Ophthalmic Manifestations of Autoimmune Rheumatic Diseases: A Literature Review

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Abstract

Background: Autoimmune rheumatic diseases (ARDs) are a group of rheumatic diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and systemic sclerosis which most infect connective tissue and cause organ damage. Autoimmune rheumatic diseases (ARDs) can manifest in many organs of the body such as the lungs, heart, kidneys, skin, and eyes. Several studies show that ARDs can cause a manifestation in the eye and can be severe. This literature study aims to describe the definition of systemic lupus erythematosus, its etiology, epidemiology, and ophthalmic manifestations. **Objective:** This literature study aims to describe and show the ophthalmic manifestations of ARDs. **Method:** This study uses a literature review as the method. **Results:** Several studies found and will be reviewed in this research about ophthalmic manifestations in patients with ARDs. **Conclusions:** Keratoconjunctivitis sicca or dry eye syndrome was found as the most common ophthalmic manifestation in patients with ARDs.

Keywords: ARDs; Rheumatic; Ophthalmic

1. Introduction

Autoimmune rheumatic diseases (ARDs) are chronic and complex autoimmune diseases that affect a wide range of organs, such as the heart, skin, musculoskeletal, and eyes. Systemic inflammation is one of the characteristics of ARDs which dysregulates the immune system and causes damage to the organ (Marder, Vinet and Somers, 2015). The conditions included in autoimmune rheumatic diseases are systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (scleroderma), and Sjogren syndrome which ARDs affected 5% of the population (Hedar et al., 2021). According to the research by Yu et al. (2013), the prevalence of ARDs was 101.3 per 100.000 populations and the prevalence between women and men was 165.1 and 40.1. ARDs affect women more than men. Based on Liu and Perl (2019), autoimmune rheumatic diseases are of unknown origin, and they represent significant causes of morbidity and mortality. Many studies show that ARDs can manifest to other organs and end up with complications. The study of ARDs manifestations in the eye needs to be done further. Ophthalmic manifestations in patients with ARDs can happen sometimes. Several studies about ophthalmic manifestations of the eyes result in keratoconjunctivitis sicca as the most common complication of the eye. The study about eye complications of ARDs needs to be done further, especially in Indonesia.

2. Ophthalmic Manifestation of Autoimmune Rheumatic Diseases

2.1. Ophthalmic Manifestation of Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease causing widespread inflammation and organ damage with relapsing, characterized by the presence of antibodies to nuclear and cytoplasmic antigens. The etiology of SLE is not well understood but the involvement of epigenetic, genetic, ecological, and environmental factors primarily leads to activation of both innate and adaptive immunity (Ameer et al., 2022). Organ involvement may occur in patients with SLE. The organ involvement manifestations of SLE are skin, kidneys, lungs, eyes, and heart. The diagnosis of SLE is based on clinical and laboratory findings. The improved classification criteria were used by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) (Ameer et al., 2022). According to Trilistyoati, Agustina, and Awalia (2021), SLE attacks multiple organs with diverse clinical manifestations.

The incidence and prevalence differ depending on the geography. The highest incidence and prevalence were reported in North America, and the lowest incidence was reported in Africa and Australia (Ameer et al., 2022). According to Rees et al. (2017), the highest estimates of incidence and prevalence of SLE were in North America 23.2/100.000 people and 241/100.000 people, and the lowest incidences of SLE were reported in Africa and Ukraine (0.3/100.000 person-years), and the lowest prevalence was in Northern Australia (0 cases in a sample of 847 people). Similar to the research conducted by Tian et al. (2022) the global SLE incidence and newly diagnosed population were estimated to be 5.14 (1.4 to 15.13) per 100.000 person-years and 0.40 million people annually. The prevalence of SLE is higher in women rather than men. Tian et al. (2022) stated that the prevalence of SLE in women, the values was 8.82 (2.4 to 25.99) per 100 000 person-years and 0.34 million people annually, while in men, the estimates were 1.53 (0.41 to 4.46) per 100 000 person-years and 0.06 million people annually.

Table 1. Summary of Ophthalmic manifestation in SLE patients articles reviewed

No	Title	Authors	Objective	Design	Ophthalmic Manifestations
1.	Ocular Manifestations of Systemic Lupus Erythematosus	El-Shereef, Mohamed and Hamdy.	to determine the ocular manifestations of systemic lupus erythematosus and its correlation with the disease activity	Fifty-two lupus patients and 20 healthy controls were included in this study. Data were analyzed by the Statistical Package for the Social Science. The differences between groups were examined by chi-square.	The most ocular manifestation was keratoconjunctivitis sicca. The least frequent was cataract and internuclear ophthalmoplegia.

2.	Ocular Manifestations of Systemic Lupus Erythematosus	Cho.	show the various ocular manifestations of SLE and discuss treatment options for eye problems	Literature review	The most common manifestation is keratoconjunctivitis sicca.
3.	Ocular manifestations of systemic lupus erythematosus in children	Ostanek et al.	The aim of the work was to asses the frequency of eye changes among patients with SLE and SLE with antiphospholipid syndrome (APS). Another aim was to asses the association between antiphospholipid antibodies and ocular lesions	There were 75 patients enrolled with SLE, 26 of them had APS. All of patients had a comprehensive ophthalmological and physical examination.	Thirty-six patients complained of ophthalmologic disturbances (48%), with dry eye being the most common symptom (20 patients)

2.2. Ophthalmic Manifestation of Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is the most common chronic inflammatory autoimmune disease and multisystemic disease mainly affects joints and the musculoskeletal (Romão and Fonseca, 2021). Rheumatoid Arthritis patients most likely have extra-articular manifestations such as rheumatoid nodules, rheumatoid vasculitis, and pleuropulmonary, neurologic, digestive, cardiovascular, cutaneous, hematologic, and ocular complications (Cojocaru et al., 2010). According to the literature by Cojocaru et al. (2010) Many of these manifestations are related to the more active and severe RA, so early and more aggressive RA drug therapies are being employed and, although evidence from randomized studies is not available, this approach would seem appropriate in view of the adverse effect of extra-articular manifestations on RA outcomes. Based on the Indonesian Journal of Rheumatology written by Fitriah and Isbagio (2018), the prevalence of RA in Indonesia is <0.4%, with an incidence rate in women and men is 2.5: 1.4. This disease can occur at different ages. Study by Kim and Sung (2021), the prevalence of RA in Korea ranges from 0.27% to 1.85% and the female-to-male ratio is between 2.7:1 and 13.5:1. Meanwhile, the meta-analysis study by Almutairi (2021), the global prevalence of RA was 460 per 100.000 population from 1980 – 2018, with a 95% prediction interval (0.06 – 1.27%).

Table 2. Summary of Ophthalmic manifestation in RA patients articles reviewed

No	Title	Authors	Objective	Design	Ophthalmic Manifestations
1.	Extra-articular Manifestations in Rheumatoid Arthritis	Cojocaru et al.	This paper focuses on extra-articular manifestations, defined as diseases and symptoms not directly related to the locomotor system	This paper briefly review extra-articular manifestations of RA with an emphasis on recent clinical research	The most frequent is keratoconjunctivitis sicca, which affects at least 10% of patients. It is frequently observed together with xerosto-mia in a secondary Sjögren's syndrome. Episcleritis, inflammation of the layer superficial to the sclera, occurs in less than 1% of patients
2.	Ocular Manifestations of rheumatoid arthritis-different forms and frequency	Zlatanović et al.	To present different ocular manifestations of RA and their requency	Examined 691patients with diagnose of RA. All examined patients were in I or II stage of disease according to criteria of the American College of Rheumatology	Ocular manifestations involved with RA are keratoconjunctivitis sicca, episcleritis, scleritis corneal changes, and retinal vasculitis. The most common manifestation of ocular involvement was keratoconjungtivitis sicca.
3.	Ocular surface involvement in patients with rheumatoid arthritis: Relation with disease activity and duration	Eldaly, Saad and Hammam	to present the frequency of ocular surface manifestations in rheumatoid arthritis (RA) patients and to determine its correlation with disease activity and duration	Cross-sectional study included 70 RA patients. Disease-activity was scored (DAS-28). All patients underwent complete ophthalmic evaluation including assessment of visual activity.	Ocular manifestations are dry eye (keratoconjungtivitis sicca), pterygium, blepharitis, scleritis, blue sclera, corneal abnormality, corneal thinning, filamentary keratitis, cataract, and retinal involvement.

2.3. Ophthalmic Manifestation of Systemic Sclerosis

The autoimmune and vascular illness known as systemic sclerosis (SSc) affects many systems and causes fibrosis in different organs with an unknown etiology. A growing body of research indicates that

the development of SSc is supported by both extra organ-specific diseases and a shared pathologic cascade affecting several organs. The first step in the common pathologic cascade is vascular damage brought on by autoimmune reactions and unidentified environmental variables. After that, aberrantly activated endothelial cells facilitate the infiltration of circulating immune cells into perivascular areas of various organs, while dysregulated angiogenesis and defective vasculogenesis promote vascular structural abnormalities, such as capillary loss and arteriolar stenosis (Asano, 2020). Systemic sclerosis also manifests in other organs such as the eye. According to Kozikowska et al. (2020), SSc affects eyes leading to various findings in ophthalmological examination.

Based on the descriptive epidemiological study by Foocharoen et al. (2023), The number of SSc cases in 2017 was 15,920 from a total Thai population of 65,204,797. The prevalence of SSc in 2017 was 24.4 per 100,000 population and the prevalence of SSc among women was 2 times greater than among men (32.7 vs. 15.8 per 100,000). The incidence of SSc was stable from 2018 to 2019 but dropped slightly in 2020 (7.2, 7.6, and 6.8 per 100,000 person-years, respectively) and most SSc cases were in northeastern Thailand (11.6, 12.1, and 11.1 per 100,000 person-years from 2018 to 2020, respectively) and the peak was between 60 and 69 years of age (24.6, 23.8, and 20.9 per 100,000 person-years from 2018 to 2020, respectively).

In the systematic review by Bergamasco et al. (2019), the reported prevalence of SSc was 7.2–33.9 and 13.5–44.3 per 100,000 individuals in Europe and North America, respectively. Annual incidence estimates were 0.6–2.3 and 1.4–5.6 per 100,000 individuals in Europe and North America, respectively. A study by Tian et al. (2023), shows the global SSc incidence and newly diagnosed population were estimated to be 8.64 per 100,000 person-years (1.78–23.57) and 0.67 million (0.14–1.84) people annually, and the global prevalence, SSc prevalence, and affected population were 18.87 per 100,000 persons (1.55–25.28) and 1.47 million (0.12–1.97) people, respectively. Relatively higher incidence and prevalence were observed in females, adults, and high-income level countries.

Table 3. Summary of Ophthalmic manifestation in SSc patients articles reviewed

No	Title	Authors	Objective	Design	Ophthalmic Manifestations
1.	Ocular manifestations in patient with systemic sclerosis	Kozikowska et al.	To determine the prevalence and type of ocular involvement in patients with systemic sclerosis	A systematic literature review was conducted using electronic databases	Eyelid and conjunctival abnormalities and dry eye disease are among the most common ocular manifestations of SSc.
2.	Ocular findings in patient systemic sclerosis	Gomes et al.	To evaluate the frequency and characteristics of ocular manifestations in outpatients with systemic sclerosis	A cross-sectional study, 45 patients with systemic sclerosis	Eyelid skin abnormalities and keratoconjunctivitis sicca were the most common ocular findings related to systemic sclerosis
3.	Ocular involvement in	Kreps et al.	to provide an overview of the	A systematic literature review	Case-control data show evidence of SSc-associated

	systemic sclerosis : A systematic literature review, it's not all scleroderma that meets the eye		current level of evidence for SSc-related ocular changes	was conducted using 3 electronic databases, according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines	ocular changes, mostly in terms of dry eye disease and choroidal changes
4.	Dry Eye in Systemic Sclerosis Patients: Novel Methods to Monitor Disease Activity	Gagliano et al.	To investigate ocular DES-related SSc patients and to establish any correlation with the severity of the disease	Retrospective, data from 60 patients with SSc underwent ophthalmic examination	Severe DES occurred in 84% of cases, and was more severe in women. The eyelids were involved in 86.6%.

2.4. Ophthalmic Manifestation of Sjogren syndrome

Sjogren syndrome (SS) which is characterized by ocular and oral dryness resulting from lacrimal and salivary gland dysfunction is one of chronic autoimmune disease and a variety of systemic manifestations may occur, involving virtually any organ system. Sjogren syndrome can be defined as primary or secondary depending on how the disease occurred and its association with other autoimmune diseases (Negrini et al., 2022). The etiology of SS is suspected by genetic predisposition, environmental factors, and hormonal factors. According to Nair and Singh (2017), genetic predisposition to Sjogren's syndrome can be attributed to the alleles within the major histocompatibility complex (MHC) class II gene region, for the environmental factors including infectious agents, particularly viruses, are considered to be involved in the pathogenesis of Sjogren's syndrome, and the hormonal factors suspected role of the estrogen deficiency can be used to explain the predominance of Sjogren's syndrome in women compared to men.

The study from Shahane and Patel (2014), estimated the annual incidence of pSS at 3.9 per 100,000 with higher prevalence noted in women compared to men (6.9 versus 0.5 per 100,000). A cross-sectional population study by Narváez et al. (2020), it is found that the prevalence of pSS in the general population of Spain was 0.25% (95% CI 0.15–0.43) or 1 person in 400. The prevalence and incidence rate in Indonesia has not been done yet. Further research on the epidemiology of SS in Indonesia needs to be done.

Table 4. Summary of Ophthalmic manifestation in SS patients articles reviewed

No	Title	Authors	Objective	Design	Ophthalmic Manifestations
1.	Ocular Manifestations and Burden Related to Sjogren Syndrome : Results of a patient Survey	Saldanha et al.	(1) Compare the burden related to dry eye with systemic symptoms of Sjogren's, (2) Estimate the burden related to ocular treatments, and (3) Compare the impact of dry eye and extraocular manifestations of Sjogren's on various aspects of patient life	Cross-sectional study	Ocular manifestations are common and have a significant impact on patient quality of life. Most patients in this study experienced significant dry eye (keratoconjunctivitis sicca).
2.	Factors associated with severe dry eye in primary Sjogren's syndrome diagnosed patient.	Fernández-Castro et al.	To explore the association of severe or very severe dry eye with extraocular involvement in patients diagnosed with primary Sjögren's syndrome	multicenter cross-sectional study of pSS patients	94% of the patients complained of dry eye and 16% developed corneal ulcer.

3. Conclusion

It can be concluded from the literature that Autoimmune rheumatic diseases (ARDs) are complex and chronic autoimmune diseases that can manifest in other organs including the eye. The most common eye manifestations of ARDs are keratoconjunctivitis sicca (KCS) or dry eye syndrome. Some literature found that keratoconjunctivitis sicca can be found in several patients with ARDs. Early diagnosis and prevention including therapy are needed to prevent the symptoms from becoming severe and avoid vision loss.

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