

Ocular surface disease: allergy, biomarkers, diabetes, keratoconus, obesity and nutrition

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Abstract

Ocular surface disease (OSD) encompasses a range of disorders affecting the cornea, conjunctiva, and tear film. This complex condition is influenced by a multitude of factors, including allergy, biomarkers, diabetes, keratoconus, obesity, and nutrition. Recent studies have highlighted the significant impact of allergies on OSD, with allergic conjunctivitis and atopic keratoconjunctivitis contributing to chronic ocular inflammation and tear film instability. Biomarkers, such as inflammatory cytokines and tear film proteins, have emerged as valuable diagnostic tools for OSD. Diabetes has been linked to an increased risk of OSD, with diabetic patients exhibiting altered tear film composition and reduced corneal sensitivity. Keratoconus, a progressive corneal disorder, has also been associated with OSD, with patients experiencing chronic eye irritation and vision disturbances. Obesity and nutrition have been identified as modifiable risk factors for OSD. A diet rich in omega-3 fatty acids and antioxidants may help mitigate OSD symptoms, while obesity has been linked to chronic inflammation and tear film instability. This review aims to provide a comprehensive overview of the complex interplay between OSD and various factors, including allergy, biomarkers, diabetes, keratoconus, obesity, and nutrition. By elucidating these relationships, clinicians can develop more effective treatment strategies and improve patient outcomes for this debilitating condition.

Introduction:

Ocular surface disease refers to a group of conditions that affect the surface of the eye, including dry eye, blepharitis, and meibomian gland dysfunction. These conditions can cause symptoms such as redness, irritation, and blurred vision, leading to discomfort and decreased quality of life for those affected. Proper diagnosis and treatment are essential to managing ocular surface disease and preserving eye health in the long term(1,2).

One key aspect of managing ocular surface disease is identifying the underlying cause of the condition. Dry eye, for example, can be caused by a variety of factors, such as environmental conditions, hormonal changes, or certain medications. By pinpointing the specific cause of the disease, healthcare providers can tailor treatment plans to address the root issue and provide targeted relief for patients. Additionally, ongoing monitoring and follow-up care are crucial in managing ocular surface disease, as symptoms may fluctuate over time and require adjustments to treatment plans (3,4). Regular eye exams and communication with healthcare providers can help ensure that individuals with ocular surface disease receive the most effective care possible.

Factors such as environmental irritants, aging, hormonal changes, and underlying health conditions can all play a role in the development and progression of ocular surface disease. Lifestyle factors, such as prolonged use of digital devices or contact lens wear, can also exacerbate symptoms. By identifying and addressing these contributing factors, healthcare providers can help patients better manage their condition and improve their overall eye health. Additionally, education on proper eye care practices and the importance of regular follow-up appointments can empower patients to take control of their ocular surface disease and prevent future complications(5).

In some cases, treatment may involve prescription eye drops or ointments to reduce inflammation and promote healing of the ocular surface. In more severe cases, procedures such as punctal occlusion or amniotic membrane transplantation

may be necessary to improve symptoms and prevent further damage. It is important for patients to work closely with their healthcare provider to develop a personalised treatment plan that addresses their specific needs and concerns. By taking a proactive approach to managing ocular surface disease, patients can not only find relief from their symptoms but also protect their vision for the long term(6,7).

Importance of identifying biomarkers for early detection and treatment of ocular surface disease cannot be overstated. By identifying biomarkers that indicate the presence of the disease at an early stage, healthcare providers can intervene sooner and implement targeted treatments to prevent progression(7-9). This can lead to better outcomes for patients, reducing the need for more invasive procedures and preserving their vision. Research into biomarkers for ocular surface disease is ongoing, and continued efforts in this area promise to revolutionize the way this condition is managed in the future(10).

One promising avenue of research involves the study of inflammatory markers in tears, which have been shown to be elevated in patients with ocular surface disease. By measuring levels of these markers, healthcare providers may be able to identify at-risk individuals before symptoms manifest, allowing for early intervention. Additionally, advancements in imaging technology have enabled researchers to detect subtle changes in the structure of the eye that may be indicative of disease progression. By combining these approaches, healthcare providers can tailor treatment plans to each individual's specific needs, improving outcomes and quality of life for patients with ocular surface disease(11-13).

II. Allergy and Ocular Surface Disease:

Link between allergies and inflammation of the ocular surface has long been established, with allergic reactions often exacerbating symptoms of ocular surface disease. Understanding this link is crucial in developing effective treatment strategies that address both the underlying allergy and the resulting inflammation. By addressing both components simultaneously, healthcare providers can better

manage symptoms and improve overall quality of life for patients suffering from both allergies and ocular surface disease(14-16).

In addition to exacerbating symptoms, allergies can also increase the risk of developing ocular surface disease in individuals who are already predisposed to these conditions. Allergens such as pollen, dust mites, and pet dander can trigger an inflammatory response in the eyes, leading to redness, itching, and discomfort. This inflammation can then further compromise the health of the ocular surface, potentially leading to chronic conditions such as dry eye syndrome or conjunctivitis(17). Therefore, it is essential for healthcare providers to not only treat the symptoms of allergies and ocular surface disease but also to address the underlying causes in order to prevent further complications and improve long-term outcomes for patients(18-20).

Common symptoms of ocular allergies and their impact on overall eye health include watery eyes, swollen eyelids, and blurred vision. These symptoms can significantly affect a person's quality of life and ability to perform daily tasks. In addition, the constant irritation from allergies can weaken the eye's natural defense mechanisms, making it more susceptible to infections and other complications. By properly managing allergies and addressing the root causes, healthcare providers can help patients maintain healthy eyes and improve their overall well-being (21-23).

It is important for healthcare providers to educate patients on how to avoid allergens and to recommend appropriate treatments such as antihistamine eye drops or allergy medications. By taking proactive steps to manage ocular allergies, patients can experience relief from symptoms and reduce the risk of long-term damage to their eyes. Ultimately, addressing ocular allergies can lead to improved eye health and a better quality of life for patients (24-25).

Treatment options for managing ocular surface disease related to allergies may also include using artificial tears to help lubricate the eyes and reduce discomfort. In severe cases, patients may benefit from prescription medications such as

corticosteroids or immunomodulators to control inflammation and immune responses. Additionally, lifestyle modifications such as wearing sunglasses outdoors and keeping windows closed during high pollen seasons can help prevent allergens from exacerbating symptoms. By working closely with their healthcare providers and following personalized treatment plans, patients can effectively manage ocular allergies and maintain optimal eye health (26-28).

It is also important for patients to regularly clean their contact lenses and switch to daily disposables if they are prone to allergies. Avoiding rubbing the eyes and washing hands frequently can also help prevent irritation and infection. In some cases, allergen immunotherapy may be recommended to desensitise the immune system to specific triggers. Overall, staying proactive and informed about managing ocular allergies is key to maintaining clear vision and comfort (29-31).

III. Biomarkers for Ocular Surface Disease:

Biomarkers are measurable indicators that can help identify and monitor the presence of ocular surface disease. These can include specific proteins, enzymes, or genetic markers that are found in the tears or tissues of the eye. By analyzing these biomarkers, eye care professionals can better understand the underlying causes of the disease and tailor treatment plans accordingly. Using biomarkers can also help track disease progression and response to therapy, providing valuable information for both patients and doctors. In summary, biomarkers play a crucial role in diagnosing and managing ocular surface disease, leading to improved outcomes for those affected (32-34).

Furthermore, ongoing research in the field of biomarkers for ocular surface disease is continuously uncovering new markers that may further enhance diagnostic accuracy and treatment efficacy. By identifying and validating these biomarkers, clinicians can potentially revolutionise the way in which ocular surface diseases are diagnosed and managed. Additionally, the development of more targeted therapies based on specific biomarkers holds promise for personalised

medicine in the field of ophthalmology. As the field continues to advance, the integration of biomarker analysis into routine clinical practice may become standard, ultimately leading to better outcomes and quality of life for patients with ocular surface disease (35-37).

Current research on potential biomarkers for early detection and treatment of ocular surface disease is crucial for improving patient care and outcomes. By identifying specific biomarkers that are indicative of disease progression or response to treatment, clinicians can tailor interventions to individual patients, maximizing effectiveness and minimizing side effects. With ongoing research and advancements in technology, the future of ophthalmology looks promising in its ability to provide personalized and targeted care for those suffering from ocular surface diseases (38).

This personalised approach not only improves patient outcomes but also enhances the overall quality of care provided. Additionally, the use of biomarkers in the early detection of ocular surface diseases can lead to more timely interventions, potentially preventing further damage to the eye (39). As researchers continue to uncover new biomarkers and refine existing ones, the field of ophthalmology is poised to make significant strides in the diagnosis and treatment of these conditions. Collaborations between clinicians, researchers, and technology experts will be essential in driving these advancements forward and ultimately improving the lives of patients affected by ocular surface diseases (40,41).

By identifying biomarkers that can accurately predict the progression of ocular surface diseases, healthcare providers can tailor treatment plans to individual patients, leading to more effective management of their condition. This personalized approach can result in better outcomes and quality of life for those affected by these diseases. With ongoing research and collaboration, the future of ophthalmology looks promising in its ability to provide targeted and timely interventions for patients with ocular surface diseases (42,43).

In addition to personalised treatment plans, advancements in technology and surgical techniques are also contributing

to improved outcomes for patients. The development of new medications, such as anti-inflammatory drugs and immunomodulators, has shown promising results in managing symptoms and slowing the progression of ocular surface diseases. Furthermore, the use of minimally invasive surgical procedures, such as corneal transplants and amniotic membrane grafts, has revolutionised the field of ophthalmology and provided new options for patients with severe cases of these diseases. As research continues to expand our understanding of ocular surface diseases, the potential for even more innovative and effective treatments continues to grow (44,45).

Diabetes and Ocular Surface Disease:

Impact of diabetes on the ocular surface and risk of developing ocular surface disease is a topic of ongoing research and clinical interest. Patients with diabetes are at a higher risk for developing ocular surface diseases such as dry eye syndrome, diabetic retinopathy, and corneal neuropathy. The impact of diabetes on the ocular surface can lead to chronic inflammation, decreased tear production, and increased risk of infection. Early detection and management of ocular surface diseases in diabetic patients are essential to prevent vision loss and improve overall eye health (46).

Management strategies for individuals with diabetes to prevent ocular surface disease include regular eye exams, maintaining optimal blood sugar levels, using artificial tears or prescription eye drops as needed, and practicing good eyelid hygiene. It is also important for diabetic patients to follow a healthy diet, exercise regularly, and quit smoking to reduce their risk of developing ocular surface diseases (43-46). By taking proactive measures and working closely with their healthcare team, individuals with diabetes can protect their vision and maintain good eye health for years to come (47).

Regular eye exams are crucial for individuals with diabetes to monitor their eye health and catch any potential issues early on. These exams can help detect conditions such as diabetic retinopathy, glaucoma, and cataracts before they progress

and cause irreversible damage to the eyes. By staying on top of their eye health, diabetic patients can ensure that any problems are addressed promptly and effectively, ultimately preserving their vision and overall quality of life. So, it is vital for individuals with diabetes to prioritize regular eye exams as part of their overall healthcare routine(46,47).

Keratoconus and Ocular Surface Disease:

Keratoconus is a progressive eye condition that causes the cornea to thin and bulge outward, resulting in distorted vision. This can lead to discomfort, sensitivity to light, and difficulty with daily tasks such as driving or reading. Additionally, keratoconus can also increase the risk of developing ocular surface diseases, such as dry eye syndrome. Proper management and treatment of these conditions are essential to maintaining good eye health and preventing further complications. Patients with diabetes should be especially vigilant in monitoring their eye health and seeking timely care from an eye care professional if any symptoms or changes in vision occur. By staying proactive and informed, individuals can take control of their eye health and preserve their vision for years to come(48,49).

Common symptoms of keratoconus-related ocular surface disease include blurry or distorted vision, increased sensitivity to light, and difficulty seeing at night. It is important for individuals experiencing these symptoms to seek prompt evaluation and treatment from an eye care specialist to prevent any further progression of the disease (50). Regular eye exams and proper management of underlying conditions, such as diabetes, are key components in preserving eye health and overall vision. By staying proactive and informed about their eye health, individuals can take the necessary steps to protect their vision and maintain a high quality of life (51,52).

Treatment options for managing ocular surface disease related to keratoconus may include the use of special contact lenses, such as scleral lenses, to improve vision and reduce discomfort. In more severe cases, surgical interventions like corneal cross-linking or corneal transplants may be necessary to stabilize the cornea and improve vision. It is important for individuals

with keratoconus to work closely with their eye care specialist to determine the best treatment plan for their specific condition. By following their doctor's recommendations and staying diligent with their eye care regimen, individuals can better manage the effects of keratoconus and preserve their vision for years to come (53,54).

Obesity and Nutrition in Ocular Surface Disease:

Link between obesity, poor nutrition, and ocular surface disease has been increasingly recognized in recent years. Research has shown that obesity and a diet high in unhealthy fats and sugars can contribute to inflammation and oxidative stress in the body, including on the ocular surface. This can lead to conditions such as dry eye syndrome, blepharitis, and even corneal damage (55). Therefore, maintaining a healthy weight and eating a balanced diet rich in vitamins and antioxidants is crucial for preventing and managing ocular surface disease. Patients should also work with their eye care provider to develop a comprehensive treatment plan that addresses both the underlying causes and symptoms of their condition (56,57).

-By reducing inflammation and oxidative stress through proper nutrition, individuals can help protect their eyes from potential damage and discomfort. Additionally, staying at a healthy weight can also reduce the risk of developing systemic conditions that may impact eye health. Overall, taking proactive steps to care for one's overall health can have a significant impact on the prevention and management of ocular surface disease (58,59).

Nutritional recommendations for individuals with ocular surface disease to improve eye health include incorporating foods rich in antioxidants, omega-3 fatty acids, and vitamins A, C, and E into their diet. Consuming foods such as leafy greens, nuts, seeds, and fatty fish can help support eye health and reduce inflammation. It is also important to stay hydrated and limit the intake of processed foods and sugars, as these can exacerbate symptoms of ocular surface disease. Working with a healthcare provider or nutritionist to develop a personalized dietary plan can be beneficial in managing the condition and promoting overall well-being (60-62).

Conclusion:

In conclusion, incorporating a variety of nutrient-dense foods into one's diet can play a significant role in maintaining eye health and managing ocular surface disease. By focusing on foods high in antioxidants, omega-3 fatty acids, and vitamins A, C, and E, individuals can support their eye health and reduce inflammation. Additionally, staying hydrated and avoiding processed foods and sugars can help alleviate symptoms of the condition. Consulting with a healthcare provider or nutritionist to create a personalized dietary plan is recommended for optimal management of ocular surface disease and overall well-being(63-65).

Implications of identifying biomarkers for early detection and treatment of ocular surface disease include the potential for more targeted and effective interventions. By identifying specific biomarkers associated with the disease, healthcare providers can detect it at earlier stages and tailor treatment plans accordingly (66-68). This personalized approach may lead to improved outcomes and quality of life for individuals living with ocular surface disease. Research in this area is ongoing, with the hope of developing more precise diagnostic tools and therapies in the future. Ultimately, the goal is to enhance the overall management of ocular surface disease and provide patients with better outcomes. By pinpointing biomarkers early on, healthcare professionals can intervene sooner and potentially prevent the progression of the disease. This proactive approach not only benefits individuals by improving their quality of life but also reduces healthcare costs associated with more advanced stages of the condition. As research continues to advance, the futu(69-72).

Future research directions for improving management of ocular surface disease include exploring new technologies like artificial intelligence and machine learning to analyze biomarkers more efficiently and accurately. Additionally, investigating the role of genetics in the development of ocular surface disease may lead to personalized treatment plans based on individual genetic predispositions. Collaborations between researchers, healthcare professionals, and pharmaceutical companies will also be crucial in developing

innovative therapies and medications to target specific underlying causes of the disease. Overall, the ongoing efforts in research and collaboration hold great potential for revolutionizing the way ocular surface disease is managed and treated in the future.

Reference:

Li X, Rabinowitz YS, Rasheed K, Yang H. Longitudinal study of the normal eyes in unilateral keratoconus patients. *Ophthalmology*. 2004.

Zadnik K, Barr JT, Gordon MO, Edrington TB. Biomicroscopic signs and disease severity in keratoconus. Collaborative longitudinal evaluation of Keratoconus (CLEK) Study Group. *Cornea*. 1996.

Hashemi H, Heydarian S, Hooshmand E, Saatchi M, Yekta A, Aghamirsalim, et al. The prevalence and risk factors for Keratoconus: a systematic review and Meta-analysis. *Cornea*. 2020.

Bak-Nielsen S, Ramlau-Hansen CH, Ivarsen A, Plana-Ripoll O, Hjortdal J. Incidence and prevalence of keratoconus in Denmark - an update. *Acta Ophthalmol*. 2019.

Hashemi H, Heydarian S, Yekta A, Ostadimoghaddam H, Aghamirsalim M, Derakhshan A, et al. High prevalence and familial aggregation of keratoconus in an iranian rural population: a population-based study. *Ophthalmic Physiol Opt*. 2018.

Santodomingo-Rubido J, Carracedo G, Suzaki A, Villa-Collar C, Vincent SJ, Wolffsohn JS. Keratoconus: an updated review. *Cont Lens Anterior Eye*. 2022.

Ahuja P, Dadachanji Z, Shetty R, Nagarajan SA, Khamar P, Sethu S, et al. Relevance of IgE, allergy and eye rubbing in the pathogenesis and management of Keratoconus. *Indian J Ophthalmol*. 2020.

Katipoğlu Z, Mirza E, Oltulu R, Katipoğlu B. May Monocyte/HDL cholesterol ratio (MHR) and Neutrophil/Lymphocyte ratio (NLR) be an Indicator of inflammation and oxidative stress in patients with Keratoconus? *Ocul Immunol Inflamm*. 2020.

Oltulu R, Katipoğlu Z, Gündoğan AO, Mirza E, Belviranlı S. Evaluation of inflammatory biomarkers in patients with keratoconus. *Eur J Ophthalmol*. 2022.

Navel V, Malecaze J, Pereira B, Baker JS, Malecaze F, Sapin V, et al. Oxidative and antioxidative stress markers in keratoconus: a systematic review and meta-analysis. *Acta Ophthalmol*. 2021.

Cross CE, Halliwell B, Borish ET, Pryor WA, Ames BN, Saul RL, et al. Oxygen radicals and human disease. *Ann Intern Med*. 1987.

Marseglia L, Manti S, D'Angelo G, Nicotera A, Parisi E, Di Rosa G, et al. Oxidative stress in obesity: a critical component in human diseases. *Int J Mol Sci*. 2014.

de Carvalho Vidigal F, Guedes Cocate P, Gonçalves Pereira L. De Cássia Gonçalves Alfenas

R. The role of hyperglycemia in the induction of oxidative stress and inflammatory process. *Nutr Hosp*. 2012.

Peluso I, Morabito G, Urban L, Ioannone F, Serafini M. Oxidative stress in atherosclerosis development: the central role of LDL and oxidative burst. *Endocr Metab Immune Disord Drug Targets*. 2012.

Almarhoun M, Biswas L, Alhasani RH, Wong A, Tchivelekete GM, Zhou X, et al. Overexpression of STARD3 attenuates oxidized LDL-induced oxidative stress and inflammation in retinal pigment epithelial cells. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2021.

Saccà SC, Cutolo CA, Ferrari D, Corazza P, Traverso CE. The Eye, oxidative damage and polyunsaturated fatty acids. *Nutrients*. 2018.

Wojakowska A, Pietrowska M, Widlak P, Dobrowolski D, Wylegała E, Tarnawska D. Metabolomic signature discriminates normal human cornea from Keratoconus-A Pilot GC/MS study. *Molecules*. 2020.

Poustchi H, Eghtesad S, Kamangar F, Etemadi A, Keshtkar AA, Hekmatdoost A, et al. Prospective Epidemiological Research Studies in Iran (the PERSIAN Cohort Study): Rationale, objectives, and design. *Am J Epidemiol*. 2018.

World Health Organization. World health organization fact sheet N311: obesity and overweight. Geneva, Switzerland: World Health Organization; 2018 Feb.

Rabinowitz YS, Rasheed K. KISA % index: a quantitative videokeratography algorithm embodying minimal topographic criteria for diagnosing keratoconus. *J Cataract Refract Surg*. 1999.

Villavicencio OF, Gilani F, Henriquez MA, Izquierdo L, Ambrósio RR. Independent population validation of the Belin/Ambrosio enhanced ectasia display: implications for keratoconus studies and screening. *Int J Keratoconus Ectatic Corneal Dis*. 2016;3(1):1-8.

Bamdad S, Sedaghat MR, Yasemi M, Vahedi A. Sensitivity and specificity of Belin Ambrosio enhanced Ectasia Display in early diagnosis of Keratoconus. *J Ophthalmol*. 2020.

World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1, diagnosis and classification of diabetes mellitus. World health organization; 1999.

Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP). Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*. 2001.

Hashemi H, Khabazkhoob M, Yazdani N, Ostadimoghaddam H, Norouzirad R, Amanzadeh K, et al. The prevalence of keratoconus in a young population in Mashhad, Iran. *Ophthalmic Physiol Opt*. 2014.

Aydin Kurna S, Altun A, Gencaga T, Akkaya S, Sengor T. Vision related quality of life in patients with keratoconus. *J Ophthalmol*. 2014.

Mahdaviazad H, Bamdad S, Roustaei N, Mohaghegh S. Vision-Related Quality of Life in Iranian patients with Keratoconus: National Eye Institute vision function Questionnaire-25. *Eye Contact Lens*. 2018.

Chan E, Chong EW, Lingham G, Stevenson LJ, Sanfilippo PG, Hewitt AW, et al. Prevalence of Keratoconus based on

Scheimpflug Imaging: the Raine Study. *Ophthalmology*. 2021.

Shirvani M, Soufi F, Nouralishahi A, Vakili K, Salimi A, Lucke-Wold B, et al. The diagnostic value of neutrophil to lymphocyte ratio as an effective biomarker for Eye Disorders: a Meta- analysis. *Biomed Res Int*. 2022.

Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, et al. Oxidative stress: Harms and benefits for Human Health. *Oxid Med Cell Longev*. 2017.

Grieve K, Georgeon C, Andreiuolo F, Borderie M, Ghoubay D, Rault J, et al. Imaging microscopic features of Keratoconic corneal morphology. *Cornea*. 2016.

Hashemi, H.; Heydarian, S.; Hooshmand, E.; Saatchi, M.; Yekta, A.; Aghamirsalim, M.; Valadkhan, M.; Mortazavi, M.; Hashemi, A.; Khabazkhoob, M. The Prevalence and Risk Factors for Keratoconus: A Systematic Review and Meta-Analysis. *Cornea* **2020**, 39, 263–270.

Anitha, V.; Vanathi, M.; Raghavan, A.; Rajaraman, R.; Ravindran, M.; Tandon, R. Pediatric keratoconus – Current perspectives and clinical challenges. *Indian J. Ophthalmol*. **2021**, 69, 214–225.

Chan, E.; Chong, E.W.; Lingham, G.; Stevenson, L.J.; Sanfilippo, P.G.; Hewitt, A.W.; Mackey, D.A.; Yazar, S. Prevalence of Keratoconus Based on Scheimpflug Imaging: The Raine Study. *Ophthalmology* **2021**, 128, 515–521.

Woodward, M.A.; Blachley, T.S.; Stein, J.D. The association between sociodemographic factors, common systemic diseases, and keratoconus an analysis of a nationwide health care claims database. *Ophthalmology* **2016**, 123, 457–465.e2.

Gordon-Shaag, A.; Millodot, M.; Shneor, E.; Liu, Y. The genetic and environmental factors for keratoconus. *BioMed Res. Int*. **2015**, 2015, 795738.

Lass, J.H.; Lembach, R.G.; Park, S.B.; Hom, D.L.; Fritz, M.E.; Svilar, G.M.; Nuamah, I.F.; Reinhart, W.J.; Stocker, E.G.; Keates, R.H.; et al. Clinical Management of Keratoconus: A Multicenter Analysis. *Ophthalmology* **1990**, 97, 433–445.

Wang, Y.; Rabinowitz, Y.S.; Rotter, J.I.; Yang, H. Genetic

epidemiological study of keratoconus: Evidence for major gene determination. *Am. J. Med. Genet.* **2000**, 93, 403–409.

Hawkes, E.; Nanavaty, M.A. Eye Rubbing and Keratoconus: A Literature Review. *Int. J. Keratoconus Ectatic Corneal Dis.* **2014**, 3, 118–121.

Bawazeer, A.M.; Hodge, W.G.; Lorimer, B. Atopy and keratoconus: A multivariate analysis. *Br.*

J. Ophthalmol. **2000**, 84, 834–836.

Pedrotti, E.; Demasi, C.L.; Fasolo, A.; Bonacci, E.; Brighenti, T.; Gennaro, N.; Ferrari, M.; Marchini, G. Obstructive Sleep Apnea Assessed by Overnight Polysomnography in Patients With Keratoconus. *Cornea* **2018**, 37, 470–473.

Sharif, K.W.; Casey, T.A.; Coltart, J. Prevalence of mitral valve prolapse in keratoconus patients. *J. R. Soc. Med.* **1992**, 85, 446–448.

Beardsley, T.L.; Foulks, G.N. An Association of Keratoconus and Mitral Valve Prolapse. *Ophthalmology* **1982**, 89, 35–37.

Alio, J.L.; Vega-Estrada, A.; Sanz, P.; Osman, A.A.; Kamal, A.M.; Mamoon, A.; Soliman, H. Corneal morphologic characteristics in patients with down syndrome. *JAMA Ophthalmol.* **2018**, 136, 971–978.

Ottas, A.; Fishman, D.; Okas, T.L.; Püssa, T.; Toomik, P.; Märtson, A.; Kingo, K.; Soomets, U. Blood serum metabolome of atopic dermatitis: Altered energy cycle and the markers of systemic inflammation. *PLoS ONE* **2017**, 12, e0188580.