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Review Article

A Comprehensive Review on Dry Eye Syndrome

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ABSTRACT

Dry Eye Disease (DED) is a multifactorial condition of the ocular surface characterized by a loss of homeostasis of the tear film. It manifests with symptoms of discomfort, visual disturbance, and tear film instability. Understanding the complexities of DED is crucial for effective diagnosis and management. This review aims to provide a comprehensive overview of DED, including its causes, current treatments, and future research directions. It addresses the impact of surgical interventions, non-pharmacological therapies, complementary and alternative medicine (CAM), and the overall quality of life and economic burden associated with DED. A thorough literature review was conducted, analyzing recent studies, clinical trials, and meta-analyses related to DED. The sources included peer-reviewed journals, clinical guidelines, and evidence-based practices. The results indicate that DED is associated with various etiological factors, including surgical interventions (e.g., refractive surgery, lid surgery, cataract surgery), medications, and environmental influences. These factors contribute to tear film instability and ocular surface inflammation. In terms of treatments, surgical procedures can lead to iatrogenic DED, requiring advanced treatments like anti-inflammatory medications and nerve-stimulating agents. Non-pharmacological therapies such as warm compresses, lid massages, and punctual occlusion have proven effective in managing DED symptoms. CAM therapies, including omega-3 supplements, cyclosporine, and ginkgo biloba, show varying degrees of efficacy in alleviating DED, though the literature on CAM is limited by inconsistent results. DED significantly impacts daily activities, causing stress and anxiety, and incurs substantial economic costs related to treatment and productivity losses. Effective strategies for prevention and management include patient education, eyelid hygiene, and environmental modifications. Collaborative care between ophthalmologists and primary care physicians is essential for early detection and management.

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In conclusion, DED is a complex condition requiring a multifaceted management approach. Future research should focus on developing non-invasive diagnostic tools and exploring innovative treatments. Understanding DED's pathophysiology is key to improving patient outcomes and reducing the economic burden.

INTRODUCTION

Moreover, the multifactorial cause of lacrimal-edge disease and of dry eye syndrome continues today to be the subject of intense and extensive studies, and at present, the involvement of essential tear defect, tear film stability, ocular surface health, ocular surface inflammation, and nerve damage sensory is generally well recognized.[1] However, the relevance of the factor of the nervous one of the flights of li plethatus has been the subject of the incorrect, not well understood studies together, with the absence of official guidelines and validation tools, leads to a condition of great underdiagnosis and lack of management of the disease.[2,3] Dry eye is a disease of the ocular surface, which is multifactorial, synergistic, and characterized by an extensive chronic symptom of tearing, burning, stinging, and visual affections.[4] In addition, despite the evident lesion of the interpalpebral ocular surface, in these patients, the term dry eye is incorrectly associated with the loss of the sensation of tearing, according to the primary importance of the lacrimal component, a subject on which only in recent years in-depth studies and interest have gone.[5] In particular, the awareness of the existence of the lacrimal functional unit has highlighted how the ocular surface is dominated by a series of constitutive elements that, through integrated anatomical, functional, and neuronal pathways, influence the lacrimal production and the dynamics of tear film distribution.[6] These include conjunctiva, cornea, lids, sensory fibers, tear glands, lacrimal glands, the sensitive trigeminal nerve, the palpebral conjunctiva, and the third instar Lacrimale.[7]

Causes and Risk Factors

Dry Eye Syndrome (DES) is a multifactorial disorder that can be caused by different factors alone or in combination with one another, affecting different layers of the tear film.[8] After the substantial increase in cases in recent years, it can be hypothesized that the daily use of electronic devices exerts an important pathogenetic weight in the genesis of the pathology.[9] Indeed, working hours in front of a computer and the use of Image and Sound Technologies (TSI) is the precise in girls, further increasing the pre-existing prevalence. Finally, the lack of outdoor activities (fundamental for better tear quality, usually performed by boys and men) responded to actual lifestyle habits and social requirements that are increasingly aimed at indoor activities with frequent use of TSI. Finally, smoking, an often-underestimated factor, must also be associated with a significant reduction in tear secretion. [10,11] Dry eye syndrome is a multifactorial disease of the tears and ocular surface occurring associated with increased osmolarity of the tear film and inflammation of the ocular surface.[12] The resulting signs and symptoms include discomfort, visual

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disturbances, tear film instability, and potentially damaging ocular surface changes. It is accompanied in the majority of cases by an unstable tear film and inflammation of the ocular surface. Advanced age, female sex, Asian race, smoking, contact lens wear, and various systemic medications are established risk factors for dry eyes.[13] The most glaring lifestyle risk factor is the excessive use of electronic devices in daily activities. In addition to overburning or intense use of the eyes (characteristic of all devices with backlighting), when one reads from these devices, we observe changes in ocular physiology such as reduced blink frequency that facilitates corneal contact and blurry vision. Other causes of Dry Eye Syndrome (DES) may include lack of adequate tears and the quality of the tears that are produced (mixed causes).[14]

Signs and Symptoms

Dry Eye Symptoms: The Ocular Surface Disease Index (OSDI), a questionnaire that is widely used in clinical practice and clinical research, was able to assess dry eye in the general population.[15] Dry eye specialists approved the OSDI, called the Symptom Assessment in Dry Eye (SANDE), the Dry Eye Questionnaire (DEQ), and Visual Analogue Scales (VAS) for some specific symptoms or general evaluations as parameters for clinical studies.[16] It is preferable to use a double scoring survey that evaluates symptoms separately from the patient's experience for clinical practice and in clinical studies.[17] For screening in the general population, it is important for the questionnaire to have a good discriminant function. In short, several survey tools are used to measure and diagnose subjective symptoms of dry eye, including the SCCAT questionnaire, the 25-item NIH Patient-Reported Outcomes Measurement Information System, the Vision-specific TAQ, and the Giselle questionnaire. [18,19] Dry Eye Signs: - Tear film instability - Hyperosmolarity - Ocular surface inflammation and damage, Dry eye is associated with the following signs and symptoms.[20] In order to confirm the diagnosis of dry eye, not only the presence of these symptoms and signs but also the presence of tear film instability and hyperosmolarity, ocular surface inflammation (as shown by positive staining), and epithelial cell marker apoptosis and mucin expression abnormalities should be considered. [21,22,]

Diagnosis and Evaluation

4.2. QRBUT Test. The QRBUT is a novel noninvasive quantitative tear film stabilometry (QRBUT) technique that utilizes high-resolution vertically integrated interferometry of polarized light with custom antireflective coatings to measure corneal polarization stability.[23] Gauthier et al. evaluated the QRBUT technique in normal and DED patients and found group differences in QRBUT between normal and all DED subgroups with significant correlation with corneal and conjunctival staining. They also found that QRBUT had a better sensitivity at detecting the difference between those with severe disease and those that had reported more severe symptoms.[24] Developed using a protocol of multiple approaches, they found the tear film is less stable under the "least comfortable" conditions seen in more severe conditions of dry eye.[25] Current Approaches. The current approach to diagnosing clinicians relies on subjective patient reports and physical examinations. The modification of the standard Schirmer's or TBUT test used to detect DED has not provided the sensitivity and specificity necessary, but better results have been obtained using different types of tear film break up tests, including instillation of lipid or water solutions; instillation of fluorescein, lissamine green, and rose bengal dyes; and phenol red threads.[26]More advanced tests include the tear prism and NIBUT, the fluorescent photobleaching test, assessment of spontaneous blink rate, ocular

surface sensitivity measurements, and tests for mucin production or goblet cells with impression cytology, immunofluorescence of goblet cell membranes or tear mucin components, as well as immunostaining of goblet cell conjunctival conjunctiva. Although clinical tests are used to diagnose dry eyes and to evaluate their severity, none of the clinical tests can differentiate between the type of dry eyes.[27]

Classification and Subtypes

Based on the generic symptom profile resemblance, it was defined the 2007 NEI/Industry Dry Eye Workshop (DEWS) classification (ocular surface disease index (OSDI) questionnaire), a worldwide accepted classification approach (clinical diagnostic score); however, Chen and associates proposed that baseline OSDI defined the symptoms of DES in one subtype, but then, a very complex structure of influences between ocular surface and lacrimal function based variables would define the remainder of the groups.[28] Selecting a smaller number of measures is useful, and the association of concurrent redness, corneal fluorescein staining, tear lactoferrin, and Schirmer result were simple, not considering the efficacy of its use.[29] Other studies were published, and DEWS II adopted the classification, emphasizing some important points of primary importance. Rationale of groupings is however important, once response to therapy is influenced by different mechanisms of the syndromes.[30] Some patients with a symptomatic profile respond better to artificial tears, education, air-conditioned company exposure avoidance, and are individuals with narrow and disrupted corneal and conjunctival nerves as new established potential mechanisms of initiation and maintenance of DES.[31] Dry eye syndrome (DES) is a common eye disease caused by ocular surface damage, associated with tear film instability, and an important public health problem with significant benefits for public health policy.[32] According to the Tear Film and Ocular Surface Society International Workshop, epithelial loss, secondary hyperosmolarity, and inflammation are typical mechanisms leading to homeostasis imbalance, causing tear film dynamic instability, tear cytokine increment and ocular surface inflammation, and corneal surface irregularity. Nowadays, the DEWS-B approach declined these disease's mechanisms in hyperosmolarity and tear amyloid fibrils increase, modifying the tear's physical-chemical property and leading to ocular surface neurosensory anomalies, a new putative pathogenic mechanism.[33]

Pathophysiology

Aside from the known pathophysiologic impacts described previously or continuing studies, dry eye also affects vision and contracted patients' quality of life. A multisystemic condition named "Sicca Syndrome" can be caused in response to the chronic irritation from inflammation and cytokine production on the ocular surface, leading to the involvement of multiple ocular structures, epidermal surface, lungs, and other structures. Nevertheless, several factors are contributing to its complexity and difficulty to diagnose and treat this disease.[34] More recent evidence indicates that inflammation is a hallmark of the pathophysiology of dry eye. Normally, the contents of proinflammatory markers and other factors in the tear fluid are measured and increased in patients with dry eye. Knowing these markers and their importance allow for describing how different events can be related when they produce ocular discomfort or dry eye. Recent transcriptome analysis has revealed specific upregulation of chemokine expression, cytokines, and immune cell recruitment in the conjunctival epithelium of dry eye patients, demonstrating the involvement of immunopathogenesis in dry eye patients.[35] This section summarizes the major pathophysiologic abnormalities that have been

described in dry eye, as well as their statistical significance and strength of association, where available.[36] It should be noted that many of these associations do not imply a causal relationship. Alterations of the ocular surface tear film, disruption of the corneal and conjunctival epithelium, lacrimal gland dysfunction, abnormalities of the ocular surface tissues adjacent to the conjunctiva and cornea, eyelid abnormalities, changes in the level of proteins involved in corneal and conjunctival nutrition or inflammation have all been postulated as possible sources of ocular discomfort or dry eye.[37] Additionally, peripheral and central nervous system abnormalities have been observed in both animals and humans. Associations may be present with age, sex, ethnicity, genetic background, systemic illnesses, lifestyle, and medications. [38,39]

Management Options

Lubricating eye drops are considered typical treatment for DES. Pharmaceutical products are designed to temporarily replace and supplement all of the visible ocular surface tear film components.[40] It causes the improvement of basic symptoms such as foreign body sensations, dryness, discomfort, and visual disturbance by washing out foreign bodies, exfoliated superficial corneal and conjunctival epithelia, and damage components of the mucin-tear-oil-tear film complex that are important for tear film stability, preserving the remaining mucin-combined oil tear film, and creating a smooth, uniform, and stable residual mucin-coupled mucin complex. Even the expression of mucin and oil in the surrounding cells. [41,42] The term DES is used to define a spectrum of disorders of the external ocular surface caused by increased osmolarity of tears and a subsequent inflammatory response. Perspectives in the management of DES have changed significantly in recent years by considering the pathogenesis of DES syndrome, and at the same time, the relative contribution of tear film instability, ocular surface damage, and hyperosmolarity to the ocular surface inflammation and damage complex of DES syndrome has been considered.[43] Considering this concept, the following approaches have been proposed: (i) prevention of tear hyperosmolarity and inflammation during or after changes in the ocular surface environment, (ii) prevention of tear hyperosmolarity and prevention or suppression of the subsequent inflammatory response when the conventional tear film and ocular surface damage, and hyperosmolarity are viewed/considered as major contributing factors, (iii) If there is ocular surface epithelial (corneal and/or conjunctival) damage, repair and regeneration must be forced as soon as possible—the cells should be provided with the environment and nutrition that support/nurture its function.[44,45,46]

Artificial Tears and Lubricants

Patient response and preference are a key driver of long-term success with artificial tear and lubricant use.[47] The complex nature of the hydroxypropyl methylcellulose (HPMC) grafted with an acrylate (polyelectric) copolymer known as Carboxy-Methylcellulose (CMC) leads to unique rheological properties that may be essential to patients' perceived treatment success. Eye drops containing lipids have better effects for the sufferers from DED due to meibomian gland anomalies.[48] New soft contact lenses integrated with chemically embedded lipid molecules and designed to work as osmotic scavengers have been shown to produce a sense of prolonged comfort.[49] ERRUCA is a safety and efficacy study reflecting the daily use of Systane Ultra to reduce the signs and symptoms in subjects with DED in all severities and was identified by the Schirmer test measurements of basal tear quality and quantity.[50] Currently, artificial tears are widely used as the first treatment option for DED. They can be applied as necessary or preservative-

free. Artificial tears replacement may provide temporary relief for some patients.[51] However, they do not address the underlying heritage of DED, and excessive or long-term use may lead to the risk of corneal edema, discomfort, photophobia, and tearing due to preservative toxicity or corneal epithelial cell damage.[52] These artificial tears are typically applied with one to four instillations per day in the treatment of mild keratoconjunctivitis sicca or dry eye.[53] The preservative-free unpreserved artificial tears are considered a safer option for those with sensitivity to preservatives. Many artificial tears include preservatives (common preservatives include benzalkonium chloride, benzododecinium bromide, chlorobutanol, and SofZia) to help control microbial contamination of the bottle for multiple-dose use.[54]

Prescription Medications

In 2019, four consensus reports, dedicated to the controversial topic of dry eye treatments, were presented by a group of experts including members of the Tear Film & Ocular Surface Society. The consensus reports indicated that cyclosporine A is a standard therapy for the management of dry eye, and ciclosporin 0.05% emulsion is most effective. Because of its immunomodulatory role and its capacity to increase tear production from lacrimal glands, ciclosporin therapy with ocular administration provides a standard strategy for dry eye.[55] Recently, sintilimab and anti-PD-L1 antibodies have been reported to suppress autoimmunity in dry eye by regulating helper T cells, the balance of Th17/Treg cells, and the secretion of pro-inflammatory cytokines and chemokines, indicating that sintilimab for autoimmune dry eye has become a potential alternative to traditional ciclosporin treatment. Treatment with menthol also seems to suppress cell migration and inhibit the production of inflammatory cytokines. A single case used cyclosporin, declared to reduce the inflammation of dry eye, and low-dose cyclosporin treatment seems to be associated with few adverse effects.[56] In addition to vitamins, biological hypotensive agents are sometimes linked to adverse side effects, which may involve bitter and poor vision. Several interaction agencies between drugs are considered to be potential partners.[57] Human leukocyte antigen (HLA-DR) is overexpressed in the corneal and conjunctival epithelia of patients with dry eye syndrome, where HLA-DR degradation is critically regulated by ubiquitin proteasome signaling.[58] Triptolide, a natural compound that inhibits several ligase activities of ubiquitin E3, could destabilize HLA-DR by activating the E3 machinery.[59] Song et al. found that submicronized triptolide eye drops can break down HLA-DR in corneal epithelial cells and conjunctival goblet cells, suppress the expression of inflammasome-, ILK-, CDK1-, and IL-6, and increase MUC5AC expression. Therefore, submicronized triptolide is a potential anti-inflammatory medication for dry eye syndrome associated with increased corneal and conjunctival HLA-DR levels. [60] Torpedoed carboxyethyl phenyl diphosphonate-laden liposome (TED-liposome) is a promising agent for dry eye. It is one kind of diphosphonate resin particles (TED polymers) that can specifically target inflammatory macrophage cells. It would not only inhibit heat-killed P. gingivalis-induced expression of tumor necrosis factor α, nitric oxide synthase (iNOS), and type 2 nitric oxide synthase (NOS2) in the macrophages in the ocular surface but also reduce the levels of IL-17 on the ocular surface.[61] Nishida et al. demonstrated that TED polymers reduced P. gingivalis-induced conjunctival production of IL-1β in the ex vivo culture. In addition, interleukin-23, a cytokine closely connected to IL-17, was also inhibited. These results indicate the therapeutic potential of TED-liposome eye drops for treating dry eye.[62]

In a sonography-guided rabbit model of chronic corneal allograft rejection, Ye et al. found that topical leflunomide reduced rejection scores and epithelial erosion on postoperative day 35 compared with the control vehicle group. They concluded that topical leflunomide delayed chronic corneal allograft rejection by downregulating alloreactive T helper cells along with their cytokines on the ocular surface and in draining lymph nodes. Furthermore, only a transient mild corneal opacity increased in the leflunomide group, suggesting safety as a topical eye drop.[63] In recent years, various prescription medications have been applied to the management of dry eye syndrome. Leflunomide, a disease-modifying antirheumatic drug, is widely used for treating rheumatoid arthritis.[64] It inhibits two crucial enzymes, dihydroorotate dehydrogenase and tyrosine kinase, involved in pyrimidine de novo biosynthesis, leading to an immunosuppressive effect.[65]

Lifestyle Modifications

To ensure comfort while reading, watching TV, or using a computer screen, blinking must be done often, and adequate tear production must be stimulated by placing a humidifying device next to work surfaces.[66] Punctal occlusion reduces excessive tear drainage by blocking the lacrimal punctum opening to the nasal cavity; it is a treatment method for severe cases. Ensuring good room lighting and adjusting computer screen height so that eyes are looking slightly down at the screen is beneficial. In age-related cases, ophthalmic lubricants can be used to hydrate one's eyes in atmospheres with low humidity or excessive air conditioning by increasing the natural tear film and providing additional proper moisture balance to the ocular surface.[67] Additionally, the 20-20-20 rule is a basic rule that can be utilized to alleviate visual discomfort; every 20 minutes, a 20-second break must be taken to look at an object positioned 20 feet away to reduce symptoms of computer vision syndrome or eye strain.[68] Avoiding air blowing into the eyes from fans, air conditioning, heaters, car vents, or excessive use of a hairdryer is beneficial. Sunglasses or sun-blocking wraparound sunglasses help protect the eyes from harmful UV rays and help maintain the natural eye moisture balance.[69] Developing and maintaining a self-administered dietary plan of omega-3 fatty acid foods or supplements can help to relieve the symptoms of ocular surface disease.[70] Omega-3 fatty acids, as free fatty acids or in the form of molecularly distilled triglycerides, were found to be more bioavailable and demonstrated positive effects in improving dry eye symptoms, as well as in modulating ocular surface inflammation.[71] They exert their effects on the lipid tear film component to improve meibomian gland functionality, secretion, and viscosity, and blink quality. Proper hydration can be achieved by minimizing caffeine intake, which is diuretic; limiting alcohol intake, noting that even moderate amounts can cause dehydration and dry eyes; increasing vitamin C and drinking plenty of water; consuming low-fat or no-fat dairy products, such as milk and yogurt; and consuming seasonal vegetables, marigold or lutein-rich foods, catechin, taurine, fatty fish, chia seeds, nuts, limes, and turkey. [72,73]

Environmental Factors

An increasing prevalence of DED suggests environmental factors could have a significant effect on its development. There have been many studies on the relationship of dry eye with potential environmental risk factors including computer, mobile phone, television, video display terminal work, heating, indoor air condition, cigarette smoking, period of outdoor activity, global warming, and the global tenant recovery from global warming. Long-term exposure to such factors can lead to DED.[74] Public health and government efforts should pay attention to

lifestyle patterns, as they may potentially influence the development of DED in the future. Prompt management of DED will certainly reduce the burden to the individual patient by preventing recurrence and reducing the long-term consequences of DED, including corneal diseases known to cause loss of visual acuity. Promoting a healthier lifestyle is based on social and economic patterns worldwide, and it is essential to prevent DED from becoming one of the leading causes of visual impairment. Ample evidence suggests that lifestyle changes have improved public health outcomes. [75] The aqueous part of the tear film is known to be responsible for moistening the eye surface and supplying nutrients as well as oxygen to it. The tear film lipid layer stabilizes the tear film and retards its evaporation. The decrease of any of these components can cause the tear film to suffer alterations and evaporation, increasing symptoms.[76] Age is considered an important dry eye risk factor, particularly over the age of 50, where both sex and race may interplay with other risk factors. There are data that are still controversial, as is the case of Body Mass Index (BMI). Dietary factors also seem to have an influence, and essential fatty acids (EFAs) have a complex beneficial role in terms of DED. While EFA supplementation indirectly influences the composition of the Meibum to decrease superficial cholesterol esters and structurally normalize the Meibum, further prospective studies are needed to delineate the role of BMI and other lifestyle factors in the association of DED, and how dietary manipulation of lipids in the tear film. [77]

Surgical Interventions

Several surgical interventions have been associated with iatrogenic dry eye secondary to damage to the corneal and conjunctival sensory nerves. Procedures that have been implicated in causing iatrogenic dry eye include refractive surgical procedures that alter the corneal geometry, lid surgery, adnexa surgery, corneal incisions, cataract surgery, and lens implant surgeries.[78] By definition, DED may have already been present but was asymptomatic and masked by preoperative topical lubricants and contact lens wear. It is important for the physician to distinguish between patients who have developed iatrogenic DED after surgery and patients who were at increased risk because they already suffered from ocular surface disease prior to the surgical intervention.[79] Generally, postsurgical iatrogenic dry eye does not resolve with lubrication, autologous serum tears, or punctal plugs; in these cases, anti-inflammatory and nerve stimulating medications may play a role. In cases of severe DED, secondary corneal complications may be treated only through neurotrophic corneal healing stimulation with agents like lifitegrast. Furthermore, primary corneal surface disease, unresponsive to lubrication, serum eye drops, and punctal occlusion, may be treated with early surgical intervention if corneal scarring becomes significant.[80] Published surgical treatments for severe corneal haze and scarring associated with severe corneal denervation include tangential or eccentric keratectomy, amniotic membrane transplantation followed by tight sutures.[81] The injection of botulinum neuromodulator has been associated with the development of DED. It has been reported that most patients who develop dry eye after receiving a botulinum toxin injection reported experiencing chronic ocular irritation, foreign body sensation, and decreased tear volume. Two patients (13%) reported frequent needle injections triggering ocular pain. Ocular surface examination was notable for decreased tear break-up time with an associated severe reduction in tear lake volume.[82] There is literature evidence to support the clinical observation that botulinum toxin injections are associated with reduction in corneal sensitivity

and decrease in blink rate, both leading to altered lacrimal dynamics and neurosensory feedback after sensory denervation.[83]The treatment of DED related to botulinum neuromodulator has been successful by combining eyelid warming from the area of the meibomian gland orifice to the mucocutaneous junction of the lid margin, punctal occlusion, a therapeutic soft bandage contact lens, and the use of preservative-free artificial tears both during the day and at night. To artificially promote corneal re-innervation, it was also suggested to apply autologous serum mononuclear cells in the form of tears every 2 h. [84] Patients were observed for 2 months and were noted to have improved ocular discomfort, relief from ocular burning sensation, smoother blink dynamics, and recovery of normal tear meniscus.[85]

Non-pharmacological Therapies

Non-pharmacological therapies commonly recommended for dry eyes include the use of warm compresses and lid massage along with lid hygiene, including blepharoexfoliation, punctal agenesis, or occlusion to prevent the loss of tears, and also proper eyelid hygiene.[86] Warm wet gauze compresses for approximately 10-15 minutes followed by lid massages for 5 minutes each time twice daily have been recommended as the most cost-effective option with a low risk of complications.[87] Studies have shown that warm compresses with a proper duration are beneficial for the treatment of dry eye in Japanese office workers who are commonly exposed to VDT use and airflow over the ocular surface by adjusting tear meniscus height, and improving both the tear breakup time and meibum quality. Furthermore, an observational study has demonstrated that the intensive warm compresses used between 2 to 4 weeks improved a wide range of dry eye symptoms at 1 and 4 weeks after treatment and provided immediate relief for symptomatic office staff. [88,89] Dry eye is a multifactorial disease of the tears and ocular surface that results in eye discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is associated with an increase in tear film osmolarity and ocular surface inflammation. It may occur after corneal refractive surgery. [90,91] During the early postoperative days, the tear osmolarity increases and then gradually returns to normal at 6 months postoperatively. Patients with dry eye syndrome experience hyperosmolarity and an increase in the sodium and chloride concentration in the tear fluid compared with normal subjects. The hyperosmolarity also decreases the corneal and conjunctival goblet cell density. Early detection, prompt treatment, and adequate management of these symptoms have a vital role in improving patient comfort, healing, visual recovery, and life quality. [92,93]

Complementary and Alternative Medicine

Patients with moderate or severe dry eye had a high use of complementary and alternative medicine. The studies found that for dry eye syndrome, omega-3 was more impressive in the objective examination than the subjective examination, whereas diquar monoglycerides had the opposite effect.[94] Cyclosporine was also useful for dry eye, reducing the signs and symptoms associated with the MGD condition, improving the presence of meibomian gland secretions, reducing grittiness, and providing relief from occasional eye pain, with the concomitant use of lubricant eyedrops and leading to an impression of drowsiness. Studies conducted on artificial tears have produced contradictory results. It has been shown that both preservative-free and different tonometry, viscoelastic materials, and polymers-based hydrating agents are effective in relieving symptoms and previous therapy on the OSDI scale. They reduced dry eye syndrome signs and symptoms in the intervention and placebo groups.[95] Ginkgo biloba has had a

protective effect on the cornea as well as improvement and regression of fluorescein staining and OSDI. Palate surgery, also known as punctal or punctal cauterization, has been shown to be effective for patients with dry eye, reducing the OSDI score.[96] Complementary and alternative medicine is common among patients with dry eye disease. One systematic review reported that 47% of these patients use CAM, which includes organic food, acupuncture, yoga, and omega 3.[97] In another survey, 60% used some type of alternative treatment, with 89% indicating that it was an effective therapy. A new analysis suggests that complementary and alternative medicine use varies across the world. The most used therapies are nutritional supplements, which include omega 3, plant extracts, and vitamins.[98] Ayurveda, homeopathy, or traditional medicine are less used. However, existing reviews on this topic have limitations, including the assessment of interventions with no positive results, unreported side effects, the intervention in patients without dry eye, and the absence of ophthalmological signs. Our review aims to provide a comprehensive overview of published systematic reviews regarding complementary and alternative medicine on dry eye syndrome. [99,100]

Complications and Associated Conditions

Corneal reflex reduced sensitivity is also a frequent clinical impairment in patients with DES or ocular pain, in which it gives important suggestions and information. Tear osmolarity therefore probably depends on changes in tear film stability and hyperosmolarity.[101] DES, through its association with significant ocular surface inflammation and discomfort, can thus interact with increasing risk of depression as well as with existing depression. DES, which is connected with impaired cognitive function, affects the quality of life and ability to perform normal activities in patients with DES.[102] DES has been related to pathogenesis as well as progression of damage in cases with moderate to severe cases, in chronic period when ocular pain or discomfort, as an essential symptom, is present. In addition, these patients are often seen by primary care physicians or eye clinicians for evaluation of DES like ocular discomfort or pain, or increased light sensitivity.[103] Final visual function is often limited by the development of posterior subcapsular cataracts, macular sub-retinal lesions, and chronic retinal detachment. Treatment modalities for DES in SLE include tear substitute eye drops, punctum plugs for severe cases, oral pilocarpine, topical autologous serum tears, and topical cyclosporine. Furthermore, lacrimal gland inflammation is accompanied by type IV hypersensitivity, which may also be related to DES by an indirect mechanism. The results of the unmasked (single masked examination) multicenter, phase II data show an impressive increase in tear production and ocular discomfort in DES. [104,105] A variety of complications can arise as a result of dry eye syndrome (DES). The following are a few of those: ocular pain and discomfort. Diagnosing DES, regardless of the heterogeneities present in the disease (in terms of clinical scenarios and the degree of impairment), is extremely difficult.[106] Also, very different findings can be obtained on questioning patients in the same clinical sample. A group of patients with DES could present symptoms and problems as well as ophthalmic parameters that were better or worse than those of another group. Eye pain and discomfort are the most frequent presenting symptoms and, at times, the principal symptoms, often reducing patient quality of life.[107] For instance, in those with an indication for invasive treatments such as amniotic membrane transplantation. The multifactorial etiology of DES and the consequently broad range of clinical expressions have a direct effect on patient

subjectivity. DES clinical diagnosis is very unreliable compared with that achieved using patients' anonymous and spontaneous responses, with the potential to provide an alternative and perhaps less subject to bias. Moreover, the interpretation of several forms of DES has been described. Many patients are therefore not diagnosed properly when clinical signs are the main diagnostic approach and also with the use of instruments such as OSDI, VAS, and DEQ-5. [108]

Epidemiology and Prevalence

Dry eye can affect patients differently, and the various terms used to describe this condition reflect this heterogeneity. Disease prevalence varies within the general population. Numerous studies have been conducted to understand the prevalence and characteristics of dry eye syndrome. Importantly, the condition has not been treated as a higher priority, and there are gaps in the knowledge about the epidemiology of dry eye.[109] Age, gender, environmental, dietary, lifestyle, medical history, cigarette smoking, contact lens use, pharmaceutical agents, indoor or outdoor environments, and hormonal factors have been infrequently studied. Data about the disease in different populations of the same race in respect to geographical environment are not comparable. According to the International Dry Eye Complex (2011), dry eye prevalence estimates range from 12% to 59% in the populations studied. [110] Dry eye syndrome is not rare. The most prevalent study was carried out in Rotterdam. The prevalence appears to decrease with older age. It was reported as 5.9% at the age of 55-64, 5.5% at the age of 65-74, and 3.91% at the age of 75 and over.[111] Thus, dry eye symptoms may be less frequent in elderly persons. The estimated prevalence of dry eye symptoms among contact lens wearers is significantly higher compared to non-contact lens wearers. Due to the large elderly population with the age of 65 and over in mid-twenty first century there is a substantial increase in the national health expenditures for the treatment of dry eye syndrome.[112] Lifestyle changes, chronic autoimmune and allergic diseases, postmenopausal hormonal changes, pharmaceutical exposure are increasing as well. All these factors have been contributing to the increasing number of patients with dry eye. [113]

Impact on Quality of Life

Indeed, there are also mentioned the reduced clearance of fluorescein dye and tear-film stability depending on fixed gazing at a computer monitor or the affectivity of ocular tear parameters in long-time VDT workers.[114] As a result, these lead to symptoms of eye fatigue, discomfort, visual disturbance, and decreased tear secretion in these individuals. Many studies have reported on the relationship between DED and diabetes or diabetes prompted ocular surface damage. The alteration mechanism underlying diabetes-induced DED has been demonstrated to be associated with decreased corneal nerve fiber density, tear production, and increased inflammation which is not caused by diabetes independently but influenced by other factors such as alcohol consumption, smoking status, and diabetes medication.[115] Patients who were affected with diabetes and revealed pathological corneal alterations denote the main ameliorated morphologic parameters in those with topical insulin therapy. These findings suggest that early beginning of therapy has a beneficial effect which mainly improves patients' symptoms and corneal signs. [116] Discomfort associated with DED may lead to stress, anxiety, and depression in many patients, ultimately altering the quality of life. A study showed that compared to control participants, those with DED had significantly lower psychological well-being indicators, self-perceptions, and general health interest scales.[117] Likewise, there are other studies that have shown a decreased quality of life in patients

affected by DED. DED affects daily activities in general, reading and using computers in particular, working at a computer, driving, and engaging in various activities that require visual effort, recreational activities, as well as quality of life.[118]

Economic Burden

The economic impact of DE is due to prescribed medications, artificial tears, punctal occlusion, nutritional supplements, in-office treatments, and procedures. The annual costs vary by time period, country, geographical location, clinical teaching setting, and distribution of urban or rural. [119,120] As the American population continues to age, coupled with increased computer usage, the incidence and severity of DE are expected to increase, placing more financial burden on the public health system of the United States.[121] Dry eye (DE) affects over 30% of the population in the world. In the United States, DE affects 5-15% of patients over the age of 65, and the prevalence increases with age. The estimated prevalence in the United States is more than 7.4 million. The prevalence of DE is much higher in developing countries, affecting more than 30% of the population in China and Japan. The cost of over-the-counter (OTC) tear substitutes, doctor visits, and prescription medications to control inflammation has to be counted and examined in detail to describe the true economic burden of DE. Hospital fees and indirect costs such as reduced working hours or reduced productivity could also contribute to the financial burden. [122]

Prevention Strategies

Regarding specific actions, we have established a list to focus on the efficacy to be confirmed and those that offer greater validity. In addition, we are aware that we must monitor environmental factors, including those related to the current epidemiological situation, for example, to odors associated with eye discomfort, as well as instruments to help calm and support the patient. In considering control factors and diseases, we realize that we must act on them assertively to prevent them. It's important to be aware that disease control, which is only at the beginning of evaluation, will undoubtedly benefit from an active patient, through a multidisciplinary approach that reinforces the need for a general consultation.[123] Finally, it is essential to offer the patient guidance to consolidate a project of life, whether the consultation appears: to set the limits of the days and times required for instant messaging or email review in connection with leisure activities and continue to encourage reflection regarding the relationship between digital no prescription and the well-being of the person.[124] 19. Current treatments do not cure the disease, so primary and secondary prevention plays a fundamental role. At present, we know that it is a multifactorial disease that affects more and more at-risk groups aged >60. We also know that environmental factors can be preventive. On the one hand, we must encourage the development of specific educational activities for at-risk patients of all ages, because these aspects focus on hand hygiene and the rigors of the correct formulation and instillation of eye drops in order to reduce sanitizing factors.[125] On the other hand, the use of specific strategies such as the use of phospholipids, cysteine, and other substances such as eye pads to reduce exposure to the computer should be encouraged. Collaboration between ophthalmologist and family physician will allow for the preventive monitoring of aging patients, for example, with a biannual eye visit. Therefore, if you extend the discussion to possible preventive actions, we find activities with which we are already familiar within the possible prevention of dry eye. [126,127]

FUTURE RESEARCH DIRECTIONS

Conventional DE medications include multiple ocular artificial tears and tropicamide eye drops, which are used to relieve pain or dryness. In

addition, DE is associated with moderate to severe pain, photopigmentation, and nighttime blindness. Other forms of DE treatments, which act as DE supplements, include pinhole lenses, dim vision lenses, and binocular hand-eye coordination exercises.[128,129]Furthermore, presymptomatic periods of DE start with frequent eye closure, blink decrease, and gradually evolve from the formation of critical film instability, and finally, the entire cornea participates in the formation of a dry spot. In addition, evidence-based non-invasive diagnostic criteria, appropriate for both clinical and research settings, recognizing dry eye as a multifactorial disease and focusing on the characteristics that ultimately lead to critical film instability, are long overdue. [130] It is imperative to understand the complexity and the various factors involved in the treatment and diagnosis of dry eye. As our understanding of this condition evolves, we must explore new and innovative methods to provide relief and improve the overall quality of life for individuals suffering from dry eye. The use of ocular artificial tears and tropicamide eye drops has been a common approach in conventional medication, but we need to broaden our horizons and consider other supplemental treatments. Pinhole lenses, dim vision lenses, and binocular hand-eye coordination exercises can play a significant role in managing dry eye symptoms and addressing the underlying causes. [131] Moreover, it is crucial to recognize the early signs and symptoms of dry eye. The presymptomatic period may manifest through frequent eye closure and a decrease in blinking. These seemingly minor changes should not be overlooked as they can indicate the onset of critical film instability. The formation of a dry spot in the cornea signifies the progression of the condition and highlights the need for intervention. [132] To accurately diagnose dry eye, we must establish evidence-based non-invasive diagnostic criteria that are applicable in both clinical and research settings. It is essential to acknowledge dry eye as a multifactorial disease, considering its numerous contributing factors. By focusing on the characteristics that ultimately lead to critical film instability, we can develop comprehensive diagnostic tools that help identify and manage the condition effectively. [133] In conclusion, the field of dry eye treatment and diagnosis is evolving, and there is a need for a holistic approach. By expanding our treatment options and exploring innovative techniques, we can alleviate the pain and discomfort associated with dry eye. Additionally, implementing evidence-based diagnostic criteria will enable us to understand the underlying causes and develop targeted interventions. The time has come for a comprehensive understanding of dry eye and the implementation of effective strategies to improve patients' lives. [134] DE is considered one of the most common eye disorders by healthcare providers. Dry eye (DE) can affect both young and older adult populations, and its prevalence has been increasing at an alarming rate, especially after the COVID-19 pandemic wreaked havoc worldwide. This rise is primarily attributed to the detrimental environmental influences that our eyes are subjected to, as well as the emergence of DE as an occupational disease.[135] Furthermore, various treatment procedures such as chemotherapy, ocular surgery (including cataract and direct laser surgery), refractive surgeries, and anti-glaucoma medications can inadvertently contribute to DE. Consequently, this multifaceted condition can lead to a wide array of distressing symptoms, ranging from a persistent sense of fatigue to a significant impairment in the overall quality of life for countless individuals. [136] It is concluded that DE is an extremely multifactorial disease in which, despite the wide range of diagnostic criteria proposed, there is still a lack of consensus on the application of these tests as well as in the pathophysiology of the disease.[137]

Therefore, new research focusing on combining these methods to reach an understanding of the disease seems to be the way forward. Future research in this field should also focus on new drugs with multitarget properties to lead to more effective treatments for different severity of symptoms of the disease or even new forms of treatment that are truly curative, such as stem cell therapy.[138]

CONCLUSION

In conclusion, dry eye disease is a common and often chronic condition that occurs when the quantity and/or quality of the tear film is inadequate. Previously, dry eye was thought to be due to tear deficiency (lack of water and electrolytes, via aqueous component). However, much research has been performed in recent years that has shown a crucial role for the lipid component of the tear film in the overall stability. Currently, it is suggested that an inadequate or imbalanced secretion of any of the three tear film layers and the lipid layer may lead to tear film instability and certain types of dry eye disease. This comprehensive review was focused on epidemiology, etiology, pathophysiology, various clinical aspects, and management strategies. Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film. Several factors are known to favor dry eye, like gender, age, ethnicity, hormonal state, environmental factors, and others. Dry eye may be initially asymptomatic and the diagnosis is carried out by symptoms, tear film instability and ocular surface damage, and tests that aim to confirm sacdade number and stability, characteristics of the meibomian glands, tear film and ocular surface. Dry eye can compromise the quality of life of patients and the treatment must be individualized.

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