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DRY EYE IN AUTOIMMUNE DISEASE (RHEUMATOID ARTHRITIS AND SYSTEMIC LUPUS ERYTHEMATOUS)

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Abstract

Background: Autoimmune diseases are systemic disorders that involve many organs, including the eyes, and play an important role in dry eyes. This review aims to elucidate the relationship between dry eye disease (DED) and autoimmune disease.

Methods: This literature review utilized a database from 2020 until 2024. The keywords “dry eye disease”, “autoimmune", “rheumatoid arthritis", and “systemic lupus erythematous” were used to collect 9 journals that had relevant topics.

Results: Autoimmune diseases such as RA and SLE can cause DED through abnormal immune response mechanisms and inflammatory factors that harm the lacrimal glands, conjunctival membranes, corneas, and meibomian glands, resulting in tissue damage and dysfunction. This can lead to a decrease in the volume of tears and faster evaporation, resulting in DED.

Conclusion: This research shows a relationship between the incidence of DED and autoimmune diseases, including RA and SLE. Therefore, even in the absence of specific eye complaints, it is important to conduct examinations related to dry eyes in patients with autoimmune conditions.

Keywords: dry eye disease, autoimmune, rheumatoid arthritis, systemic lupus erythematous

Introduction

Dry eye disease (DED) is a chronic disease of the ocular surface characterized by abnormal tear film composition, tear film instability, and ocular surface inflammation, affecting 5% to 50% of the population worldwide. Autoimmune diseases are systemic disorders with multi-organ involvement, including the eye, and play a significant role in dry eye.[1] Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.[2]

DED can caused by systemic diseases, which include Sjogren syndrome (SS) and other autoimmune or connective tissue disorders such as rheumatoid arthritis and lupus, and thyroid disease.[3] Most of

the inflammatory rheumatic diseases are systemic conditions with several clinical and pathological manifestations outside of the joints. The eye has a distinguished innate and adaptive immune system underpinned by even the presence of the blood–retina barrier and the alymphatic status of its inner structure. The liquid components of the eye, namely the aqueous and vitreous humors, are separated from the blood by tight junctions (occluding junctions or zonulae occludentes), which contribute to maintaining the ideal microenvironment of the eyeball. Inflammatory rheumatic diseases can have destructive effects since as a consequence of vascular abnormality immunoregulatory molecules present in ocular fluids are changed and the environment within the eye becomes modulated.[4]
DED is found in approximately 10-95% of patients with immunity-related disorders; 38-47% of individuals with RA experience DED, while the percentage is 13.4-39.5% for systemic lupus erythematosus (SLE), 95% for SS, and 37-79% for systemic sclerosis (SSc). Patients with autoimmune diseases experience impaired and weak immune systems, leading to abnormal immune responses and disrupted immune regulation. This impairment puts the lacrimal gland, conjunctival membrane, cornea, and meibomian glands at high risk, causing tissue damage and dysfunction. In individuals with autoimmune diseases, a notable proportion of immune cells, predominantly T lymphocytes, infiltrate the lacrimal duct and accessory lacrimal gland. This infiltration leads to autophagy and apoptosis of acinar, ductal, and myoepithelial cells. This disrupts the function of the lacrimal gland and reduces tear secretion.[1]

Methods

After conducting a literature search using the keywords "dry eye disease," "autoimmune," "rheumatoid arthritis," and "systemic lupus erythematosus." in the Pubmed and ScienceDirect databases, we obtained 25,976 articles containing these keywords. In addition, 113 articles were excluded due to duplication issues. Based on publication years from 2020-2024 we obtained 5,309 corresponding articles. Out of all the articles, only 1.959 can be accessed (Figure 1).
Studies were included if they met following criteria: (1) original research articles reporting on the dry eye disease in autoimmune disease (RA and SLE); (2) studies presenting data on risk factor of DED and DED in autoimmune disease; and (3) studies involving human participants with a diagnosis of DED. We did not include research that: (1) were not complete scientific articles; (2) were reviews, letters, or commentaries; (3) were written in languages other than English; (4) were reevaluations of prior or initial studies.

Results

After going through an identification and screening process based on inclusion and exclusion criteria, we collected various literature relevant to this topic, as presented in Table 1.

Table 1. The result of literature searching

No	Author	Year	Study Desain	Group 1	Group 2	Result
1.	Jelle Vehof, et.al	2020	Cross-sectional study	72.636 patients control	7.230 patients with DED	Many systemic disorders showed strong associations with dry eye. High odds ratios were found for autoimmune disorders, such as Sjögren's syndrome (OR 60.3 (27.0–134.5)), rheumatoid arthritis (OR 1.9 (1.8–2.2)), systemic lupus erythematosus (SLE) (OR 4.2 (2.1–8.5)), systemic sclerosis (OR 3.0 (1.4–6.5)), sarcoid (OR 1.9 (1.4–2.7)), and Graves' disease (OR 4.6 (3.2–6.5)).
2.	Weifang Ma, et.al	2020	Cross-sectional study	20 patients control	30 patients with RA	The TBUT of the RA group was significantly less than that of the control group, while the CFS, MS, EMS, and MSS were higher. The TBUT of the symptomatic RA group was significantly less than that of the asymptomatic group, and the CFS was higher. In the active RA group, only the CFS was higher than that of the stable group, and there was no significant difference between

						the two groups for other parameters. Furthermore, there was no significant correlation between the course of RA and the dry eye (P > 0.05).
3.	Nashwa M. Abd-Allah, et.al	2020	Cross-sectional study	42 patients with DED symptoms	-	Of 42 RA patients, 30 had definite dry eye. DAS-28 did not show significant correlation with any of ocular tests for dryness while the duration of RA was significantly positively correlated with Schirmer test and OSS. The biopsy results of RA patients with severe dry eye show no evidence of SS. The severity of dry eye is not correlated with activity of RA but with its duration.
4.	Chun-Shuo Hsu, et.al	2020	Cohort study	5210 patients without SLE	521 patients with SLE	patients with SLE exhibited a significantly prevalence (68.1% vs. 60.5%, P = 0.001) and frequency (median 5.51 vs. 1.71 per 10 years, P <0.001) for outpatient ophthalmologist visits compared with patients without SLE. Risk of dry eye syndrome (adjusted incidence rate ratio [IRR] 4.45, P < 0.001), cataract (adjusted IRR 3.18, P < 0.001), and glaucoma (adjusted IRR 2.23, P = 0.002) were significantly higher in patients with SLE.
5.	Zeiad H. Eldaly, et.al	2020	Cross-sectional study	70 patients with RA	-	Ocular manifestations are significant in patients with RA. The most common ocular manifestation is dry eye. Ocular manifestations are significantly associated with the disease duration and should be expected regardless of disease activity in RA patients.
6.	Kimberley Yu, et.al	2021	Cohort study	535 adult patients with moderate to severe DED	-	More severe DED signs were associated significantly with Sjögren syndrome (mean composite signs severity score 0.52 with disease vs. 0.43 without disease; p < 0.001), facial rosacea (0.47 vs. 0.43; p = 0.002), rheumatoid arthritis (0.47 vs. 0.42; p = 0.002), peripheral artery disease (0.50 vs. 0.43; p < 0.001), and daily smoking history (0.45 vs. 0.43; p = 0.047). Thyroid dysfunction, osteoarthritis, diabetes, irritable bowel syndrome, hypercholesterolemia, hypertension, and hypertriglyceridemia were not associated significantly with DED signs. No conditions were associated significantly with OSDI.
7.	Jose Vicente Garcia-Marques, et al	2022	Cross-sectional study	44 patients control	76 patients with DED	Individuals with systemic rheumatological diseases have a 2.8 times greater risk of developing DED in univariate regression (p = 0.047)
8.	Zhengyu Gu, et.al	2022	Cross sectional study	72 healthy subjects	96 SLE patients without secondary SS	The proportion of SLE patients who met the TFOS DEWS II DED diagnostic criteria was significantly higher than the control group.
9.	Mohamed Salah El-Din, et. al	2022	Cross-sectional study	100 eyes control	100 eyes SLE patients (40 with clinical dry eye and 60 patients without clinical dry eye).	There is significant reduction of tear meniscus dimensions, central corneal thickness and epithelial thickness in SLE patients compared to age-matched controls using AS-OCT.
10.	Dana A. Alrabghi, et.al	2023	Cross-sectional study	541 responden	-	Several risk factors have been significantly associated with adults' dry eye, including low humidity (Pvalue= 0.002), reading, driving, or watching electronic screens for extended durations (P-value=0.019), autoimmune diseases (P-value=0.033), and undergoing eye procedures (P-value-0.013).
11.	Ching-Han Tseng, et.al	2023	Cohort study	5083 patients control	5083 patients with SLE	SLE was associated with increased risks of DED and corneal surface damage.

12.	Yuerong Ren, et.al	2023	Cross-sectional study	30 controls	90 autoimmune rheumatic patients	The autoimmune rheumatic patients showed significant higher OSDI score, fewer basal tear secretion, more severe CFS and conjunctivochalasis than controls.

Risk factor analyses on DED

Dry eye syndrome is a multifactorial disease of the tears and ocular surface that can cause discomfort and visual disturbance, with potential damage to the ocular surface. These symptoms could affect quality of life and activities of daily living.[5] The TFOS DEWS II Epidemiology Report noted that there an extensive risk factors for DED because the tear film and ocular surface from part of the functional unit, which is influenced by lifestyle, environmental conditions, and systemic and ocular disease.[6]

Sociodemographic, behavioral, environmental, and medical factors can play a crucial role in developing DED symptoms, influencing the patient's quality of life.[7] In a cross-sectional study in the Netherlands, independent risk factors associated with DED included female gender, contact lens use, keratoconus, allergic conjunctivitis, Bell's palsy, Graves' disease, glaucoma (treated with drops or surgery), cataract surgery, refractive surgery, autoimmune disorders, liver cirrhosis, psychiatric pathologies, atopy, osteoporosis, sinusitis, and sleep apnea.[8]

In a cross-sectional study conducted by Vehof et.al on 79,866 subjects in the Netherlands, it was found that many systemic disorders showed strong associations with dry eye. High odds ratios were found for autoimmune disorders, such as Sjögren's syndrome (OR 60.3 (27.0–134.5)), rheumatoid arthritis (OR 1.9 (1.8–2.2)), systemic lupus erythematosus (SLE) (OR 4.2 (2.1–8.5)), systemic sclerosis (OR 3.0 (1.4–6.5)), sarcoid (OR 1.9 (1.4–2.7)), and Graves' disease (OR 4.6 (3.2– 6.5)).[8]

A cross-sectional study conducted by Alrabghi et.al on 541 subjects showed that several risk factors were significantly associated with dry eyes in adults, including low humidity (p value= 0.002), reading, driving, or watching electronic screens for extended durations (p value=0.019), autoimmune disease (p value=0.033), and undergoing eye procedures (P-value-0.013).[7] Another study conducted by Marqu´es et.al on 120 Caucasian subjects aged 18 -89 years showed that potential risk factors for DED namely female gender, hours of sleep per day, menopause, anxiety, systemic rheumatological disease, use of anxiolytic drugs, daily medication, ocular surgery, poor food quality, more ultra-processed foods in the diet, not drinking caffeine and hours exposure to AC per day.[9]

Rheumatoid Arthritis-Related Dry Eye

Rheumatoid arthritis (RA) is a common systemic inflammatory disease, characterized by persistent synovitis, systemic inflammation, and autoantibodies (particularly rheumatoid factor and citrullinated peptide). Most relevant studies show that dry eyes were the most frequent ocular complication in RA patients, while others include scleritis, episcleritis, keratitis, etc. Although some patients with RA may develop secondary Sjögren Syndrome (SS) with a prevalence varying from 4% to 50%, dry eye is common even in RA patients without secondary SS.[1]

A study conducted by Weifang et.al on 30 patients with RA and 20 control patients showed that patients with RA exhibited a shorter tear film breakup time (TBUT), severe meibomian gland loss, degenerated blepharon lipids, severe corneal epithelial injury, and obvious changes in the blepharon morphology compared with the control group.[10] Another study conducted by Nashwa et.al on 42 RA patients showed that there were 30 RA patients with dry eyes. The severity of dryness measured by the Schirmer test, TBUT, and OSS didn't show a significant correlation with RA activity assessed by DAS- 28. However, the duration of RA was significantly positively correlated with the Schirmer test and OSS ($p<0.0001$ and $p = 0.003$, respectively), but not with TBUT.[11]

RA has been reported to be associated with a dry eye even in the absence of SS. In a study conducted by Kimberley et.al on 535 patients with DED, it was shown that 7% of patients (38 people) had RA without SS, and these patients were associated with a significantly more severe composite dry eye signs score.[12]

Patients with autoimmune rheumatic diseases often have ocular manifestations, especially ocular surface disorders such as conjunctivitis, keratitis, and dry eye disease. Research conducted by Ren

et.al showed that autoimmune rheumatism patients showed significantly higher Ocular Surface Disease Index (OSDI) scores, less basal tear secretion, and more severe CFS and conjunctivochalasis than controls.[13] Another study conducted by Eldaly et.al also showed that 70% of RA patients had ocular manifestations and 54.7% of them had dry eyes.[14]

Systemic Lupus Erythematous-Related Dry Eye

Around one-third of patients with SLE (Systemic Lupus Erythematosus) experience ocular symptoms. SLE tends to present with multiple factors of induced dry eye, including disorders of the lacrimal gland, cornea, and meibomian glands.[1] In SLE patients, various ocular manifestations have been reported and nearly every structure of the eye from the eyelid in the front to the optic nerve at the back may be involved. DED is considered one of the most common ocular manifestations in SLE patients, and some patients also meet the criteria for secondary Sjögren's syndrome, which is also an autoimmune disease and can lead to self-attack of lacrimal and salivary glands secondary to SLE.[15]

A cohort study conducted by Tseng et.al comparing the risk of DED and corneal surface damage between subjects with and without SLE showed that patients with SLE exhibited significantly greater risk of DED and corneal surface damage, especially for recurrent corneal erosion compared with the control group.[16] Another cohort study conducted by Hsu et.al showed that patients with SLE exhibited a significantly prevalence (68.1% vs. 60.5%, $P = 0.001$) and frequency (median 5.51 vs. 1.71 per 10 years, $P < 0.001$) for outpatient ophthalmologist visits compared with patients without SLE. Risk of dry eye syndrome (adjusted incidence rate ratio [IRR] 4.45, $P < 0.001$), cataract (adjusted IRR 3.18, $P < 0.001$), and glaucoma (adjusted IRR 2.23, $P = 0.002$) were significantly higher in patients with SLE.[17]

Based on a cross-sectional study conducted by Zheng et.al on 96 SLE patients without secondary Sjögren's syndrome (SS) and 72 healthy subjects, the results showed that the proportion of SLE patients who met the TFOS DEWS II DED diagnostic criteria was significantly higher than the control group.[18] A study by Mahmoud et.al showed a significant reduction in tear meniscus dimensions, central corneal thickness, and epithelial thickness in SLE patients compared with age-matched controls using AS-OCT. All tear film parameters were significantly reduced in the SLE group with or without dry eye symptoms compared to the control group.[19]

Discussion

DED is a highly prevalent, multifactorial condition hallmarked by tear film instability, hyperosmolarity, ocular surface damage, and loss of ocular surface homeostasis. Common symptoms include foreign body sensation, visual disturbances, ocular dryness, and irritation, which can result in reduced quality of life, reduced quality of sleep, and large financial and humanistic burdens.[20]

The pathophysiology of initiation and perpetuation of DED is complex and multifaceted. However, local inflammation of the ocular surface plays a key role in the vicious cycle of dry eye, which includes oxidative stress, epithelial cell damage, and increased tear film osmolarity.[20] The TFOS DEWS II Epidemiology Report notes that there are many risk factors for DED due to the tear film and the ocular surface is part of a functional unit, which is influenced by lifestyle, environmental conditions, as well as systemic and ocular diseases.[6]

Autoimmune disorders are a series of chronic immune imbalances and autoimmune-mediated diseases. In general, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and primary Sjogren's syndrome (pSS) are common autoimmune diseases that can involve multiple systems and organs of the body, including joints, skin, lacrimal glands, and ocular. Dry eye is one of the most common eye disorders in patients with autoimmune diseases. The pooled prevalence of DED was 16% in SLE patients, and symptoms as well as abnormal Schirmer tests were found in 26% and 24% of SLE patients, respectively. Furthermore, the proportion of dry eyes in other autoimmune diseases, such as RA and pSS, are 71.4%, and 35%, respectively. Therefore, dry eyes are one of the most common types of complications of autoimmune diseases.[21]

DED in Rheumatoid Arthritis

A cross-sectional study conducted by Marqu´es et.al assess systemic, environmental and lifestyle risk factors for DED in a Mediterranean Caucasian population showed that female gender, hours of sleep per day, menopause, anxiety, Systemic rheumatological diseases, use of anxiolytic drugs, daily medication, eye surgery, poor food quality, more ultra-processed foods in the diet, not drinking caffeine and hours of exposure to air conditioning per day are potential risk factors for DED. In a research study, it was found that individuals with systemic rheumatological diseases have a 2.8 times greater risk of developing DED in univariate regression ($p = 0.047$), but this is not statistically significant in multivariate analysis.[9]

The systemic rheumatoid disease causes increased concentrations of inflammatory cytokines in the ocular air-fluid and conjunctival epithelium, leading to inflammatory infiltration and structural damage to the lacrimal gland.[9] Dry eye is the most common ocular manifestation of RA. RA is the most common autoimmune disorder associated with dry eye.[11] Research conducted by Weifang et.al showed that there were significant differences between the RA group and the control group in TBUT and meibomian gland examinations. This suggests that patients with RA may have varying degrees of meibomian gland dysfunction (MGD). The meibomian glands are the largest sebaceous glands in the human body, and their main function is to secrete sebum and form the outer structure of the tear layer. The meibomian glands play an important role in maintaining the stability of the air layer of the eye.[10]

Both innate and adaptive immunity are involved in the pathogenesis of dry eye. Previous studies based on clinical and laboratory studies have found that Th1 and Th17 cells can modulate the immune response on the ocular surface. The immune system in rheumatic disease sufferers is disturbed, resulting in an abnormal immune response and unbalanced immune regulation. Large immune cells and inflammatory factors harm the lacrimal glands, conjunctival membranes, cornea, and meibomian glands, resulting in tissue damage and dysfunction. A large number of immune cells, the majority of which are T lymphocytes, infiltrate the lacrimal ducts and accessory lacrimal glands in patients with rheumatic and immune diseases, causing autophagy and apoptosis of acinar, ductal, and myoepithelial cells, disruption of lacrimal gland function and decrease. in ocular air secretions.[1]

DED is a common ocular manifestation in rheumatoid arthritis RA, a chronic inflammatory autoimmune disorder. The pathomechanism of DED in RA involves a complex interplay of immunological, inflammatory, and cellular factors. The following is an overview with some relevant references :

- Inflammatory Cytokines: RA is characterized by an overactive immune response, leading to the release of pro-inflammatory cytokines such as TNF-alpha and interleukins (IL-1, IL-6). These cytokines play a role in the inflammation of lacrimal glands and ocular surface tissues, contributing to DED.[22]
- Autoimmunity and Autoantibodies: autoimmune processes in RA can result in the production of autoantibodies such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP). These autoantibodies may contribute to the inflammatory cascade and affect the ocular surface.[23]
- Lymphocytic Infiltration: infiltration of lymphocytes into lacrimal glands and the ocular surface has been observed in RA. This infiltration contributes to the disruption of normal tear film production and stability.[24]
- Mucin Dysfunction: altered mucin expression and function on the ocular surface are associated with DED in RA. Mucins are crucial for maintaining the stability of the tear film, and their dysfunction can lead to increased evaporation and instability.[25]
- Meibomian Gland Dysfunction (MGD): MGD, a common contributor to DED, can be exacerbated in RA. Inflammation in the meibomian glands may lead to alterations in lipid composition, affecting the quality of the tear film.[26]

- Neurological Factors: neurological changes in RA may influence the neural control of lacrimal gland secretion, leading to reduced tear production.[27]

DED in Systemic Lupus Erythematous

SLE disease has the potential to involve many parts of the eye system, including the lacrimal gland and cornea. All around SLE patients suffer from eye involvement, where keratoconjunctivitis sicca or dry eye is the most common manifestation.[16] Research conducted by Hssu et.al showed that the risk of developing dry eye syndrome increases significantly in SLE patients, regardless of gender or age group. Dry eye syndrome is common in SLE patients due to inflammation of the lacrimal glands.[17] As significant risk factors for dry eye, the function of the meibomian glands and the lipid layer worse was found in SLE patients without secondary SS, which caused a decrease in tear volume and more rapid evaporation. SLE tends to appear with a variety of factors causing dry eyes, including abnormalities in the lacrimal glands, cornea, and meibomian glands.[1]

DED is a common ocular manifestation in SLE, a chronic autoimmune disease. The pathomechanism of DED in SLE involves a complex interplay of immunological, inflammatory, and cellular factors. Following is a brief overview with some relevant references :

- Autoimmunity inflammation: SLE is characterized by systemic autoimmune inflammation. This inflammation can extend to the ocular surface, leading to a disruption of the lacrimal functional unit and the tear film.[28]
- Immunological factor: dysregulation of the immune system in SLE involves the production of autoantibodies, including anti-SSA/Ro and anti-SSB/La antibodies. These antibodies can target the lacrimal glands and the ocular surface, contributing to DED.[29]
- Lymphocytic infiltration: infiltration of lymphocytes into the lacrimal glands and the ocular surface is a common finding in SLE. This infiltration can result in glandular dysfunction and reduced tear production.[30]
- Mucin dysfunction: alterations in mucin expression and function on the ocular surface have been observed in SLE. Mucins play a crucial role in maintaining the stability of the tear film, and their dysfunction can contribute to DED.[31]
- Neurological factors: neurological abnormalities in SLE can affect the neural control of lacrimal gland secretion, leading to decreased tear production.[32]
- Medication-induced dry eye: some medications used in the treatment of SLE, such as antimalarial drugs and corticosteroids, can contribute to dry eye symptoms as a side effect.[33]

Most dry eye diagnoses can be missed in patients with autoimmune diseases. Severe dry eyes are common in patients with autoimmune diseases. Additionally, decreased corneal sensation is a feature of severe dry eye that may alter the patient's perception of eye irritation symptoms. Overall, examination for dry eye is important and should be performed in autoimmune patients, even if there are no specific eye complaints.[1] Our study contributes to the growing body of evidence supporting the occurrence of dry eye in autoimmune diseases.

There are several limitations in this research, namely that diversity in methodology and sample size in various studies can cause heterogeneity. Several factors can influence the incidence of DED, such as prolonged exposure to monitor screens, hours of exposure to AC per day, use of contact lenses, food, sleep quality, use of certain medications, and various other factors.

Conclusions

In conclusion, this comprehensive review shows an association between the incidence of DED and autoimmune diseases, including RA and SLE. Although there may be no specific complaints in autoimmune patients, dry eyes should be investigated, especially among those suffering from rheumatoid arthritis or systemic lupus erythematosus.

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The authors declare that they have no conflicts of interest

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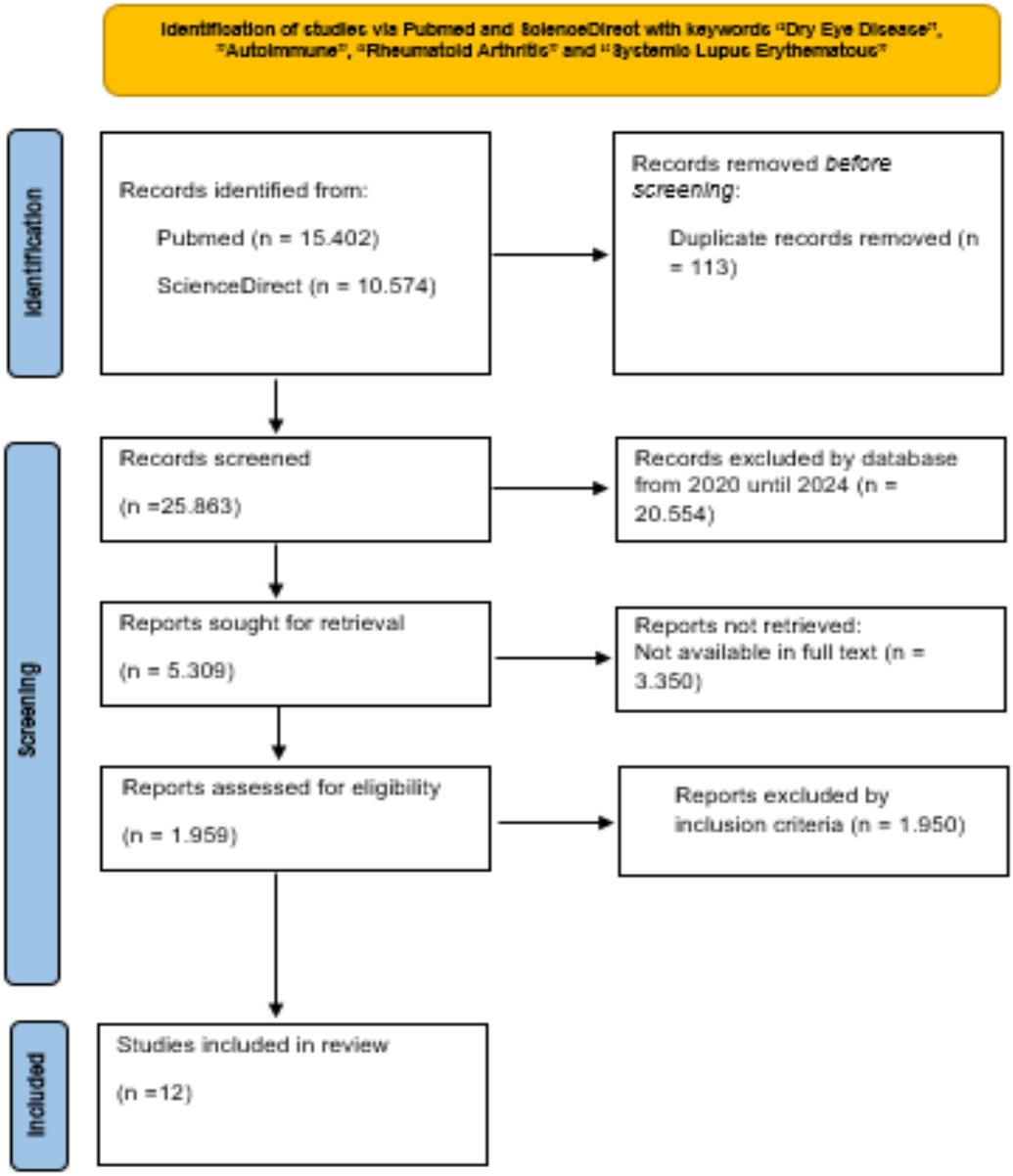

Figure 1. PRISMA flow was used in this literature