Polskie Towarzystwo Okulistyczne
www.pto.com.pl

KLINIKA OCZNA 2021, 123, 1: 8–13
Received: 28.06.2020 **Accepted:** 29.07.2020

REVIEW ARTICLE

Access this article online

Website:
www.klinikaoczna.pl

DOI:
https://doi.org/10.5114/ko.2021.104746

Diagnostics, classification and treatment of dry eye syndrome in the era of COVID-19

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ABSTRACT

Aim of the study was to present options in the diagnosis and management of dry eye syndrome (DES) and coronavirus prevention.

Material and methods: A review and analysis of the available scientific materials and articles in PUBMED and ClinicalKey database dedicated to the ocular COVID-19 manifestations and the Dry eye disease along with Consensus of the Eye Surface Academy and DEWS II guidelines.

Results: Dry eye syndrome is one of the most common eye conditions worldwide in a daily medical practice. The ocular manifestation of COVID can resemble DES. It is recommended that during properly conducted diagnostics, the patient should be properly classified in terms of severity of symptoms. A diet rich in vitamins and flavonoids and the use of polyunsaturated fatty acids are common recommendations for both DES treatment and prevention of COVID-19. This in particular validates the appropriate use of these substances. Fatty acids such as α-lipoic or γ-linolenic are proven to have the most effective anti-inflammatory properties.

Conclusions: In the era of pandemia the ocular manifestation and transmission of COVID has to be always considered since every patient could be a coronavirus carrier. Many substances might be effective in treating and relieving symptoms of dry eye syndrome and coronavirus prevention. PUFAs are proven to have the most effective impact on the inflammation nature of COVID-19 disease.

KEY WORDS: polyunsaturated fatty acids, DES, supplementation, dry eye syndrome, PUFAs, COVID-19.

INTRODUCTION

The first cases of coronavirus disease (COVID-19) were reported in China, in December 2019. Since then, the disease has been spreading fast around the world, also in Poland. The pathogen of COVID-19 is a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), identified as a member of the family *Coronaviridae* [1, 2]. The extensive experience of Chinese physicians and scientists in the fight against the coronavirus pandemic points towards the possibility of ocular manifestations of the infection and the risk of coronavirus transmission through the eyes. Ocular disorders can be the first presenting symptoms of COVID-19 and the only signs of infection [3]. The common symptoms of dry eye syndrome (DES) include excessive tearing, dryness, burning sensation, and blurred vision. All of them cause discomfort, leading to frequent rubbing and touching of the eye area, and thus increasing the risk of infection. Based on the cases reported in China, dry eye syndrome can be either a contributing factor to SARS-CoV-2 infection or its sole manifestation. With respect to measures preventing COVID-19 infection, an important role has been attributed to the optimal treatment of underlying diseases (diabetes mellitus, bronchial asthma and others – including dry eye syndrome) as well as physical activity and appropriate diet which enhance immunity by decreasing pro-inflammatory factors and increasing the level of antioxidants. Regarding the healthy diet, WHO experts place a special emphasis on a sufficient intake of vegetables and fruit that are rich in vitamins and flavonoids, and supplementation with polyunsaturated fatty acids (PUFAs) [4]. Among other functions, the latter are an essential product for the synthesis of anti-inflammatory prostaglandins. However, omega-3, omega-6 and vitamin supplementation is also considered as one of the recommended strategies in the management of dry eye syndrome [5].

AIM OF THE STUDY

The aims of the paper are to review the diagnostic and therapeutic options for dry eye syndrome (DES), and present COVID-19 prevention measures.

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MATERIAL AND METHODS

Review of research papers and articles on the ocular manifestations of COVID-19 and dry eye syndrome found in the PubMed and ClinicalKey databases, as well as the Consensus Statement of the Ocular Surface Academy, and TFOS DEWS II Guidelines.

DEFINITION OF DRY EYE SYNDROME

With the advancement of medicine and expansion of knowledge, the definition of DES has evolved over the years. According to the new definition adopted by the international Dry Eye Workshop (DEWS): "dry eye is a multifactorial 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" [6].

CLASSIFICATION

According to recent studies, DES can be divided into three types based on the pathophysiological characteristics. They include aqueous deficient dry eye (ADDE) – resulting from lacrimal gland dysfunction; evaporative dry eye (EDE) – the predominant type, attributed to causes related to the eyelids (including meibomian gland dysfunction (MGD)) and the ocular surface; and mixed dry eye [6]. Another division is based on the severity of the condition evaluated using the Ocular Surface Disorder Index (OSDI), and includes mild, moderate and severe types of DES [7].

EPIDEMIOLOGY

Epidemiological data show that EDE is the more widespread type of dry eye syndrome [8-10]. Overall, the prevalence of DES is estimated at 5 to 34%. The discrepancy of the estimates is thus considerable, and can be explained by differences in the studied populations, geographical areas, and wide-ranging criteria used in the diagnostic work-up of DES. Some of the studies were based on subjective symptoms, and others on physical manifestations. In the latter analyses, DES was identified in a greater proportion of cases, as the condition is known to be asymptomatic in a large number of individuals, especially in less advanced stages. DES is more common in the female sex (women are affected up to 1.5 times more frequently than men) and in Asian populations. Furthermore, the incidence of DES rises with age. According to the results of Polish epidemiological studies based on the ocular surface disease questionnaire, DES affects even up to 63% of the Polish population [5].

PATHOPHYSIOLOGY

The human tear film consists of three components: lipid, aqueous and mucous layers. The underlying causes of each form of dry eye syndrome (ADDE and EDE) include hyperosmolarity, setting off ocular defense mechanisms, and inflammatory response which, by assuming a chronic character, causes damage to the ocular surface and, consequently, causes the disease to gain increasing momentum. An increase in tear film osmolarity is an important factor associated with tear film disorders. Osmolarity is affected by a number of factors including the degree of body hydration, characteristics of the lipid layer of the tear film, frequency of blinking, and environmental aspects. Hyperosmolarity stimulates epithelial cells on the ocular surface to secrete pro-inflammatory substances including MAP kinase, pro-inflammatory cytokines (IL-1α, IL-1β), tumor necrosis factor α (TNF-α), and proteases such as metalloproteinase 9 (MMP9). These molecules stimulate the influx of inflammatory cells to the surface of the eye. The cells produce their own inflammatory mediators, leading to the apoptosis of epithelial and goblet cells, and damage to the corneal nerves. The processes result in abnormal hydration of the ocular surface causing hyperosmolarity and thus closing the vicious circle [11]. An increase in hyperosmolarity on the ocular surface also occurs in patients with diabetes mellitus as a result of hyperglycemia, setting off a cascade of inflammatory responses and the MAP kinase pathway as well [12]. Other pathomechanisms underlying the development of DES in diabetic patients include reduced corneal sensitivity decreasing basal tear secretion, corneal neuropathy leading to tear film instability, and pathological stimulation of the lacrimal gland by the autonomic system impaired by diabetic neuropathy [13].

RISK FACTORS

Over the years, a number of risk factors have been demonstrated to contribute to the development of DES. They can be divided into several groups: ophthalmic factors (meibomian gland dysfunction, wearing contact lenses, pterygium, refractive eye surgery, allergic conjunctivitis); general factors (age, sex, race, connective tissue diseases, Sjögren's syndrome, androgen deficiency, hematopoietic stem-cell transplantation, diabetes mellitus, rosacea, viral infection, thyroid disease, mental disorders, low dietary intake of fatty acids); factors related to drug treatments (estrogen replacement therapy, treatment with antihistamines, antidepressants, anxiolytics and isotretinoin, cholinolytics, diuretic agents, β-blockers); and environmental factors (computer use, air pollution, low humidity) [6]. A particularly important role in identifying the cause of DES and initiating appropriate treatment is attributed to thorough history taking and determination of specific risk factors in individual patients.

DIAGNOSTIC WORK-UP

The diagnosis of DES can be made on the basis of a number of non-invasive and invasive diagnostic methods, but experts agree that in each case the diagnostic process should begin with methods associated with a lower burden for the patient. The recommended diagnostic sequence in patients with suspected dry eye syndrome includes clinical history, symptom questionnaire, fluorescein tear break-up time (FBUT) test, fluorescein staining of the ocular surface with yellow filter with evaluation based on a grading scale, Schirmer I test (with or without anesthesia), and/or Schirmer II test

with nasal cavity stimulation, assessment of morphological features of eyelid margins and meibomian glands, and evaluation of meibomian gland secretion (expression). According to the DEWS II guidelines, the Ocular Surface Disease Index (OSDI) is the primary instrument for the diagnosis of DES and assessment of its severity (with scores corresponding to the normal eye condition or mild, moderate, or severe DES). The questionnaire consists of 12 questions related to the ocular irritation symptoms, their effects on vision, and symptom-inducing environmental factors. The questionnaire gives a score on a scale of 0 to 100 points, with higher scores corresponding to more severe ocular surface disorders [7].

TREATMENT AND SUPPLEMENTATION

The aim of DES treatment is to eliminate discomfort-causing symptoms and improve the patients' quality of life. The most prevalent therapeutic option and first-line treatment of DES is based on hypotonic eye drops with hyaluronic acid. However, the drops do not stay long on the surface of the eye. Moisturizing eye drops are an element of symptomatic treatment. Where artificial tears prove insufficiently effective, patients can be prescribed treatment with mucolytic agents (acetylcysteine) or therapies involving temporary or permanent closure of the tear duct openings (using silicone plugs, rods, punctal cautery, punctoplasty), and even tarsorrhaphy. In more severe cases, the only method to break up the vicious circle is to suppress inflammation and reduce the hyperosmolarity of the tear film. To this end, patients may be prescribed anti-inflammatory and immunomodulatory drugs such as corticosteroids and cyclosporin A, and osmoprotective agents including trehalose, L-carnitine, betaine, glycerol, and erythritol [8]. Corticosteroids relieve the symptoms and prevent corneal epithelial damage, while cyclosporin increases tear secretion, reduces inflammation-induced loss of goblet cells, and causes regression of epithelial cell metaplasia [14-16].

Guidelines issued by the Polish Society of Ophthalmology (PTO) and the Ocular Surface Academy experts highlight the potential benefits of supplementation with polyunsaturated fatty acids. PUFAs can be particularly beneficial in patients with MGD-associated DES. The oral intake of omega-6 fatty acids, linolenic acid (LA) and gamma-linolenic acid (GLA) significantly increases the PGE1 content in tears, which has been demonstrated in a multicenter study. PGE1 has anti-inflammatory properties including the inhibition of TNF-α, IL-1 and IL-6 [17], and its action depends on the availability of DGLA derived from the essential fatty acids LA and GLA by the activity of the enzymes desaturase and elongase [18]. Furthermore, PUFAs stimulate the secretion of tears and markedly reduce the concentration of leukocyte DR (HLA-DR), which serves as a marker of inflammation, in the conjunctival epithelial cells [19]. Several studies have also shown that gamma-linolenic acid (GLA) produces anti-inflammatory effects by increasing the concentration of dihomo-gamma-linolenic acid (DGLA), which steps up the synthesis of anti-inflammatory prostaglandins [20]. Oral supplementation with omega-6 fatty acids is effective in patients with DES which is caused by a variety of factors such as Sjörgen's syndrome or contact lens use, or develops after PRK [17, 21, 22].

There are also reports of the beneficial effects of α-lipoic acid (omega-3 acid) which are attributable to its antioxidant properties. α-lipoic acid was shown to increase tear production and secretion, as evidenced by the results of the Schirmer test [23].

Another substance with potential applications in inhibiting the inflammatory cascade is honokiol, a strong antioxidant which is known to suppress, among others, nitric oxide, protein kinases C-α, and NF-κB [24, 25]. Honokiol has a number of studied mechanisms of action, and its benefits in ophthalmology have been shown primarily in the posterior segment of the eye, where it inhibits the hypoxia-inducible factor (HIF) pathway, thus producing anti-angiogenic effects [26]. In addition, patients with DES secondary to diabetic neuropathy may benefit from the neuroprotective properties of honokiol which are probably linked to the promotion of alternative endogenous biochemical pathways and modulation of various inflammatory mechanisms [27].

Many vitamins are also known to improve the condition of the ocular surface. Based on study findings, vitamin A and its active form retinol inhibit the pathway of apoptosis and enhance the quality of tears [28, 29]. Vitamin B_{12} relieves neuropathic pain in severe DES cases [30]. Vitamin C supplementation markedly reduces oxidative stress by lowering the level of nitric oxide and the density of conjunctival goblet cells, and tear stability [31, 32]. In patients with vitamin D deficiency, supplementation reduces the hyperemia of eyelid margins, alleviates subjective symptoms, and improves the Schirmer test scores [33]. Similarly, flavonids contained in green tea and blueberry extracts have a favorable effect on the Schirmer test results and reduce the severity of symptoms reported by patients [34, 35]. In addition, substances such as selenium and curcumin decrease the amount of reactive oxygen species on the ocular surface [36, 37].

OCULAR SURFACE AND COVID-19

The first cases of coronavirus disease (COVID-19) were reported in China, in December 2019. Since then, the disease has been spreading rapidly around the world, and the global death toll from the pandemic has already surpassed 1.2 million people [38]. The pathogen of COVID-19 is a novel coronavirus called severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], identified as a member of the family *Coronaviridae.* Another coronavirus, called SARS-CoV-1, was responsible for severe acute respiratory syndrome [1]. Compared to SARS-CoV-1, SARS-CoV-2 has a similar binding receptor and pathological characteristics [1, 2]. The extensive experience of Chinese physicians and scientists in the fight against the coronavirus pandemic points towards the possibility of ocular manifestations of the infection as well as the risk of coronavirus transmission through the eyes, which raises additional concerns in daily ophthalmology practice [39]. The probable sites of viral penetration into the eye are the angiotensin-2 converting enzyme (ACE2) as a receptor and the

TMPRSS2 protein which has high affinity for the coronavirus. Their presence in the corneal and conjunctival cell membranes has been scientifically demonstrated [39]. The dynamics of the tear film is one of the factors contributing to the spread of SARS-CoV-2 from the infected eye surface through the tear ducts to the respiratory and digestive systems [40]. Ocular manifestations can be the first presenting symptoms of COVID-19 and the only signs of infection. One of the earliest reported cases worldwide involved a Chinese coronavirus expert who used a protective N95 face mask, but failed to protect his eyes. The initial symptoms of infection were similar to DES, and preceded the onset of pneumonia [3]. A similar case was reported in a 29-year-old nurse who, aside from fever, reported only excessive tearing and redness in both eyes [41]. In another study, swabs were taken from the conjunctival sac from a total of 33 individuals who had been diagnosed with coronavirus a week earlier. The people did not report any ophthalmic symptoms. In two patients, a high viral load was found in tears, and confirmed by double RT-PCR testing [42].

In view of the above cases, many ophthalmologists recommend that every patient with acute symptoms involving the ocular surface should be treated as potentially infected with COVID-19. Another recommendation is that patients should be informed about the possibility of infection transmission through the surface of the eye. In addition, they need to be advised against touching the area around the eyes, mouth and nose [43]. The American Ophthalmological Society encourages contact lens wearers to switch to glasses during the pandemic as a means to prevent infection. Also, ophthalmologists are advised to restrict the examination of patients to the necessary minimum, use disposable equipment whenever possible, disinfect surfaces with wipes containing 70-90% ethanol or 0.1% sodium hypochlorite (successfully inactivating coronaviruses), wear disposable face masks and gloves, and use slit lamp breath shields [44].

PHYSICAL METHODS OF EVAPORATIVE DRY EYE TREATMENT

Warm compresses at a temperature adjusted to the melting point of the content of the meibomian glands (32-45°C), applied regularly twice a day for a period of two weeks, may have a beneficial effect not only on the tear film, but also on the function of the meibomian gland in patients with MGD. Eyelid warming can be performed either with self-made compresses or ready-made medical devices such as Blephasteam goggles, MGDRx EyeBag compresses or EyeGiene mask. Another potentially effective procedure involves massaging the eyelid to physically express trapped material from the clogged gland. Devices such as LipiFlow, designed to empty the content of the glands while heating them to therapeutic temperatures (42.5°C), are also commercially available. Intense pulsed light (IPL) is used to deliver intense pulses of non-coherent light at a wavelength of 500 nm to 1,200 nm in the therapy of a variety of conditions, including MGD. The pulse energy stimulates the meibomian glands to function properly, activating the acini, which results in improved production of the lipid layer and reduced tear evaporation. Studies indicate that the treatment enhances the quality of the tear film and relieves the symptoms of DES. An invasive procedure supporting the treatment of DES is intraductal meibomian gland probing (MGP), first described in 2010. Data obtained from studies conducted to date suggest that MGP may improve the condition of patients with MGD who do not respond to conventional treatment [7].

DISCUSSION

Dry eye syndrome is a multifactorial disease with a complex mechanism, frequently leading to diagnostic and therapeutic problems [6]. The coronavirus pandemic, which has been spreading since late 2019, further complicates the diagnostic work-up and necessitates more intensive treatment of patients because the ocular presentation of both nosological entities may be very similar, while rubbing the eyes may be conducive to COVID-19 infection [1, 2]. In light of the above, it is recommended that any patient with acute symptoms should be treated as potentially infected with COVID-19 [43]. Dry eye syndrome is one of the most common conditions encountered by ophthalmologists in their daily practice, and the presentation of the disease may resemble the ocular manifestation of COVID-19 [5, 41]. Consequently, patient examination should be restricted to the necessary minimum, and members of personnel must be provided with protective equipment [44]. A properly conducted diagnostic process should aim to correctly classify patients in terms of the severity of symptoms, and individualize treatment [7]. Based on the current state of knowledge, in addition to the relief of symptoms, it is also possible to treat the cause underlying the pathomechanism of the syndrome [11]. The use of topical and systemic agents, together with patient education, seem to provide the most effective strategy to eliminate ocular discomfort. A diet based on vegetables, fruit and fish, and rich in vitamins, flavonoids and polyunsaturated fatty acids, is recommended both for the treatment of DES and the prevention of coronavirus infection, which provides a strong justification for an appropriate dietary regimen [4, 5]. Fatty acids (α-lipoic, γ-linolenic, etc.) have well-documented anti-inflammatory properties [17, 23]. Among other effects, they increase the concentration of PGE1, which is an inhibitor of TNF-α, IL-1, and IL-6 [17]. Oral supplementation is effective in the therapy of DES caused by various factors, such as MGD, Sjögren's syndrome or PRK, because these pathologies have an underlying inflammatory basis [17, 21, 22]. Similar benefits can probably be expected after using substances such as honokiol, curcumin or selenium, as they possess antioxidant properties as well [24, 25, 36, 37]. A number of vitamins and flavonoids present in fruits and vegetables, as well as commercially available supplements for oral use, contribute to reducing the symptoms of DES and improving the quality of the tear film. Such properties are well-documented for vitamins A, B_{12}, C, and D [28-35]. Physical methods used in the treatment of MGD play a major role in restoring homeostasis of the ocular surface. Warm compresses have the best documented efficacy, but at more

advanced stages of the disease, it may be more therapeutically beneficial to apply IPL, express the meibomian glands or opt for meibomian gland probing [7].

CONCLUSIONS

In the current pandemic, the ocular route of infection should be taken into consideration, and each patient should be handled as a possible coronavirus carrier. A number of substances can be incorporated into the diet or used in the form of ready-made supplements as a potentially effective strategy for treating and relieving the symptoms of DES and preventing COVID-19. Polyunsaturated fatty acids have the best documented therapeutic effect by contributing to the relief of the inflammatory nature of the disease. Omega acids, vitamins and other dietary supplements should be considered on an individual basis in each patient.

DISCLOSURE

The authors declare no conflict of interest.

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