Special Issue

Systemic Health and Dry Eye

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Dry eye disease (DED) is a local ocular surface disease caused by a multitude of factors and involves multiple interacting mechanisms. The prevalence of DED is rapidly increasing in the modern aged society, and it is considered a major ocular condition with a high prevalence among the elderly, who frequently have multiple comorbidities. Systemic medical conditions can have a negative impact on ocular health. In addition, a variety of systemic drugs can also induce DED via multiple mechanisms. The adequate management of general systemic diseases may control DED progression. Furthermore, according to the antiaging theory, an appropriate lifestyle intervention is preventive for both DED and general systemic disease. In this article, we focus on systemic health and DED to provide a broad overview of the association between systemic health, particularly in relation to aging, and DED. Ophthalmologists should carefully interview patients with DED regarding systemic comorbidities to deliver optimal treatment. A systemic approach, including the use of supplements and lifestyle intervention, should be used in addition to conventional local treatment.

Keywords: dry eye, systemic health, metabolic syndrome

Dry eye disease (DED) is a local ocular surface disease caused by a multitude of factors and involves multiple interacting mechanisms. In previous studies, one of the most clearly documented risk factors for DED was aging.[1] The prevalence of DED is rapidly increasing in the modern aged society. It is a major ocular condition with a high prevalence among the elderly, who frequently have multiple comorbidities. Systemic medical conditions can have a negative impact on ocular health. In addition, a variety of systemic drugs can also induce DED via multiple mechanisms.[2] The adequate management of general systemic diseases may control DED progression. Furthermore, according to the antiaging theory, an appropriate lifestyle intervention is preventive for both DED and general systemic disease. In this article, we focus on systemic health and DED to provide a broad overview of the association between systemic health, particularly in relation to aging, and DED.

Recent Worldwide Progress

The recognition of systemic comorbidities is imperative. Possible conditions associated with DED include metabolic diseases (thyroid disease, diabetes mellitus [DM], and hyperlipidemia), cardiovascular diseases (ischemic heart disease, cardiac arrhythmias, peripheral vascular disorders, stroke, pulmonary circulation disorders, and migraine), immunologic diseases (allergies, rosacea, systemic lupus erythematosus, and myasthenia gravis), degenerative diseases (arthritis and benign prostatic hyperplasia), mental diseases (posttraumatic stress disorder and depression), and malignancies.[1] However, the type and strength of these associations were not consistent among studies,[3–6] probably because of differences in ethnic, social, and environmental backgrounds. Furthermore, most population-based studies evaluated DED by using questionnaires and did not conduct objective ocular examinations. The major studies that have evaluated systemic health and DED are summarized in Table 1.[3–6] With careful consideration of various factors, recently, the Dry Eye Workshop II judged and summarized risk factors of DED, as shown in Table 2.

Also, recently, a meta-analysis concerning the association between the risk factors for metabolic syndrome and DED reported that patients with hypertension, hyperglycemia, and hyperlipidemia exhibited a higher risk of developing DED ($P < 0.05$), particularly the typical symptoms.[7]

Recent Progress in Japan

Among various risk factors, aging is one of the most important factors for the pathogenesis of DED.[1] Consumption of excess calories leads to an acceleration of the aging process, an increase in oxidative stress, and increased incidence of age-related diseases, including cancer and diabetes. Recent advances in our understanding have provided a new way of thinking about interventions in the aging process. Although the aging process is complex, calorie restriction (CR), which refers to a dietary regimen low in calories but without undernutrition, has been known to extend lifespan, as clearly evidenced in various animal species.[8,9] CR profoundly affects the physiologic and pathophysiologic alterations associated with aging and suppresses the incidence of numerous age-related diseases.[10–12] The anti-aging theory, which indicates that DED is a phenotype of the accelerated aging condition of systemic health, is followed throughout Japan.[13] Accordingly, not only systemic diseases (comorbidities) but also predisease conditions, including lifestyle factors, have been investigated in association with DED, and several pioneer works have been published.[14–18]

First, several animal studies reported that excess oxidative stress is systemically associated with lacrimal dysfunction[19,20] and CR maintains tear secretion and reduces oxidative stress.[21] Next, the Osaka study, which conducted a cross-sectional study concerning dry eye among office workers, found several new systemic health factors associated with DED, such as metabolic syndrome, low exercise habit, sedentary lifestyle, poor sleep quality, and subjective happiness.[15,17,18] The Osaka Study

Table 1. Previous Cross-Sectional Studies Concerning Systemic Health and DED

Reference	Location	Number	Year	Systemic Health-Related Factors Associated to Dry Eye	OR	95% CI
Ferrero et al.[44]	France	1045	2017	Sun protection (vs. often) never	0.32	0.12–0.82
				Hypertension	1.59	1.06–2.78
				Anxiolytics	1.75	1.06–2.88
Roh et al.[45]	South Korea	17364	2016	Dyslipidemia	1.63	1.38–1.93
				Thyroid disease	1.79	1.41–2.28
				Chronic renal failure	2.56	1.40–4.70
				Degenerative arthritis	1.56	1.30–1.86
				Rheumatoid arthritis	1.44	1.00–2.08
Tan et al.[3]	Singapore	1007	2015	Antihypertensive medication	1.84	0.99–3.44
Yang et al.[46]	China	789	2015	DM	1.408	1.031–1.924
				Hepatitis C	3.326	1.632–6.776
				Connective tissue disease	2.157	1.679–2.771
				Benign prostatic hyperplasia	3.892	2.476–6.116
				Rosacea	3.747	1.972–7.120
				Posttraumatic stress disorder	1.449	1.043–2.013
Paulsen et al.[47]	United States	3275	2014	Allergies	1.59	1.22–2.08
				Arthritis	1.44	1.12–1.85
				Thyroid disease	1.43	1.02–1.99
Ahn et al.[4]	Korea	11,666	2014	Thyroid disease	1.7	1.2–2.4
				Severe stress	1.7	1.1–2.6
Wang et al.[5]	China	48,028	2012	Ischemic heart disease	1.36	1.14–1.61
				Hyperlipidemia	1.68	1.60–1.77
				Cardiac arrhythmias	1.55	1.43–1.69
				Peripheral vascular disorders	1.57	1.39–1.79
				Stroke	1.31	1.22–1.41
				Migraines	1.76	1.57–1.98
				Myasthenia gravis	2.85	1.52–5.35
				Rheumatoid arthritis	2.86	2.63–3.10
				Systemic lupus erythematosus	3.98	2.93–5.42
				Asthma	1.25	1.14–1.36
				Pulmonary circulation disorders	1.37	1.29–1.45
				Diabetes with complications	1.31	1.23–1.38
				Hypothyroidism	1.94	1.79–2.10
				Liver diseases	1.71	1.62–1.82
				Peptic ulcers	1.76	1.66–1.86
				Hepatitis B	1.64	1.49–1.81
				Deficiency anemias	1.31	1.19–1.45
				Depression	2.11	1.93–2.31
				Psychoses	1.87	1.68–2.08
				Solid tumors without metastasis	1.41	1.27–1.56
Uchino et al.[6]	Japan	3294	2011	Hypertension (men)	1.56	1.04–2.35
				Myocardial infarction or angina (women)	2.64	1.51–4.62
Schaumberg et al.[48]	United States	25,444	2009	High blood pressure (men)	1.28	1.12–1.45
				Benign prostatic hyperplasia (men)	1.25	1.09–1.44
Lee et al.[49]	Indonesia	1058	2002	History of smoking	1.5	1.0–2.2

CI, confidence interval; OR, odds ratio.

documented significantly low tear volumes in subjects diagnosed with metabolic syndrome (MetS) and those aged ≥40 years (Fig. 1).[22] MetS is the term for a group of risk factors for diabetes, hypertension, and other lifestyle diseases. It is considered an accelerated aging condition and is related to excessive oxidative stress. Because MetS adversely impacts productivity, more local governments and businesses in Japan are implementing measures to combat this condition. Due to genetic and environmental differences, the obesity rate in Japan is not as high as that in the Western world. However, the Japanese are reported to be more susceptible to damage from MetS than are Europeans or Americans.[23] Moreover, lifestyle changes among the Japanese have increased the prevalence of MetS, primarily in the working-age population. Furthermore, a previous study reported that 73% of those aged ≥60 years have dry eye, indicating a higher incidence of dry eye in the older Japanese population.[24] Taken together, the study shows that aging is an important risk factor for dry eye and MetS may have an influence on the increasing prevalence of dry eye. The finding that MetS is related to DED has been recently confirmed by studies from other countries.[25,26]

Moreover, the association between DED and MetS was reinforced by the finding that subjects with DED were found to exercise less.[17] Recent studies reported that, in addition to low levels of physical activity, a prolonged period of sedentary behavior (sitting for instance) is a risk factor for various health problems, including chronic diseases, such as cardiovascular disease, diabetes, and MetS.[27–29] Because physical inactivity and a sedentary life style are detrimental to health, addressing these behaviors has become a global public health priority.[30]

Table 2. Risk Factors for DED Summarized by Dry Eye Workshop II Reports[1]

Consistent*	Probable†	Inconclusive‡
Nonmodifiable		
Aging	Diabetes	Hispanic ethnicity
Sex, F	Rosacea	Menopause
Race, Asian	Viral infection	Acne
Meibomian gland dysfunction	Thyroid disease	Sarcoidosis
Connective tissue diseases	Psychiatric conditions	Menopause
Sjogren's syndrome	Pterygium	
Modifiable		
Androgen deficiency	Low fatty acid intake	Smoking
Computer use	Refractive surgery	Alcohol
Contact lens wear	Allergic conjunctivitis	Pregnancy
Hormone replacement therapy		Demodex infestation
Hematopoietic stem cell transplantation		Botulinum toxin injection
Environment: pollution, low humidity, sick building syndrome		
Medications: antihistamines, antidepressants, anxiolytics, isotretinoin	Medications: anticholinergic, diuretics, beta-blockers	Medications: multivitamins, oral contraceptives

* Consistent evidence implies the existence of at least one adequately powered and otherwise well-conducted study published in a peer-reviewed journal, along with the existence of a plausible biologic rationale and corroborating basic research or clinical data.

† Suggestive evidence implies the existence of either inconclusive information from peer-reviewed publications or inconclusive or limited information to support the association but either not published or published somewhere other than in a peer-reviewed journal.

‡ Inconclusive evidence implies either directly conflicting information in peer-reviewed publications or inconclusive information but with some basis for biologic rationale.

The World Health Organization has included a sedentary lifestyle as a new health risk in addition to smoking and obesity. Office workers who were sitting for long hours in front of visual display terminals (VDTs) tended to exhibit sympathetic dominance and suffer from lower back pain and/or painful eyes.[31,32] Eye strain is an important contributor to the development of DED, a disease that has been neglected as a component in the health management of office workers. The results show that a high level of physical activity is associated with a low risk of DED and that sedentary behavior is associated with DED. Tear film breakup time and ocular surface staining scores were significantly associated with International Physical Activity Questionnaire scores; furthermore, tear film breakup time was significantly associated with sedentary time.[17]

Furthermore, a statistically significant positive correlation between dry eye symptoms and happiness ratings was found.[18] In other words, subjects with worse dry eye symptoms tended to be less happy. Another finding was poor sleep quality among subjects with dry eye.[16]

On the basis of the abovementioned facts and findings that these lifestyle factors associated with DED (in addition to prolonged VDT exposure), we believe that lifestyle intervention, including exercise and an appropriate diet, is a promising treatment strategy for DED. Also, an improvement in lifestyle along with conventional topical treatment was a promising strategy for the management of DED. Thus, strategies for DED management are mainly becoming preventive in nature.

There is clear evidence regarding the benefits of exercise for patients with various systemic diseases, including physical (e.g., DM) and mental (e.g., depression) diseases. Sano et al.[33] reported that exercise increased the secretion of tears in a mouse model of DM. A combination of exercise, diet, and positive thinking has been found to have positive effects on the symptoms of DED.[34,35]

Moreover, it has been reported that abdominal breathing reduces the sympathetic nervous system and consequently increases the secretion of tears.[36] It has been reported that work involving the use of VDTs affects heart rate variability and sympathetic nervous activity.[37,38] Abdominal breathing is associated with low levels of sympathetic nervous activity and high levels of parasympathetic nervous activity.[39] The major outcome of this study was the increase in tear meniscus volume due to abdominal breathing. Based on the results of the current study, we suggest that appropriate abdominal breathing may be recommended for the treatment of DED. Especially for VDT users in offices, abdominal breathing can be easily applied to improve the tear meniscus volume.

As other promising systemic interventions, omega 3 and other supplements, including lactoferrin and lactic acid bacteria, have been reported to be effective in the management of DED, especially in VDT loading.[40,41] Because DED is considered to be associated with oxidative stress and inflammation, such dietary foods may have anti-inflammatory or anti-oxidative stress properties against dry eye.[42,43]

Future Directions

Further studies based on the concept that the ocular surface and lacrimal unit are part of the systemic network (including the physical and mental domains) of the human body are necessary. The relationship between systemic diseases characterized by chronic inflammation, such as DM and rheumatoid arthritis, and DED needs further and detailed investigation. In addition, the mechanisms by which mental conditions, such as depression, posttraumatic stress disorder, and sleep disorder, result in DED should be evaluated. Concrete and practical approaches such as the antiaging approach (supplements and lifestyle intervention) should be used for the management of DED. Each treatment strategy for DED should be customized on the basis of the patient's systemic health (physical and mental), lifestyle, and risk factors, in addition to the ocular surface condition. Overall, the management of DED should be based on a preventive approach.

Conclusions

Systemic health is a very important factor for the management of DED. In particular, elderly individuals, who constitute a high-

risk population for DED, often exhibit systemic problems and are generally consuming medicines. It should be noted that, although DED is a local disease, it is connected with the systemic condition of the individual. Ophthalmologists should be aware that not only detailed ocular investigations but also systemic examinations, including assessment of both physical and mental conditions, are necessary for patients with DED. In the near future, ocular surface examinations may be replaced by machine diagnosis because of advancements in technology such as artificial intelligence. However, ophthalmologists should perform comprehensive assessments in addition to technical evaluations before arriving at a final and accurate decision regarding DED.

In conclusion, our findings suggest that ophthalmologists should carefully interview patients with DED regarding systemic comorbidities to deliver optimal treatment. A systemic approach, including the use of supplements and lifestyle intervention, should be used in addition to conventional local treatment.

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