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Pathophysiology of dry eye disease and novel therapeutic agents

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Background: Dry eye disease (DED) is one of the most common ocular surface diseases, which is caused by decreased tear production or increased evaporation. It is a growing public health concern as it influences the quality of life and work and visual function.

Aim: This review will update health care professionals about some of the latest research concerning DED and its treatment.

Method: An extensive literature search was conducted on studies that investigated the aetiology, pathophysiology and treatment options of DED.

Results: The search returned 51 articles that were included in this review. All reviewed papers showed that DED is characterised by the loss of homeostasis, resulting in tear film instability, hyperosmolarity and inflammation of the ocular surface.

Conclusion: The causes of DED are complicated and multifactorial but currently, inflammation of the ocular surface is believed to be the main cause. The many different potential topical and systemic treatments have evolved to provide a targeted and effective treatment option from which clinicians can choose. Most of the potential new drugs have been designed to control inflammation and restore the usual or normal quantity of tears.

Contribution: The goal of treatment should be to improve the patient's symptoms and/or may be even the signs if present, and a good relationship between the patient and doctor is crucial for the management plan.

Keywords: dry eye; DEWS; homeostasis; health-related quality of life; ocular surface; hyperosmolarity; inflammation; tear film instability.

Introduction

Dry eye disease (DED) is a relatively common ocular condition with a prevalence ranging from 5% to 50% in the middle-aged and adult population of various age groups across different countries and worldwide.[1,2,3,4,5,6,7,8,9] It has been reported that DED can affect any race and is more common in women than in men. In women at the ages of 50–52 years of age, there is an imbalance between the oestrogen and androgen hormones when menopause occurs.[8,9] This imbalance incites inflammation in the lacrimal gland and ocular surface, disrupting the normal homeostatic mechanism of the lacrimal gland and ocular surface.[4]

Dry eye disease is a disabling disease that can have detrimental effects on both visual function and on an individual' health-related quality of life (HRQL) and can have a significant socio-economic impact.[10,11,12,13,14,15] Because of financial costs and its impacts on quality of life, DED is a true public health care issue as it affects the ability to perform certain crucial daily activities (such as driving, reading, watching television and computer related work), which need visual attention and thus affects the quality of life.[10,11,12,13,14,15]

Dry eye is understood entirely differently today as compared to two decades ago; however the disease itself has not changed, but the understanding has improved. Traditionally, DED was defined as a disorder of the eye caused by the instability of the tear film because of tear deficiency or excessive evaporation and causes damage to the ocular surface.[16] In 2017, the International Dry Eye Workshops[17] (DEWS) of the Tear Film and Ocular Surface Society (TFOS) defined DED as a:

> [*M*]ultifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage and neurosensory abnormalities play etiological roles.

This definition is a minor revision of the International DEWS of the TFOS that was published in 2007.[18] Both the DEWS and DEWS II recognise dry eye as a disease, which suggests that there must also be diagnostic and management criteria.[19] Loss of homeostasis is a term that accounts for a variety of unknown factors.

Homeostasis is currently defined as a self-regulating process by which biological systems maintain stability while adjusting to changing external conditions.[20] It is a dynamic process that can change internal conditions as required to survive external challenges. Tear homeostasis is achieved automatically by the lacrimal function unit (LFU), which consists of the ocular surface structures (cornea, eyelids, conjunctiva and meibomian glands), goblet cells and the lacrimal glands and the neural connections. Even the innate and adaptive immune systems are involved in regulating the ocular surface environment to protect and maintain ocular homeostasis.[20,21,22,23]

The open eye is constantly subjected to dehydrating stress because of evaporation of tears and adverse environmental conditions, such as excessive and prolonged use of visual display unit, low relative humidity and/or excessive wind or air conditioning but is protected from drying up and damage by homeostatic mechanisms that regulate tear secretion and distribution in response to negative feedback cycle signals from the ocular surface. Failure or disruption of homeostatic mechanisms leads to a vicious cycle of hyperosmolarity and instability of the tear film, wetting defects, increased friction and mechanical irritation at the ocular surface, inflammation of the ocular surface and the lacrimal gland and neurosensory abnormalities.[24,25]

With the increasing cases of DED in recent years, the disease is receiving much more attention as it can lead to ocular discomfort that affects the work and quality of life of an individual. Hence, the purpose of this paper was to update health care professionals on the latest research of DED and related treatments.

Methods

A comprehensive literature search was conducted using Medline and ScienceDirect. A total of 210 articles published from 1980 to 2023 were found in relation to dry eye treatment or management. Of these, 51 articles were included in this analysis (see Figure 1). Exclusion criteria included case reports, non-English studies and articles that were unrelated to the primary subject of this review.

Ethical considerations

Ethical clearance to conduct this study was obtained from the University of Limpopo, Research Ethics Committee (No. TREC/196/2015:IR).

Results

The database search identified 210 articles. After removing 33 duplicates, the titles and abstracts of the remaining 177 articles were screened. After the screening, 66 articles were further excluded as they were irrelevant to the topic. The full text of the remaining 60 articles was reviewed. There were a further 60 articles that did not clearly report the pathogenesis of DED, and they were excluded; hence 51 articles were finally included in this review.

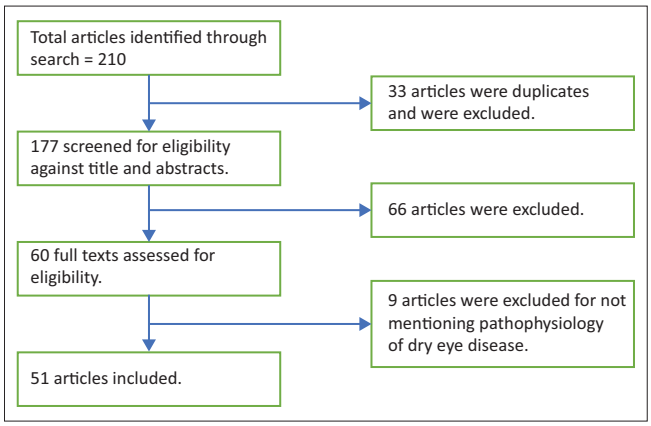

FIGURE 1: Flow diagram of study selection for review.

Discussion

The ocular surface is covered with a specialised stratified epithelium that serves as a barrier to environmental, microbial and inflammatory insults. Conjunctival epithelium has a high density of mucus-producing goblet cells and a variety of resident immune cells that function primarily in antimicrobial defence. The open eye, especially the cornea epithelium, is constantly subjected to extrinsic desiccating stress through evaporation of tears, but the eyes withstand daily environmental challenges from damage by the homeostatic mechanisms that regulate tear secretion and distribution in response to signals from the ocular surface.[6,17,18.21,22] It has been reported that the lacrimal gland and ocular surface epithelia also produce several antimicrobial factors that are present in the tear film to maintain a microenvironment.[24,25]

Dysfunction of more than one tear producing cells and/or glands leads to unstable tear film. Increased tear osmolarity (hyperosmolarity) is the hallmark or core mechanism of DED that activates stress signalling pathways in the ocular surface epithelium and triggers production of innate inflammatory molecules that initiate a vicious cycle that leads to decline in tear function and worse symptoms. The inflammatory cascades induce and contribute to corneal epithelial cell death and loss of goblet cells.

Tear hyperosmolarity is common to all subtypes of DED. Numerous extrinsic and/or intrinsic factors promote an unstable hyperosmolar tear film, which creates a vicious inflammatory cycle that leads to ocular surface damage. Hyperosmolar stress has a direct proinflammatory effect on the ocular surface epithelium as it activates mitogenic-activated protein kinase that stimulates secretion of proinflammatory cytokines and chemokines and induces apoptosis.[24] This is an important source of symptoms and compensatory responses

that ultimately lead to chronic ocular surface damage.[24,25] Stress to the ocular surface (extrinsic or intrinsic) is believed to be the pathogenic triggering mechanism.

Diagnosis of dry eye disease

The common symptoms of DED include gritty feeling, burning or itching in the eyes, foreign body sensation, dryness of eyes, eye redness, pain, excess tearing, photophobia in some cases, blurred vision, fluctuating vision and visual fatigue.[18,26,27,28,29] Sometimes the symptoms are associated with a stringy discharge.[18] However, the cause of DED can be difficult to determine because of seasonal weather conditions, most notably wind and sunshine. It is important that a proper diagnostic approach considers all the factors that contribute to the vicious cycle during the patient's clinical presentation, so that an effective, long-lasting and personalised treatment can be administered.

Dry eye disease has multifactorial aetiologies and pathophysiology that lead to tear instability and signs and symptoms of ocular surface disease. However, there is a poor correlation between the signs and symptoms of DED. The diagnosis of DED is based on the combination of symptoms, signs and clinical test given that any one of these alone could misdiagnose patients. Although clinical history and examination remain the key DED diagnostics, ancillary testing with newer imaging technology has added much-needed resources. Although the invasive tear breakup time (TBUT) and Schirmer test are the traditional testing methods and remain essential components for tear film stability and volume (production), they are subjective and influenced by many factors, such as fluorescein volume.[30] Several non-invasive tests now provide objective measure of the tear film stability, such as tear meniscus height, lipid layer thickness and non-invasive TBUT, tear osmolarity, inflammatory biomarkers and meibomian gland imaging.[31,32]

Ocular surface cell staining is one of the evaluation indexes of the severity of dry eye. When the integrity of ocular surface cells has been damaged, they can be stained to display the defects. The degree and area of staining are related to the severity of the ocular surface damage and can be used to evaluate the barrier function and integrity of epithelial cells.[33] Although fluorescein sodium stain is commonly used in clinical setting, lissamine green and rose Bengal staining are sometimes used.

Treatment for dry eye disease

The treatment of DED is challenging because of a lack of a single clinical assessment and the variation of symptoms. The medical management of DED may range from education, environmental or dietary modifications, artificial tears and topical and/or systematic anti-inflammatory medications.[33,34,35,36,37,38,39,40,41,42]

Artificial tears are the first line of treatment.[33,34,35,36,37,38,39,40,41,42] They are used as lubricant eye drops. Preservatives are added to some artificial tears to reduce the risk of bacterial contamination and to prolong shelf-life, but potentially may become a risk of adverse effects with frequent use for an individual.[28] In moderate-to-severe DED with ocular surface inflammation, anti-inflammatory and immune-suppressive treatments are essential.[26,27] The control and reduction of ocular surface inflammation is another key component of any treatment regime as it is an important contributor to the vicious cycle of DED. Non-steroidal anti-inflammatory drugs (NSAIDs), such as pranoprofen and sodium hyaluronate, can relieve the symptoms of DED by effectively stimulating the secretion of tears.[31] However, NSAIDS are not recommended for patients with mild DED because of low humidity and smoke exposure. Non-steroidal anti-inflammatory drug ointments contain antibiotics (such as erythromycin and bacitracin), which are commonly used for treatment of meibomian gland dysfunction.[39]

Topical corticosteroids (such as prednisolone, fluometholone, dexamethasone and loteprednol etabonate) are effective in the treatment of moderate-to-severe DED for 2–4 weeks as prolonged use may result in complications such as glaucoma, cataract and ocular infection.[18,41] Topical cyclosporine A is an immunosuppressant, which is used for management of ocular surface inflammation of moderate-to-severe DED.[40] Unlike corticosteroids, cyclosporine A requires a longer period to become effective in controlling inflammation.

Vitamin A (retinol) is naturally present in tear film of healthy eyes, and it plays a pivotal role in production of the mucin layer (the innermost layer of the tear film).[26,41] Vitamin A deficiency leads to loss of the mucin layer, which is crucial for a healthy tear film.[41] Vitamin A drops protect the eye from inflammation, toxins and allergens. It has been reported that cyclosporin A eye drops combined with Vitamin A was found to significantly increase the amount of tear secretion in dry eye of rats, prolonged the tear film break up time.[42] Oral supplementation with essential fatty acids (omega-3 and omega-6) has been reported to decrease inflammatory mediators in dry eye patients by improving ocular irritation symptoms and tear stability and can inhibit conjunctival dendritic cell maturation.[39] Omega-3 fatty acid may be suggested nowadays to help relieve DED. As supplementation with commensal microbiota has anti-inflammatory effect in autoimmune conditions (such as diabetes mellitus and inflammatory bowel disease), it is possible that metabolites of commensal bacteria or probiotic could have a therapeutic potential for DED.

Future of dry eye disease treatment

Dry eye disease, whether a result of aqueous deficiency or evaporative disorder, is both a primary and secondary disease because of many different pathological conditions of the eye. It has been treated as an inflammatory process and has benefited many patients; however, there is a need for drugs to target the inflammatory cascade. There are numerous

promising pharmaceutical agents that are being developed for treatment of DED.[43,44,45,46,47,48,49,50,51]

Rebamipide (Otsuka Pharmaceutical Co, Tokyo, Japan) is a mucin secretagogue, which is used for the treatment of gastric mucosal disorders and gastritis.[45] Goblet cell loss in the conjunctiva and decreased mucin of the corneal surface are recognised features of aqueous tear deficiency. Rabamipide is a potential drug to stabilise the mucin component of the tear film. Nerve growth factor has been shown to have mucin secretagogue activity in conjunctival cells and can play a role in corneal wound healing.[44] Human serum albumin (R-Tech Ueno, Tokyo, Japan) is being investigated for the treatment of severe DED.[45,46]

Devices are being developed for dry eye therapy. The Oculoeve neurostimulator device (Oculeve Inc, San Fransisco, CA, USA) will be inserted into the mucosa membrane in the nasal cavity to stimulate tear production.[45,46] The EyeGate II system (EyeGate, MA, USA) I designed to deliver drugs to the conjunctiva and sclera while a small current will be applied to the ocular surface to create an electric field that will mobilise charged particles across the anterior and posterior segment of the eye will also be helpful.[45,46] The drug delivered by this system may achieve higher concentration than it would if delivered topically.

Autologous serum tears provide a natural substitute for many bioactive proteins, vitamins and lipids that are typically present in human tears, and they provide symptomatic relief in many subtypes of DED.[47,48,49]

Dry eye disease is a difficult disease to pin down considering its many possible aetiologies, signs and symptoms. Artificial intelligence promises to potentially aid DED diagnosis and management in the future.[50,51]

Conclusion

The purpose of this review was to update health care professionals of the challenges and management of DED, as lubrication with a variety of artificial tear supplements is palliative and not corrective of the underlying pathology of the disease. An effective approach for the treatment of DED should include assessment of the patients' lifestyle and pharmacological interventions. The goal of treating DED is to improve patients' symptoms and signs while restoring tear homeostasis.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

Both authors, S.D.M. and L.M-L., contributed equally to this work.

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Data availability

The data that support the findings of this study are available on reasonable request from the corresponding author, S.M.

Disclaimer

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References

1. Stapelton F, Alves M, Bunya S. TFOS DEW II epidemiology report. Ocul Surf. 2017;15(3):334–365. https://doi.org/10.1016/j.jtos.2017.05.003
2. McCann P, Abraham AG, Mukhopadhyay A. Prevalence and incidence of dry eye and meibomian gland dysfunction in the United States: A systematic review and meta-analysis. JAMA Ophthalmol. 2022;140(12):1181–1185. https://doi.org/10.1001/jamaophthalmol.2022.4394
3. Farrand KF, Fridman M, Stillman IO. Prevalence of diagnosed dry eye disease in the United States among adults aged 18 years and older. Am J Ophthalmol. 2017;182:90–96. https://doi.org/10.1016/j.ajo.2017.06.033
4. Lemp MA. Advances in understanding and managing dry eye disease. Am J Ophthalmol. 2008;146(3):350–356. https://doi.org/10.1016/j.ajo.2008.05.016
5. Schaumberg DA, Sullivan DA. Dana MR. Epidemiology of dry eye syndrome. Adv Exp Med Biol. 2002;506:989–998. https://doi.org/10.1007/978-1-4615-0717-8_140
6. Yazdani M, Fiskadal J, Chen X. Tear break-up time and dry eye disease severity in a large Norwegian cohort. J Clin Med. 2021;10:a884. https://doi.org/10.3390/jcm10040884
7. Bikbov MM, Kazakbaeva GM, Rakhimova EM. The prevalence of dry eye in very old population. Acta Ophthalmol. 2021;100(3):262–268. https://doi.org/10.1111/aos.14937
8. Garza-Leon M, Valencia-Garza M, Martinez-Leal B. Prevalence of ocular surface disease symptoms and risk factors in group of university students in Monterrey, Mexico. J Ophthal Inflamm Infect. 2016;6(1):a44. https://doi.org/10.1186/s12348-016-0114-z
9. Papas EB. The global prevalence of dry eye disease: A Bayersian view. Ophthalmic Physiol Opt. 2021;41(6):1254–1266. https://doi.org/10.1111/opo.12888
10. Gomes JAP, Santos RM. The impact of dry eye disease treatment on patient satisfaction and quality of life. A review. Ocul Surf. 2019;17(1):9–19. https://doi.org/10.1016/j.jtos.2018.11.003
11. Uchino M, Schaumba DA. Dry eye disease impact on quality of life and vision. Curr Ophthalmol Rep. 2013;1(2):51–57. https://doi.org/10.1007/s40135-013-0009-1
12. Tong L, Waduthantri S, Wong TY. Impact of symptomatic dry eye on vision-related daily activities: The Singapore Malay eye study. Eye. 2010;24(9):1486–1491. https://doi.org/10.1038/eye.2010.67
13. Grubbs JR, Tolleson-Rinehart S, Huynh R. A review of quality of life measures in dry eye questionnaires. Cornea. 2014;33(2):215–218.
14. Yu J, Asche CV, Fairchild CJ. The economic burden of dry eye disease in the United States; a decision free analysis. Cornea. 2011;30(4):379–387. https://doi.org/10.1097/ICO.0b013e3181f7f363
15. Reddy P, Grad O, Rajegalan K. The economic burden of dry eye; a conceptual framework and preliminary assessment. Cornea. 2004;23(8):751–761. https://doi.org/10.1097/01.ico.0000134183.47687.75
16. Lemp MA. Report of the National Eye Institute. Industry Workshop on clinical trials in dry eyes. CLAO J. 1995;21:221–232.
17. Craig JP, Nichols KK, Akpek EK. TFOS DEWS II definition and classification report. Ocul Surf. 2017;15(3):276–283.
18. Tear Film and Ocular Surface Society. The definition and classification Subcommittee of the International Dry Eye Workshop. 2007. Ocul Surf. 2007;5(2):75–92. https://doi.org/10.1016/S1542-0124(12)70081-2
19. Wolffsohn JS, Arita R, Chalmers R. TFOS DEWS II diagnostic methodology report. Ocul Surd. 2017;15(3):539–574.
20. Billman GE. Homeostasis: The underappreciated and far too often ignored central organizing principle of physiology. Front Physiol. 2020;11:a200. https://doi.org/10.3389/fphys.2020.00200
21. Stern ME, Gao J, Siemasko KF. The role of the lacrimal functional unit in the pathophysiology of dry eye. Exp Eye Res. 2004;78(3):409–416. https://doi.org/10.1016/j.exer.2003.09.003
22. Mochizuki M, Sugita S, Kamai K. Immunological homeostasis of the eye. Prog Retin Eye Res. 2013;33:10–27. https://doi.org/10.1016/j.preteyeres.2012.10.002

23. Aragona P, Giannaccare G, Mencucci R. Modern approach to the treatment of dry eye, a complex multifactorial disease: A P.I.C.A.S.S.O. board review. Br J Ophthalmol. 2021;105(4):446–453. https://doi.org/10.1136/bjophthalmol-2019-315747
24. Boudouin C, Messmer ER, Aragona P. Revisiting the vicious cycle of dry eye disease: A focus on the meibomian gland dysfunction. Br J Ophthalmol. 2016;100:300–306. https://doi.org/10.1136/bjophthalmol-2015-307415
25. Brom AJ, de Paiva CS, Chauhan SK. TFOS DEWS II Pathophysiology report. Ocul Surf. 2017;15(3):438–510. https://doi.org/10.1016/j.jtos.2017.05.011
26. Aragona P, Rolando M. Towards a dynamic customized therapy for ocular surface dysfunction. Br J Ophthalmol. 2013;97:955–966. https://doi.org/10.1136/bjophthalmol-2012-302568
27. Mittal R, Patel S, Galor A. Alternative therapies for dry eye disease. Curr Ophthalmol. 2021;32(4):348–361. https://doi.org/10.1097/ICU.0000000000000768
28. Wolffshohn JS, Trave Huarte S, Jones L. Clinical practice patterns in the management of dry eye disease: TFOS international survey. Ocul Surf. 2021;21: 78–86. https://doi.org/10.1016/j.jtos.2021.04.011
29. Clayton JR. Dry eye. N Engl J Med. 2018;379:e19. https://doi.org/10.1056/NEJMc1808906
30. Greiner JV, Finnemare VM, Exford JM. Effect of fluorescein installation methods on the tear film lipid layer. Adv Exp Med Biol. 2002;506:507–512. https://doi.org/10.1007/978-1-4615-0717-8_71
31. Bron AJ, Tomlinson A, Foulks GN. Rethinking dry eye disease: A perspective on clinical implication. Ocul Surf. 2014;12(2 Suppl):S1–S31.
32. Wu Y, Wang C, Wang X. Advances in dry eye disease examination techniques. Front Med. 2022;8:a826530.
33. Wu D, Tong L, Prasath A. Novel therapeutics for dry eye disease. Ann Med. 2023;55(1):1211–1212.
34. Sheppard J, Shen LB, Periman LM. Dry eye disease: Identification and therapeutic strategies for primary care clinicians and clinical specialists. Ann Med. 2023;55(1):241–252.
35. Roucaute E, Huertas-Bello M, Sabater AL. Novel treatment for dry eye syndrome. Curr Opin Pharmacol. 2024;74:a102431. https://doi.org/10.1016/j.coph.2024.102431
36. Kojima T, Dogru M, Kawashima M. Advances in the diagnosis and treatment of dry eye. Adv Retinal Eye Res. 202;78:a100842.
37. Jones L, Downie LE, Roro D. TFOS DEWS II Management and therapy report. Ocul Surf. 2017;15(3):575–628. https://doi.org/10.1016/j.jtos.2017.05.006
38. Hyon JY, Han SB. Dry eye disease and vitamins: A narrative literature review. Appl Sci. 2022;12(9):a4567.
39. Al Mahmood AM, Al-Swailen SA. Essential fatty acids in the treatment of dry eye syndrome: A myth or reality? Saudi J Ophthalmol. 2014;28(3):195–197.
40. Alanazi SA, El-Hiti GA, Al-Baloud AA. Effects of short-term oral vitamin A supplement on the ocular tear film in patients with dry eye. Clin Ophthalmol. 2019;13:599–604. https://doi.org/10.2147/OPTH.S198349
41. Aragona P. Topical cyclosporine: Are all indications justified? Br J Ophthalmol. 2014, 98:1001–1002. https://doi.org/10.1136/bjophthalmol-2013-304728
42. Kim M, Lee Y, Mehra D. Dry eye: Why artificial tears are not always the answer. BMJ Open Ophthalmol. 2021;6:e697.
43. Vickers LA, Gupta PK. The future of dry eye treatment: A glance into the therapeutic pipeline. Ophthalmol Ther. 2015;4:69–78. https://doi.org/10.1007/s40123-015-0038-y
44. Pflegfelder SC, de Paiva CS. The pathophysiology of dry eye disease: What we know and future directions for research. Ophthalmology. 2017;124(11 suppl):s4–s13.
45. Kinoshita S, Awamura S, Oshiden K. Rebamipide (OPC-12759) in the treatment of dry eye: A randomized, double-masked, multicenter, placebo-controlled phase II study. Ophthalmology. 2012;119(12):2471–2478. https://doi.org/10.1016/j.ophtha.2012.06.052
46. Takeji Y, Urashima H, Aoki A. Rebamipide increases the mucin-like glycoprotein production in corneal epithelial cells. J Ocul Pharmacol Ther. 2012;28(3):259–263. https://doi.org/10.1089/jop.2011.0142
47. Celebi AR, Ulusoy C, Mirza GE. The efficancy of autologous serum eye drops for severe dry eye syndrome: A randomized double-blind crossover study. Graefes Arch Clin Exp Ophthalmol. 2014;252(4):619–626. https://doi.org/10.1007/s00417-014-2599-1
48. Liu Y, Hirayama M, Cui X. Effectiveness of autologous serum eye drops combined with punctal plugs for the treatment of Sjogren syndrome-related dry eye. Cornea. 2015;34(10):1214–1220. https://doi.org/10.1097/ICO.0000000000000542
49. Metheetrairut C, Ngowyutagon P, Tunganuntarat A. Comparison of epitheliotrophic factors in platelet-rich plasma versus autologous serum and their treatment efficacy in dry eye disease. Sci Rep. 2022,12(1):a8906. https://doi.org/10.1038/s41598-022-12879-x
50. Zhang Z, Wang Y, Zhang H. Artificial intelligence-assisted diagnosis of ocular surface disease. Front Cell Dev Biol. 2023;11:a1133680. https://doi.org/10.3389/fcell.2023.1133680
51. Shimizu E, Ishikawa T, Tanji M. Artificial intelligence to estimate the tear film breakup time and diagnose dry eye disease. Sci Rep. 2023;13(1):a5822. https://doi.org/10.1038/s41598-023-33021-5