Experimental Gerontology 47 (2012) 483–490

Contents lists available at SciVerse ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Review

Aging and dry eye disease

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ARTICLE INFO

Article history:
Received 16 February 2012
Received in revised form 21 March 2012
Accepted 23 March 2012
Available online 28 April 2012

Section Editor: T.E. Johnson

Keywords:
Aging
Meibomian gland dysfunction (MGD)
Dry eye disease
FOXO
Retinoic acid
Androgens
Stem cell
Growth hormone
Insulin-like growth factor-1 (IGF-1)
Insulin sensitivity

ABSTRACT

Dry eye disease is a prevalent eye disorder that in particular affects the elderly population. One of the major causes of dry eye, meibomian gland dysfunction (MGD), shows increased prevalence with aging. MGD is caused by hyperkeratinization of the ductal epithelium of meibomian gland and reduced quantity and/or quality of meibum, the holocrine product that stabilizes and prevents the evaporation of the tear film. Of note, retinoids which are used in current anti-aging cosmetics may promote the development of MGD and dry eye disease. In this review, we will discuss the possible mechanisms of age-related MGD.

1. Introduction

The tear film plays an essential role in maintaining ocular surface integrity and health. It is structured in several layers that optimally maintain moisture on the ocular surface. The inner most is an underlying layer of glycocalyx that contains mucin, a highly glycosylated protein synthesized by the conjunctiva and cornea epithelial cells; a middle aqueous layer that is primarily secreted by lacrimal gland; and an overlying lipid layer that is released by the meibomian gland (Nichols et al., 2011). The lipid layer prevents the evaporation of the tear film. Disruption or deficiency of the tear film causes increased sheer stress on the ocular surface that may lead to dry eye disease. If untreated, dry eye disease may result in perforation of the cornea, visual impairment and blindness (International Dry Eye Workshop, 2007).

In the United States, it is estimated that 40 million people are affected by dry eye disease. Dry eye disease is classified into two types: aqueous-deficient and evaporative. The former is due to decreased tear secretion from the lacrimal gland, whereas the latter is caused primarily by meibomian gland dysfunction (MGD). One example of the aqueous-deficient dry eye is Sjögren's syndrome (SS), an autoimmune disease that affects approximately a million Americans. This disorder is associated with lymphocyte accumulation in lacrimal gland, an immune-mediated destruction and/or dysfunction of acinar and ductal epithelial cells, and a decline in aqueous tear output (International Dry Eye Workshop, 2007). The second type, caused by MGD which also frequently occurs in SS, is believed to be the leading cause of dry eye disease worldwide (Nichols et al., 2011). It is estimated that MGD is a contributing factor for over 2/3 of all dry eye cases (Shimazaki et al., 1995). In one report, MGD accounted for 78% of dry eye patients (Horwath-Winter et al., 2003). In Asian populations of adults older than 40 yr, the prevalence of MGD is estimated to be 46.2–69.3%, although the prevalence is lower in Caucasians of the same age group (Schaumberg et al., 2011).

The evaporative dry eye, or MGD, is shown to have a strong positive correlation with aging (Den et al., 2006; Hykin and Bron, 1992; Schaumberg et al., 2003, 2009; Sullivan et al., 2006). In fact, aging is one of the major risk factors for MGD (Schaumberg et al., 2011). Therefore the scope of this review will focus on MGD in aging research.

2. Meibomian gland biology

The meibomian gland is a large sebaceous gland located in the eyelids (Fig. 1). It was named after Heinrich Meibom, the German physician and anatomist who described this gland in detail in 1666. As a sebaceous gland, meibomian gland synthesizes and releases a

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doi:10.1016/j.exger.2012.03.020

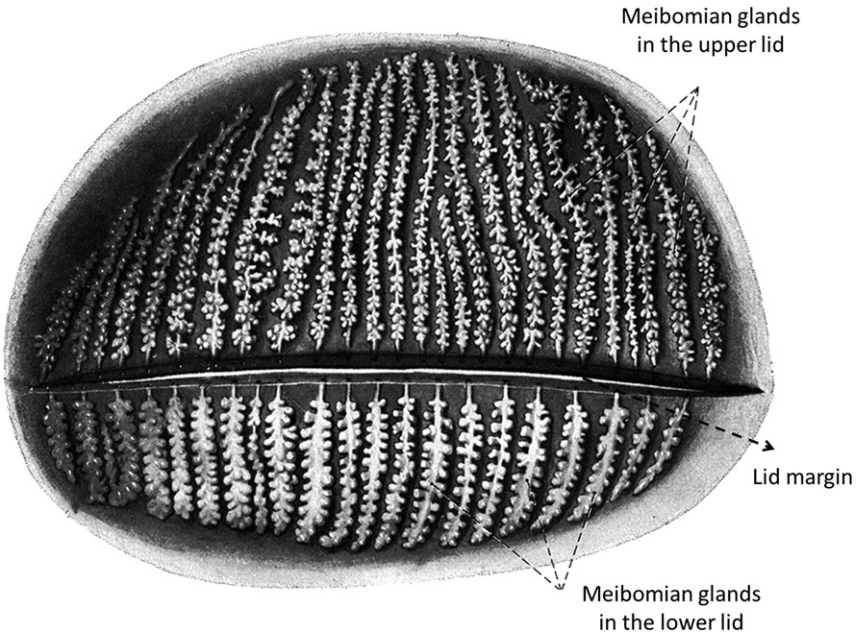

Fig. 1. Topography of the meibomian glands in the upper and lower eye lids. The drawing depicts a posterior view with the anterior part of the lid removed and the connective tissue made translucent so that the glands are exposed.
Reproduced from Springer Science + Business Media: DER OPHTHALMOLOGE, Teil I: Anatomie, Embryologie und Histologie der Meibom-Drüsen, volume 106, 2009, page 872–983, Knop N, Knop E, Fig. 3, which originated from Sobotta: Atlas der Anatomie des Menschen © Elsevier GmbH, Urban & Fischer Verlag München; with kind permission from Elsevier and Springer.

mixture of lipids and proteins called meibum onto the ocular surface to prevent evaporation of the tears. Unlike other sebaceous glands, the meibomian gland is richly innervated and is not associated with hair follicles.

A single meibomian gland is composed of multiple secretory acini that are arranged circularly around a central duct, with the acini being connected to the central duct via short ductules (Fig. 2A). The acinus is composed of secretory meibocytes that differentiate and mature until they become loaded with lipids in a hypermature state, upon which they disintegrate and release the whole cell content (meibum) in a holocrine manner. Meibum is released into the central duct where it moves toward the orifice (opening) on the lid margin and eventually to the ocular surface. Due to their holocrine nature, meibomian gland cells have to undergo constant renewal. New meibocytes emerge from the acinar periphery and differentiate (mature) as they migrate to the lateral duct of the meibomian gland and the cell content, meibum, released to the tear film.

It is believed that MGD is primarily caused by hyperkeratinization of the ductal epithelium and reduced quantity and/or quality of meibum (Knop et al., 2011). On the one hand, obstruction causes low delivery of meibum to the ocular surface, causing evaporative dry eye. On the other hand, the obstruction of the duct by hyperkeratinization and/or viscous meibum causes accumulation of meibum within the ductal system due to the continuous secretion from the acini. Persistent meibum accumulation results in a progressive increase in pressure and thus widening of the ductal system including the small connecting ductules. This results in acinar atrophy with a loss of meibocytes and eventually a squamous metaplasia that may result in full cornification of the epithelia of the ducts and acini (Knop et al., 2011). A comparison of the structure of normal and obstructed human meibomian gland is shown in Fig. 2 (Knop et al., 2009a, 2011). The consequence is reduced meibum secretion and gland dropout, increased evaporation and hyperosmolarity of the tears, increased sheer stress, onset of inflammation at the ocular surface and unstable visual acuity (Knop et al., 2011).

3. MGD and aging in humans

As mentioned earlier, aging is a major risk factor for MGD. In a cross-sectional study involving 177 subjects aged 21–93 yr, a significant association between abnormalities in the lid margin or meibomian glands and aging is observed (Den et al., 2006). Another cross-sectional study of 80 subjects aged 5–87 yr found that lid margin vascularity, cutaneous hyperkeratinization and meibomian gland orifice narrowing increased with age (Hykin and Bron, 1992). Aging in men and women is associated with a significant increase in lower lid erythema, telangiectasia, keratinization, irregular posterior margins, orifice metaplasia and opaque secretions (Sullivan et al., 2006). The number of active meibomian glands also decreases by half from 20 to 80 yr (Norn, 1987) and gland dropout is visible at old age (Arita et al., 2008). Histology of 83 human meibomian gland samples from 17 to 87 yr at autopsy reveals acini atrophy, cystic dilatation of acini and/or ducts and basement membrane thickening of acini (Obata, 2002).

Tear film break up time (TBUT), a clinical measurement of the tear stability, decreases with old age (Arita et al., 2008; Sullivan et al., 2006). Aging is also associated with significant changes in the lipid profiles of human meibomian gland secretions (Sullivan et al., 2006). One type of lipid, cholesteryl esters, is significantly increased in adults compared to infants and children (Shrestha et al., 2011). However, the significance of this related to MGD is not clear because MGD patients secrete meibum that contains lower levels of cholesteryl esters (Shrestha et al., 2011). In terms of meibomian gland cells, recently, it has been shown that aging meibomian glands have decreased meibocyte differentiation and cell cycling (Nien et al., 2011).

4. MGD and aging in animal studies

There are very limited number of animal studies on MGD and aging. In one report, older mice (12 and 24 mo) showed less lipid content and acinar tissue atrophy compared to the young mice (2 and 6 mo) (Nien et al., 2009). Further, the cellular location of peroxisome proliferator-