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MENOPAUSE AND DRY EYE DISEASE – A REVEIW ARTICLE

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ABSTRACT Dry eye disease is a multifactorial ocular surface disorder which can cause debilitating symptoms of burning, foreign body sensation, decreased vision and ultimately affecting quality of life. Among its many risk factors, menopause is considered as an established and an important etiology. It is more prevalent in the females in menopausal and perimenopausal age group which is believed to be due to changes in balance in sex hormones. All the components of the tear film including aqueous layer, lipid and mucin have been influenced by sex hormones like estrogens and androgens. Various mechanisms involving menopause like decrease in hormones production and alterations at their receptor level, interplay to change the ocular surface homeostasis resulting in dry eye disease(DED). Various studies have reported potential role of hormone replacement therapy (HRT) in menopause associated dry eye symptoms. The purpose of this review article is to highlight the hormonal effect on dry eye and to underscore the relationship between dry eye disease and menopause.

KEYWORDS : Dry eye, menopause, hormones

INTRODUCTION:

According to the International Dry Eye Workshop in 2007, Dry Eye Disease (DED) is a multifactorial disease of the tear film 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 tear film and inflammation of the ocular surface. [1] The symptoms of dry eye vary from patients to patients. Symptoms of dry eye include ocular discomfort, foreign body sensation, burning, grittiness, photophobia, blurring, tired eyes and contact lens intolarence. In some patients symptoms are debilitating. DED is one of the main reasons that patients visit eye doctors in the United States. [2] Depending on how it is defined and the population studied, prevalence of dry eye disease ranging from 7% to 33%. [3,4]

Women are 1.5 to three times more likely than men to have the condition. [5,6] DED is prevalent in post menopausal females but women with premature ovarian failure also have a higher risk of dry eye. [7] Various studies have demonstrated that there is a relation between hormones and DED in this group. [8,9,10] It has been established that Androgen have an effect on tear production and function. [8] Systemic hormone replacement therapy has been both harmful and beneficial depending on the hormones and the patients. [11] However , the correlation between systemic estrogen and testosterone and DED is less clear. Studies have shown that Androgen given topically to the eyelids, or as eye drops, promising results with decreased systemic side effects. [12,13]

HORMONAL EFFECT:

Dry eye remains a major challenge in postmenopausal women. Tear film has three components- the aqueous layer secreted by the lacrimal gland, the lipid layer secreted by the meibomian glands, and mucin secreted by the conjunctival goblet cells. Production of all three layers of tear film is influenced by sex steroid hormones-estrogen, progesterone and androgen. Ocular tissue is considered to be a target organ for sex steroid hormones since there are estrogen, progesterone, and androgen receptor mRNAs which have been shown to translate into receptor proteins in the lacrimal gland, meibomian gland, lid, palprebral and bulbar conjunctivae, cornea, iris and ciliary body, lens, and retina in rats, rabbits, or humans. The sex steroid hormones exert their effect possibly by influencing gene expression through other pathways and by eliciting acute responses that affect ocular surface homeostasis. [14,15] The loss of sex steroid hormones in the postmenopausal period may lead to dry eye by causing reduced corneal thickness as well as alterations in homeostasis and in the layers of the tear film. Structural and functional weakening of lacrimal and meibomian glands, attributed to menopause, and significant thinning of the lipid and aqueous layers, as a result of hyposecretion, may result in increase in evaporation leading to increasd tear film osmolarity. This hyperosmolarity activates inflammatory cascades in the cornea and conjunctiva, resulting in subjective symptoms of dry eye. [16]

However, the exact relationship between serum sex hormone level and symptoms of dry eye remain controversial. A study done by Albamowicz et al. found that estrogen and testosterone were both increased in a group of women with dry eye compared to a matched group without dry eye, but this different was not significant. [8] On the other hand, Gagliano et al. stated that postmenopausal women with severe evaporative dry eye had lower levels of estradiol and testosterone than the control group.[17]

DRY EYE:

Patients with dry eye may present clinically with symptoms of irritation, burning, blurred vision, tearing, foreign body sensation, photophobia, contact lens intolerance, redness, mucous discharge, increased frequency of blinking and symptoms that worsen later in the day. Etiological risk factors that have been identified were older age, female gender, arthritis, smoking , multivitamine use, thyroid disease, gout whereas caffeine use was associated with a decreased risk. [18] A thorough ocular history including topical medications, contact lens wear, allergy, ocular surgery and a thorough medical history and smoking need to be evaluated to identify potential contributing factors. On ocular examination, decreased tear meniscus with increased tear break-up time is noted. On slit lamp examination corneal staining is seen. Schirmer's test shows decreased tear production in aqueous deficiency. There is increased tear osmolarity and decreased level of lactoferrin and lysozyme. Medical treatment of dry eye includes topical artificial tear substitute, anti-inflammatory agents, mucolytic agents, autologous serum and systemic omega 3 fatty acids and Tetracyclines. Surgical treatment includes punctual plugs, permanent punctual occlusion, Tarsorrhaphy, eye lid surgery, mucus or amniotic membrane transplantation. Other measures include contact lens and moist chamber spectacle. [19]

Hormonal therapy has been found to play an important role in the treatment of menopause related dry eye.

HOR MONE REPLACEMENT THERAPY:

The influence of hormone replacement therapy (HRT) in menopausal women remains unclear. According to some authors it improves the quality and the volume of the tear film, whereas some believe that it increases the risk of dry eye. It is possible that HRT may alleviate dry eye symptoms by increasing goblet cell density. [20] It is debated whether HRT increases, decreases or does not affect dry eye. Schaumberg et al. reported that estrogen plus progesterone HRT significantly increased the risk over no HRT.[21] It has been reported that high doses of both estrogen only and estrogen plus progesterone HRT result in increased dry eye symptoms compared with lower doses of the same treatment. [11] Other studies have found that HRT actually decreases ocular complaints and increases the tear production. [22,23] The effect of estrogen plus progesterone therapy are less clear, but the most recent study showed a dose- dependent increased risk of dry eye symptoms in women who were on estrogen and estrogen plus progesterone HRT. [11]

TOPICAL ANDROGEN TREATMENT:

From various studies it seems clear that hormones in general, and particularly androgen represent an important trophic factor for the ocular surface, and that their deficiency predisposes to inflammation. It has been reported that androgens play an important role in tear production and consistency through their effects on meibomian and lacrimal function. [13]

It has been seen that systemic androgens are beneficial in dry eye and can provide some symptomatic improvement. This is effective in women with abnormally low level of testosterone, men on androgen blockers, and patients with complete androgen insensitivity syndrome. [24]

HRT especially androgen administered systemically can have significant side effects which are undesirable for peri-and post-menopausal women. To avoid this undesirable effects, androgen eye drops have been introduced to limit the systemic absorption. A study done by National Institute of Health found that 30% of dry eye patients became asymptomatic after receiving a testosterone eye drop compared to 8% in the control group after 6 months of treatment. [25] Only problem was irritation. Later Connor et al. had used a transdermal preparation to be applied to the eyelids, which resulted in a 51% decrease in dry eye symptoms. [12] In a study, 10 out of 12 patients receiving testosterone eye drops with cyclodextrin had significant improvement in signs and symptoms after 2 weeks . These transdermal preparations and newer conjugated androgen eye drops produce symptom relief and are tolerable to most patients.[13]

However the influence of androgen therapy still remain controversial. In a recent prospective-controlled study, dry eye syndrome getting testosterone treatment, did not find any additional benefit in signs and symptoms from placebo for topical testosterone or systemic testosterone and estrogen. [26]

SELECTION OF CANDIDATES FOR TREATMENT:

Though several factors influence patient selection, age and endogenous hormonal levels-seem to be the most important factors. It has been demonstrated that HRT improved tear production in dry eye patients, but the effect was only significant in patients <50 years old.[27] Other studies have shown that estrogen can be helpful in early menopausal period but both systemic and ocular adverse may be more with estrogen in later life. Though younger patients benefit more from andogen eye drop but Connor et al demonstrated that androgen eye drop did not show same degree of symptom relief in premenopausal women.[12]

Endogenous androgen level is another determinant of treatment response. Studies have shown that women with abnormally low testosterone levels experienced complete symptomatic relief from androgen eye drops and systemic testosterone therapy. [28]] Men on androgen blockers and patients with complete androgen insensitivity syndrome are also good candidates for androgen therapy. [24]

FUTURE STUDY TO EVALUATE DRY EYE IN MENOPAUSE:

There is scarcity of large randomized studies with long follow up times to evaluate the effect of HRT in DED in menopausal age group. There are many numerous positive results seen in smaller prospective studies with shorter follow-up time which will eventually encourage for larger studies with longer follow-up. In addition studies should focus on women on peri-menopausal age group and within 10 years of attaining menopause as these patients are candidates most likely to show the greatest benefit. [27] Moreover it is important to investigate the optimal route of hormonal therapy, its side effect and the risk benefit ratio also need to be considered before starting the treatment.

CONCLUSION:

The changes of sex hormone milieu play an important role in the pathophysiology of DED in both perimenopausal and menopausal age group. Unfortunately DED remains unrecognised in this group of women. Very rarely they need more than any simple measure such as lubrication to get relief. Rarely anti-inflammatory , immunomodulatory and surgical interventions are needed in more severe cases of DED. In a present situation various HRT therapies, both systemic and topical are also coming up. It is hencefort important for all health care providers to understand dry eye disease so as to diagnose , treat and seek ophthalmologic intervention where ever necessary.

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