Fernández-Torres J, Pérez-Hernández N, Hernández-Molina G, et al. Risk of Wnt/ β -catenin signalling pathway gene polymorphisms in primary Sjögren's syndrome. *Rheumatology (Oxford, England)*. 2020;**59**(2): 418-425
- [50] Gravani F, Papadaki I, Antypa E, et al. Subclinical atherosclerosis and impaired bone health in patients with primary Sjogren's syndrome: Prevalence, clinical and laboratory associations. *Arthritis Research & Therapy*. 2015; **17**(1):99
- [51] Pasoto SG, Augusto KL, Alvarenga JC, Takayama L, Oliveira RM, Bonfa E, et al. Cortical bone density and thickness alterations by high-resolution peripheral quantitative computed tomography: Association with vertebral fractures in primary Sjögren's syndrome. *Rheumatology (Oxford, England)*. 2016;**55**(12):2200-2211
- [52] Salman-Monte TC, Sanchez-Piedra C, Fernandez Castro M, et al. Prevalence and factors associated with osteoporosis and fragility fractures in patients with primary Sjögren syndrome. *Rheumatology International*. 2020;**40**(8): 1259-1265
- [53] Geng Y, Zhao Y, Zhang Z. Tubulointerstitial nephritis-induced hypophosphatemic osteomalacia in Sjögren's syndrome: A case report and review of the literature. *Clinical Rheumatology*. 2018;**37**(1):257-263
- [54] Nagae H, Noguchi Y, Ogata S, et al. Osteomalacia secondary to renal tubular acidosis due to Sjögren's syndrome: A case report and review of the literature. *CEN Case Reports*. 2012;**1**(2):123-127
- [55] Vivino FB, Carsons SE, Foulks G, et al. New treatment guidelines for Sjogren's disease. *Rheumatic Diseases Clinics of North America*. 2016;**42**(3): 531-551
- [56] Price EJ, Rauz S, Tappuni AR, et al. The British Society for Rheumatology guideline for the management of adults with primary Sjögren's syndrome. *Rheumatology*. 2017;**56**(10):1643-1647
- [57] Ramos-Casals M, Brito-Zeron P, Bombardieri S, et al. EULAR recommendations for the management of Sjogren's syndrome with topical and systemic therapies. *Annals of the Rheumatic Diseases*. 2020;**79**(1):3-18