

OCULAR SURFACE DISORDERS

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Chapter 4 The epidemiology of dry eye disease

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INTRODUCTION

In order to fully understand the signs, symptoms, and treatment of any disease, it is imperative to first understand the relationship of the various factors that determine the distribution and frequency of the disease in a population. The study of this interconnected and complicated relationship is the study of epidemiology of dry eye disease (DED). This chapter will describe, in particular, the factors that help to explain the distribution of DED across the world, the similarities and differences, and what we know about the overlap and relationship between the various ocular surface disorders.

DEFINITION AND CHALLENGES IN OCULAR SURFACE EPIDEMIOLOGY

In the process of identifying the prevalence of a disease, a working definition is needed to guide the process. Thus, the definition of DED resulting from the 1995 National Eye Institute/Industry Workshop included ocular symptoms in addition to one or more ocular signs: 'Dry eye is a disorder of the tear film due to tear deficiency or excessive tear evaporation which causes damage to the interpalpebral ocular surface associated with symptoms of ocular surface associated with symptoms of ocular discomfort' (Lemp 1995). This original definition was updated in 2007 in the DEWS report and maintained many of the key features, and added components that further explored the etiology and underlying factors, while focusing on the multifaceted aspects of the disease: 'Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface' (DEWS 2007a).

Although the definition has become fairly well-recognized and accepted, it is still challenging to distinguish who has DED and who does not and even, perhaps more pertinent, to decide how DED can (or should) be subcategorized (DEWS 2007a). Currently, there is no singular, definitive test to diagnose DED (DEWS 2007b). Additionally, there is not even an accepted, standardized combination of clinical tests to diagnose DED, although several are utilized clinically as well as in patient-based research. One reason for this lack of accepted tests may be the absence of correlation between subjective feelings of irritation and discomfort and the results of clinical DED tests (DEWS 2007b; Nichols et al. 2004b). Yet another reason might be the lack of repeatability for DED clinical tests (Nichols et al. 2004a); however, newer objective osmolarity testing (Eperjesi et al. 2012) as well as modifications to existing testing such as tear film break-up time (TFBUT) (Pult & Riede-Pult 2012) demonstrates improved reliability and repeatability. Furthermore, much of DED diagnosis is based upon 'subjective' symptoms that may be influenced by varied levels of pain tolerance and cognitive responses to physical sensations found among different individuals (DEWS 2007b).

PREVALENCE

An accurate snapshot into the prevalence of DED is difficult to capture since various studies have employed different definitions of 'DED' as well as different study methods, that is, surveys, examinations, or a combination of both (DEWS 2007b). Current estimation of DED prevalence in the United States among women younger than 50 years is about 5.7%, which increases to 9.9% at older than 75 years and more. Age-adjusted prevalence is about 7.8% for women older than 50 years and more (Schaumberg et al. 2003). Meanwhile, the prevalence of DED among men of age 50–54 years is estimated at 3.9% and increases to 7.7% for men older than 80 years and more. The age-standardized prevalence was 4.3% for men older than 50 years and more (Schaumberg et al. 2009). In both studies, cross-sectional surveys were filled out by thousands of women and men. The definition of DED for both included either a clinical diagnosis of DED or severe symptoms of constant or frequent dryness and irritation (Schaumberg et al. 2003, 2009). In addition, a study in Taiwan including Chinese individuals older than 65 years found that 33.7% of the 1361 participants were symptomatic of DED (one or more symptoms often or all of the time) and 96% displayed at least one positive clinical sign such as TFBUT ≤10 sec. positive corneal staining, or a Schirmer's score ≤5 mm/5 min (Lin et al. 2003). However, in overview of eight large epidemiological studies of DED, a prevalence range of approximately 5–35% was revealed (DEWS 2007b). Once again, there was a difference in DED definitions, populations, and age groups. In general, trends in the prevalence of DED have emerged; namely, the disease seems to affect women more than men (Lin et al. 2003, Moss et al. 2000, Schaumberg et al. 2003, 2009) and its frequency increases with age (Moss et al. 2000, Schaumberg et al. 2003, 2009).

Since 2007, new prevalence data on DED have been published routinely. Several recent examples include a cross-sectional survey conducted in July 2010 of 1902 senior high school students in Shouguang, a county of Shandong Province, China, where the prevalence of DED was found to be 23.7%, which is significant because DED is clinically considered to be a disease of the elderly. In contrast, a recent study of US military veterans at the Miami and Broward Veterans Affairs eye clinics (Galor et al. 2011) showed an overall DED prevalence of 12% in male and 22% in female patients, with female gender imparting a 2.40 × increased risk [95% confidence interval (CI) 2.04–2.81] over male gender. This demonstrates the importance of using consistent definitions of DED in the assessment of prevalence when comparing across studies. **Table 4.1** highlights the most commonly reported prevalence studies, including updates from the 2007 DEWS epidemiology report (DEWS 2007b).

Table 4.1 A summary of the most commonly reported prevalence studies on dry eye disease (DED)

Study	Sample size	Year	Age group (years)	Prevalence (%)
Salisbury Eye Study (Schein et al. 1997, 1999)	2,420	1999	≥65	14.6
Beaver Dam (Munoz et al. 2000)	3,722	2000	≥48	14.4
Sumatra (Lee et al. 2002)	1,058	2002	≥21	27.5
Women's Health Study (Schaumberg et al. 2003)	36,995	2003	≥49	7.8
Blue Mountains (Chia et al. 2003)	1,075	2003	≥50	16.6
Melbourne Visual Impairment Project (Chia et al. 2003)	926	2003	≥40	5.5
Shihpa (Lin et al. 2003)	2,038	2003	≥65	33.7
Japanese High School (Uchino et al. 2008)	3,433	2008	15–18	4.3, males; 8.0, females
Physician's Health Studies I and II (Schaumberg et al. 2009)	25,655	2009	≥50, ≥80	3.9, 7.7
Beijing Eye study (Jie et al. 2009)	4,439	2009	≥40	21
Henan Eye Study (Guo et al. 2010)	657	2010	≥65	30.3
Miami Veterans (Galor et al. 2011)	16,862	2011	≥65	12, males; 22, females
Koumi, Japan (Uchino et al. 2011)	2,791	2011	≥40	12.5, males 21.6, females
Korea (Han et al. 2011)	657	2011	≥65	30.3
Shouguang, China High School (Zhang et al. 2012)	1,902	2012	15–18	23.7

INCIDENCE

The incidence of a disease may be thought of as the rate at which new cases of that specific condition arise over a specific time period. The incidence of DED was discovered to be 13.3% over a 5-year time interval (Moss et al. 2004), and was followed by a 10-year report demonstrating an incidence of 21.6% (95% CI 19.9–23.3%) (Moss et al. 2008). The incidence of DED was significantly associated with increasing age. In addition, after adjusting for age, the incidence was greater for individuals who had a history of allergy or diabetes, who used antihistamines or diuretics, and who reported poorer self-rated health. Moreover, the incidence was less for individuals who used angiotensin-converting enzyme inhibitors or who consumed alcohol (Moss et al. 2004). Follow-up data from the same research team demonstrated similar findings, with the additional new findings of higher incidence after adjusting for age, thyroid disease not treated with hormones, and use of antianxiety medications, antidepressants, oral steroids, or vitamins (Moss et al. 2008). In addition to previously reported variables, incidence was lower for those with a sedentary lifestyle (Moss et al. 2008).

Several medical conditions have been found to increase DED risk, including post-traumatic stress disorder [odds ratio (OR) 1.97, 95% CI 1.75–2.23], depression (OR 1.91, 95% CI 1.73–2.10), thyroid disease (OR 1.81, 95% CI 1.46–2.26), and sleep apnea (OR 2.20, 95% CI 1.97–2.46) (all analyses adjusted for gender and age). The use of several systemic medications, including antidepressant medications (OR 1.97, 95% CI 1.79–2.17), antianxiety medications (OR 1.74, 95% CI 1.58–1.91), and antibenign prostatic hyperplasia medications (OR 1.68, 95% CI 1.51–1.86), was likewise associated with an increased risk of DED (Moss et al. 2004, 2008). Recent findings validate the association of post-traumatic stress disorder, depression, and medications taken for these conditions with DED; whether causal or a downstream effect, depression is commonly reported by patients with DED and may have clinical significance in managing the condition.

FINANCIAL BURDEN OF DED

The financial burden of DED may be significant especially when one considers the high prevalence of this condition (Mizuno et al. 2012). The financial burden results from costs such as office visits, surgical interventions, prescription and over-the-counter medications, specialized eyewear, and humidifiers (DEWS 2007b). Indirect costs such as lost work time, decreased productivity, and alterations in the work environment also contribute to the economic burden (DEWS 2007b). The financial burdens are recognized in many countries around the world. A recent Japanese study included 118 patients, 47 of whom had Sjögren's syndrome (SS) and an average age of 64.1 ± 11.2 years, consistent with the typical age of a DED patient. The direct cost per person was determined to be US$530 per year (Mizuno et al. 2012). Furthermore, a study involving six European countries found that the average cost to manage DED patients per year was about US$622 (Clegg et al. 2006). These costs included office visits, medications, and surgical procedures such as tarsorrhaphy and punctual plug occlusion (Clegg et al. 2006). Furthermore, another study estimated that office visits for SS patients were estimated at US$211 in 2003 (Reddy et al. 2004). Finally, a 2009 study estimated that in the United States alone, 7–10 million individuals spent $320 million per year on artificial tear preparations (Gayton 2009). Indirect costs of DED are a cause for concern for the patient as they often involve loss of work time. One study estimated the opportunity cost of multiple office visits per year for DED to be about US$500 (Mizuno et al. 2012). Furthermore, it has been estimated that because of ocular discomfort, DED patients and SS patients do not attend 2–5 days of work per year, respectively, yet the loss of productive work hours can far exceed that time estimate (Nelson et al. 2000). Of the severe DED patients in the study, 11% were forced to cut back on working hours and experienced DED symptoms 191–208 working days per year (Nelson et al. 2000). The economic burden of DED, therefore, appears significant and detrimental.

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QUALITY OF LIFE

DED has a displayed a significant correlation with a decline in quality of life in a number of studies (Mertzanis et al. 2005, Miljanovic et al. 2007, Pflugfelder 2008, Schiffman et al. 2003). Persons who suffer from DED are likely to report very frequent symptoms of both dryness and irritation (DEWS 2007b), and these symptoms are commonly included in many definitions of DED in epidemiological studies. Individuals diagnosed with DED or severe symptoms were found to have measurably more difficulty than those without DED in carrying out common and important tasks. These tasks included reading, completing professional work, using a computer, driving at night or during the day, and watching television (Miljanovic et al. 2007). Furthermore, a utility assessment was conducted among individuals diagnosed with DED (Schiffman et al. 2003) to quantify patient preferences for health outcomes. A typical utility assessment scale ranges from 0 to 1.0, and the closer the score is to 1.0, the better the quality of life (Schiffman et al. 2003). In this study, individuals rated their own DED at a mean value of (0.81) with a range of 0.16–0.97. Furthermore, they rated moderate DED at (0.78), severe DED at (0.72), and severe DED requiring tarsorrhaphy at (0.62). These results display the perceived decrease in quality of life in proportion to increasing severity of DED. In comparison, moderate to severe angina historically was reported at (0.71) and a disabling hip fracture at (0.65). The reported score for severe DED resulting in loss of utility was similar to the score reported for moderate to severe angina. This exposes the severity at which DED sufferers view their own condition (Schiffman et al. 2003), which is often underestimated by practitioners (Chalmers et al. 2005).

SPECIFIC OCULAR SURFACE CONDITIONS

Sjögren's syndrome

Sjögren's syndrome is considered an autoimmune disease characterized by chronic inflammation involving the exocrine glands, which may result in a severe form of DED and/or dry mouth (DEWS 2007a; Nikolov & Illei 2009). The syndrome has a strong female predominance; estrogens are believed to be contributory whereas androgens (e.g. testosterone) are believed to be protective (Nikolov & Illei 2009). It is estimated that SS affects women nine times more frequently than men (Segal et al. 2009). The peak of onset is around menopause, and the change in androgen–estrogen ratio is viewed as a risk factor, rather than the absolute level of estrogen; it is hypothesized that there exist contributing genetic, environmental, and random factors that may cause SS (Nikolov & Illei 2009). Ocular complaints may include burning, grittiness, fatigue, blurred vision, and watery eyes from reflex tearing, which can be significant to patients. Over time, there may be deterioration in ocular surface, ulceration, tear film debris, and mucus strands adhering to the cornea (Nguyen et al. 2007). In addition, the impact of SS on quality of life is substantial; patients have been reported more likely to be disabled and suffer pain, fatigue, depression, and cognitive symptoms than the controls (Segal et al. 2009). Depression was reported in 37% of SS patients versus 12% of controls (same age and gender) in a recent study (Segal et al. 2009). Moreover, SS patients were more likely to experience hospitalization and more frequent infections, and use multiple medications; patients' out-of-pocket dental expenses for the past year were reported three times greater than those for the peer group (Segal et al. 2009).

Meibomian gland dysfunction

Meibomian gland dysfunction (MGD) is defined as a 'chronic diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative or quantitative changes in glandular secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation and ocular surface disease' (Nelson et al. 2011). Currently, there exist a number of studies that evaluate symptoms as well as clinical correlates, such as lid telangiectasia, gland orifice capping, gland drop-out, and TFBUT, to help determine a more accurate prevalence of MGD in the context of DED (Schaumberg et al. 2011). The prevalence of MGD reported in the literature varies greatly from 3.5% to almost 70% and depends on the methods used to define MGD (Schaumberg et al. 2011). Even given these differences across studies, the prevalence in Asian populations appears higher than that reported in populations consisting mostly of Caucasians. For example, the reported prevalence was 60.8, 61.9, and 69.3% in the Shihpai Eye Study (Lin et al. 2003), the Japanese study (Uchino et al. 2006), and the Beijing Eye Study (Jie et al. 2009), respectively (Schaumberg et al. 2011). In contrast, the reported prevalence was 3.5% in the Salisbury Eye Evaluation Study (Schein et al. 1999) and 19.9% for the Melbourne Visual Impairment Project (Chia et al. 2003). However, each of these studies utilized different definitions of MGD, different clinical signs, and different age groups, so a direct comparison is cautioned (Schaumberg et al. 2011). Knop et al. (2011) provide an excellent and thorough explanation of MGD. They report possible causes of MGD including hyperkeratinization as a reason for obstructive MGD, which causes degenerative gland dilation and atrophy without inflammation. Factors enhancing epithelial keratinization include aging, hormonal alterations, medication toxicities, and even contact lens wear (Knop et al. 2011). Furthermore, it was reported that androgens promoted the production of lipids and decreased keratinization, and that androgen deficiency may lead to MGD (Schirra et al. 2006). Furthermore, abnormalities of the lid margin and also meibomian gland dropout increase significantly with age, notably for age >50 years (Den et al. 2006). Additionally, aging has been associated with significant changes in lipid profiles of human meibomian gland secretions. The secretions of polar and neutral lipids were greater for younger men and women (mean age 37.3 and 36.4 years) than for older men and women (mean age 70.1 and 70.6 years) (Sullivan et al. 2006). Moreover, increasing age was correlated with increasing opacification of meibomian gland secretions as well as eyelid and eyelid margin changes (Sullivan et al. 2006). It was hypothesized in this same study that an androgen deficiency, at least in part, may explain the effects of aging on meibomian glands.

Contact lens dry eye

Contact lens wear has been associated with DED. It is estimated that the frequency of contact lens contact lens dry eye is becoming the accepted terminology is about 50% with approximately 17 million wearers affected in the United States alone (Ramamoorthy & Sinnott 2008). In a study including 360 subjects, several factors were reported to be significantly associated with DED status, including recent lens refitting, artificial tear or rewetting drop usage, and high-water-content lenses (Ramamoorthy & Sinnott 2008). Patient-related factors associated with DED status included DED diagnosis or symptoms in the absence of contact lenses, decreased satisfaction with current contact lenses, reduced daily wear time, and reduced ability to wear lenses for as long as desired. Another large study ($n = 730$) to determine fre-

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quency and factors associated with contact lens dissatisfaction and discontinuation found that 26.3% expressed contact lens dissatisfaction and another 24.1% had permanently discontinued contact lens wear. The primary reason for both dissatisfaction and discontinuation was dryness and discomfort (Richdale et al. 2007). There are factors to consider regarding dry and contact lens wear. One may consider if these individuals have predisposing factors even before contact lens wear is attempted or if contact lenses, in fact, induce DED.

SUMMARY

In summary, the field of DED epidemiology has been steadily progressing over the past 5–10 years. New prevalence and incidence data, as well as data assessing associated factors, have increased significantly, and our understanding of fundamental epidemiological concepts related to DED is becoming widely accepted. The next 10 years seem equally promising.

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UNDER PROOFS

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