CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2562897

Available online at: http://www.iajps.com ***Review Article***

DRY EYE DISEASE IN POSTMENOPAUSAL WOMEN: A REVIEW OF THE LITERATURE

Turki Nasser AlSwalem [1], Abdulelah Hassan Alluhaybi [2], Abdurrahman Abdullah Almatrafi [2], Alanoud Khalid Almuhanna [2], Mayar Khalid Shaffei [2], Rahaf Emad Hejazi [2], Rawan Rajallah Aljohani [2], Jannah Abdulrahman Alkinani [3], Fatimah Abdullah Alnassir[4], Khalid Abdullah Almatrafi [5], Nesreen Abdullah Alumair [6]

[1] Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia, [2] Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia, [3] Faculty of Medicine, Ibn Sina National Collage, Jeddah, Saudi Arabia, [4] Faculty of Medicine, Dar Al Uloom University, Riyadh, Saudi Arabia, [5] General Practitioner, Aladel Primary Healthcare Center, Ministry of Health, Makkah, Saudi Arabia, [6] Faculty of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

Abstract:

This review examines the etiology and pathophysiology of dry eye disease in postmenopausal women and describes the steroid reproductive hormone influences that may contribute to its development. We have reviewed the relevant studies on dry eye disease related to hormonal status and hormone therapy (HT) in both animal models and humans. Although both low and high estrogen levels have been associated with symptoms of dry eye disease, low androgen levels are a more consistent factor in its etiology. Postmenopausal HT with estrogen or estrogen plus progestogen has shown a limited benefit for dry eye symptoms and may even result in progression of Meibomian gland dysfunction, decreased tear film breaks up time, and tear flow reduction. However, systemic or local androgen treatment has shown promising results in improving dry eye symptoms. Because of the high incidence of dry eye among postmenopausal women that may be related to the hormonal treatment, we propose that a multidisciplinary approach should be considered between gynecologists and ophthalmologists in management of this disorder.

Key Words: *Dry eye disease, Estrogens, Eye, Postmenopause, Women*

Corresponding author:

Turki Nasser Al-Swalem,

Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia.

QR code

Please cite this article in press Turki Nasser Al-Swalem et al., ***Dry Eye Disease In Postmenopausal Women: A Review Of The Literature.,*** *Indo Am. J. P. Sci, 2019; 06(02).*

INTRODUCTION:

Dry eye disease is particularly problematic in older women. In this review, we aim to raise gynecologists' awareness of the etiology of dry eye disease by addressing the pathophysiology of dry eye disease in relation to age-related steroid reproductive hormone changes. We will suggest that gynecologists play proactive roles in diagnosing and managing what is acknowledged to be a significant ophthalmic disorder.

According to the International Dry Eye Workshop in 2007, dry eye disease is defined as ''a multifactorial disease of 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.'' [1].

Postmenopausal women are at greater risk of dry eye disease than younger women and men [2]. A review of population based epidemiologic studies of dry eye found that estimates of the prevalence range from 7.8% to 33.7%, depending on the population studied and the assessment methods used [3]. In one population aged between 43 and 86 years, dry eye disease occurred in 13.3% and 21.6% during 5-9 and 10-year10 follow-up periods, respectively; the incidence was greater in women (25.0%) than in men (17.2%) and was significantly associated with age [4].

This review examines the etiology and pathophysiology of dry eye disease in postmenopausal women and describes the steroid reproductive hormone influences that may contribute to its development.

METHODOLOGY:

Sample

We performed comprehensive search using biomedical databases; Medline, PsycInfo and Pubmed, for studies concerned with placenta previa published between 1981 - 2019 in in English language. Keywords used in our search through the databases were as {Dry, eye, and Postmenopause}. More relevant articles were recruited from references lists scanning of each included study.

Analysis

No software was used, the data were extracted based on specific form that contain (Title of the study, name of the author, Objective, Summary, Results, and Outcomes). Double revision of each author outcomes was applied to ensure the validity and minimize the errors.

RESULTS and DISCUSSION:

Pathophysiology of Dry Eye

A normal tear film has three major components: a mucin layer associated with the glycocalyx of the superficial layer of corneal and conjunctival epithelial cells, an aqueous layer comprised of lacrimal gland secretions, and a lipid layer produced by modified sebaceous (Meibomian) glands. A sensorimotor loop maintains a normal tear film by balancing aqueous production to tear evaporation. Cold corneal thermoreceptors detect tear evaporation, and signal via neurotransmission to brainstem centers to maintain lacrimal gland fluid production. Nociceptors detect mechanical and chemical irritants, inflammation, and hyperosmolarity, and the sensory signals elicit autonomic motor signals to the lacrimal glands to stimulate tear production [5]. Ocular tissue is considered as a target organ for sex steroid hormones because there are estrogen, progesterone, and androgen receptor mRNAs, which translate into receptor proteins in the lacrimal gland, Meibomian gland, lid, palpebral and bulbar conjunctivae, cornea, iris and ciliary body, lens, and retina in rats, rabbits, or humans [6,7]. Estrogen, progesterone, and androgens bind to their specific cytosolic receptors and modulate gene transcription and expression at these target organs, especially in the Meibomian and lacrimal glands, resulting in different effects on the status of the ocular surface tissues. Evidence that Meibomian gland epithelial cells also express transmembrane, G-protein-coupled receptors for estrogen have been reported in preliminary form, raising. the possibility that steroid reproductive hormones both influence gene expression through other pathways and elicit acute responses that impact ocular surface homeostasis.

Hormonal Influences On Dry Eye

An extensive review of work on hormonal influences on dry eye appeared in the ophthalmic literature in 2004 [8]. Several authors have addressed this topic more recently [9-11]. In addition to the gonadal hormonal changes that occur during menopause, that is, the decreases of gonadal estrogen and androgen production, age-related decreases in adrenal production of dehydroepiandrosterone (DHEA), the major precursor for extragonadal synthesis of testosterone and its metabolites, might contribute to the higher incidence of postmenopausal dry eye disease. A study in women with premature ovarian failure and associated estrogen and androgen deficits showed that they were more likely to have ocular

surface damage and symptoms of dry eye compared with age matched controls. This finding implies that ovarian hormonal changes may contribute to dry eye disease, but it does not address the impact of decreased adrenal DHEA production, which begins earlier in life. A case-control study of hormone levels in postmenopausal women with evaporative dry eye disease found that women with low levels of 17b-estradiol (estradiol), estrone, and testosterone had more severe dry eye [12]. To our knowledge, dry eye has not been reported to be associated with estrogen resistance or aromatase deficiency. However, dry eye symptoms have been found to increase in women using aromatase inhibitors as adjunctive or prophylactic therapy for breast cancer [13,14]. On the contrary, women with increased estrogen level associated with oral contraceptive use also reported dry eye symptoms [15]. In accord with a preliminary report that dry eye symptoms increase during pregnancy, a state characterized by low levels of free estradiol (due to high sex hormone-binding globulin levels), and high levels of progesterone and prolactin, laboratory studies with rabbits have demonstrated that lacrimal gland fluid production decreases, and that rose Bengal staining, an indicator of ocular surface inflammation, increases during pregnancy [16,17]. Estrogens are generally thought to promote autoimmune development, whereas androgens are generally thought to have protective or immunosuppressive effects. The notion that hormonal influences on dry eye disease might be mediated through autoimmune inflammatory phenotypes causing lacrimal gland physiological dysfunction and ocular surface inflammation stems, in part, from studies demonstrating that androgen administration suppresses inflammation in some murine models of Sjo¨gren's disease [18]. There also is considerable support for the thesis that reproductive steroid hormones levels impact Meibomian gland function.

Systemic estrogen plus progestogen effects

There have been controversial results surrounding the effect of estrogen plus progestogen therapy in postmenopausal women using different outcome measurements of dry eye disease such as symptoms of dry eye, Meibomian gland dysfunction, tear stability, tear flow, and ocular surface pathology

Localized estrogen and progestogen effect

Estrogen and progestogen effects on meibomian gland

Depending on the dose, supraphysiological levels of estrogen can impair sebum production with or without causing sebaceous gland regression in human subjects [19]. Physiological levels of estrogen antagonized testosterone-supported sebum production in castrated male rats [20,21]. There are estrogen and progesterone receptors in the meibomian gland, and both hormones influence the expression of numerous genes. Estrogen inhibits the stimulatory effects of androgens on androgen receptor expression in sebaceous glands [22]. Estradiol alters expression of a number of androgen-regulated genes in ways that might be expected to contribute to lipid layer abnormalities, although the implications for dry eye disease remain to be determined. Progesterone also downregulates meibomian gland gene expression, but with a limited effect compared with that of estrogen. Estrogen deficiency due to aromatase knockout in mice has no effect on meibomian gland histology [23].

DRY EYE IN POSTMENOPAUSAL WOMEN:

Menopause, Estrogen and progestogen effects on lacrimal gland There is conflicting evidence on the effects of estrogen and progesterone on the lacrimal gland. Recent studies indicate that ovariectomy decreases fluid production and TBUT and increases ocular surface staining in rats [24,25]. Administration of estrogen exacerbated the changes. Estrogen and progesterone exacerbated the inflammatory process in the lacrimal gland of a murine Sjo¨gren's syndrome model.48 Other researchers showed anti-inflammatory effects, inhibiting lymphocyte infiltration in a murine model and preventing ovariectomy-induced apoptotic processes in the rabbit lacrimal gland [26,27]. However, findings with aromatase knockout mice suggest that estrogen is neither proinflammatory nor anti-inflammatory in C57BL/6J mice. Compared with androgen, estrogen and progesterone are much less influential on gene expression and sexual dimorphism of the lacrimal gland. Estrogen and progestogen effects on ocular surface. The ocular surface has been found to be an estrogendependent organ that varies with hormonal changes during the menstrual cycle. Before menopause, the conjunctival maturation index, including the proportion of basal, parabasal, intermediate, and superficial conjunctival cells, changes throughout the cycle [28]. With an elevated estrogen level, there is an associated decrease in corneal sensitivity, which could decrease tear production in the lacrimal gland [29,30]. Treatment with estrogen was found to upregulate release of proinflammatory cytokines by immortalized corneal epithelial cells, a phenomenon that would presumably exacerbate dry eye pathology. However, this finding has not been substantiated in a study with primary corneal epithelial cells. In a study on mucin regulation in mice, neither estrogen nor progesterone altered mucin distribution or expression. In contrast, a study

in rabbits found that estrogen stimulated mucin secretion from goblet cells [31,32].

CONCLUSSION:

Dry eye disease is prevalent among postmenopausal women. Hormonal imbalance influences the pathophysiology of dry eye. Systemic estrogen alone or estrogen plus progestogen therapy has resulted in conflicting effects on dry eye disease, mostly with no benefit or even an increased risk, whereas systemic or local androgen treatment showed dry eye improvement. However, the evidence still is limited. We suggest that gynecologists consider dry eye disease as an endocrinological disease and take HT into account in cooperation with ophthalmologists in diagnosis and management of this condition.

DISCLOSURE:

No conflicts of interests with respect to the authorship or publication of this article.

REFERENCES:

1. Lemp MA, Bron AJ, Baudouin C, et al. Tear osmolarity in the diagnosis and management of dry eye disease. Am J Ophthalmol 2011;151:792-798; e1.
2. Sullivan DA, Hammitt KM, Schaumberg DA, et al. Report of the TFOS/ARVO Symposium on global treatments for dry eye disease: an unmet need. Ocul Surf 2012;10:108-116.
3. Smith JA. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf 2007;5:93-107.
4. Moss SE, Klein R, Klein BE. Long-term incidence of dry eye in an older population. Optom Vis Sci 2008;85:668-674.
5. Rosenthal P, Borsook D. The corneal pain system. Part I: the missing piece of the dry eye puzzle. Ocul Surf 2012;10:2-14.
6. Suzuki T, Kinoshita Y, Tachibana M, et al. Expression of sex steroid hormone receptors in human cornea. Curr Eye Res 2001;22:28-33.
7. Wickham LA, Gao J, Toda I, Rocha EM, Ono M, Sullivan DA. Identification of androgen, estrogen and progesterone receptor mRNAs in the eye. Acta Ophthalmol Scand 2000;78:146-153.
8. Sullivan DA. Tearful relationships? Sex, hormones, the lacrimal gland, and aqueous-deficient dry eye. Ocul Surf 2004;2:92-123.
9. Truong S, Cole N, Stapleton F, Golebiowski B. Sex hormones and the dry eye. Clin Exp Optom 2014;97:324-336.
10. Rocha EM, Mantelli F, Nominato LF, Bonini S. Hormones and dry eye syndrome: an update on what we do and don't know. Curr Opin Ophthalmol 2013;24:348-355.
11. Versura P, Giannaccare G, Campos EC. Sex-steroid imbalance in females and dry eye. Curr Eye Res 2015;40:162-175.
12. Gagliano C, Caruso S, Napolitano G, et al. Low levels of 17-betaoestradiol, oestrone and testosterone correlate with severe evaporative dysfunctional tear syndrome in postmenopausal women: a case-control study. Br J Ophthalmol 2014;98:371-376.
13. Turaka K, Nottage JM, Hammersmith KM, Nagra PK, Rapuano CJ. Dry eye syndrome in aromatase inhibitor users. Clin Experiment Ophthalmol 2013;41:239-243.
14. Cuzick J, Sestak I, Forbes JF, et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet 2014;383: 1041-1048.
15. Chen SP, Massaro-Giordano G, Pistilli M, Schreiber CA, Bunya VY. Tear osmolarity and dry eye symptoms in women using oral contraception and contact lenses. Cornea 2013;32:423 428.
16. Schechter JE, Pidgeon M, Chang D, Fong YC, Trousdale MD, Chang N. Potential role of disrupted lacrimal acinar cells in dry eye during pregnancy. Adv Exp Med Biol 2002;506(pt A):153-157.
17. Ding C, Lu M, Huang J. Changes of the ocular surface and aquaporins in the lacrimal glands of rabbits during pregnancy. Mol Vis 2011;17:2847-2855.
18. Sato EH, Sullivan DA. Comparative influence of steroid hormones and immunosuppressive agents on autoimmune expression in lacrimal glands of a female mouse model of Sjogren's syndrome. Invest Ophthalmol Vis Sci 1994;35:2632-2642
19. Strauss JS, Kligman AM, Pochi PE. The effect of androgens and estrogens on human sebaceous glands. J Invest Dermatol 1962; 39:139-155.
20. Ebling FJ. The effects of cyproterone acetate and oestradiol upon testosterone stimulated sebaceous activity in the rat. Acta Endocrinol (Copenh) 1973;72:361-365.
21. Ebling FJ, Skinner J. The measurement of sebum production in rats treated with testosterone and oestradiol. Br J Dermatol 1967;79:386-392.
22. Azzi L, El-Alfy M, Labrie F. Gender differences and effects of sex steroids and dehydroepiandrosterone on androgen and oestrogen alpha receptors in mouse sebaceous glands. Br J Dermatol 2006;154:21-27.

23. Darabad RR, Suzuki T, Richards SM, et al. Influence of aromatase absence on the gene expression and histology of the mouse meibomian gland. Invest Ophthalmol Vis Sci 2013;54:987-998.
24. Singh S, Moksha L, Sharma N, Titiyal JS, Biswas NR, Velpandian T. Development and evaluation of animal models for sex steroid deficient dry eye. J Pharmacol Toxicol Methods 2014;70:29-34.
25. Song X, Zhao P, Wang G, Zhao X. The effects of estrogen and androgen on tear secretion and matrix metalloproteinase-2 expression in lacrimal glands of ovariectomized rats. Invest Ophthalmol Vis Sci 2014;55:745-751.
26. Ishimaru N, Saegusa K, Yanagi K, Haneji N, Saito I, Hayashi Y. Estrogen deficiency accelerates autoimmune exocrinopathy in murine Sjogren's syndrome through fas-mediated apoptosis. Am J Pathol 1999;155:173-181.
27. Azzarolo AM, Eihausen H, Schechter J. Estrogen prevention of lacrimal gland cell death and lymphocytic infiltration. Exp Eye Res 2003;77: 347-354.
28. Kramer P, Lubkin V, Potter W, Jacobs M, Labay G, Silverman P. Cyclic changes in conjunctival smears from menstruating females. Ophthalmology 1990;97:303-307.
29. Millodot M, Lamont A. Influence of menstruation on corneal sensitivity. Br J Ophthalmol 1974;58:752-756.
30. Riss B, Binder S, Riss P, Kemeter P. Corneal sensitivity during the menstrual cycle. Br J Ophthalmol 1982;66:123-126.
31. Lange C, Fernandez J, Shim D, Spurr-Michaud S, Tisdale A, Gipson IK. Mucin gene expression is not regulated by estrogen and/or progesterone in the ocular surface epithelia of mice. Exp Eye Res 2003;77:59-68.
32. Aragona P, Puzzolo D, Micali A, Ferreri G, Britti D. Morphological and morphometric analysis on the rabbit conjunctival goblet cells in different hormonal conditions. Exp Eye Res 1998;66:81-88