Sex Hormones and Ocular Dryness

Subjects: Ophthalmology

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Dry eye syndrome (DES) is strictly connected to systemic and topical sex hormones. Breast cancer treatment, the subsequent hormonal therapy, the subsequent hyperandrogenism and the early sudden menopause, may be responsible for ocular surface system failure and its clinical manifestation as dry eye disease. This local dryness is part of the breast cancer iatrogenic dryness, which affects overall mucosal tissue in the fragile population of those with breast cancer.

Keywords: dry eye syndrome ; breast cancer ; sex hormones ; ocular surface equilibrium

1. Introduction

Dry eye syndrome is the most common ocular surface disorder, affecting one in five people, with increased prevalence in women than men [1].

The epidemiological sexual disparity of dry eye prevalence suggests sex hormone changes may influence the composition of the tear film as well as the function of different ocular surface structures and components [2][3][4][5][6]. Sex hormones, estrogen, progesterone, and testosterone, are known to play important and different roles in ocular surface homeostasis. As such, sex hormones are vital in the production of the main components of our tear film, including the aqueous layer, lipid, and mucin. The absolute hormone levels, their fluctuations, and changes in hormone receptor (HR) responsiveness are all important factors in determining ocular surface stability.

Systemic sex hormones and their local receptor expression levels may up- or downregulate themselves during the physiological fluctuation of menstrual cycles or menopause [7][8][9][10].

Moreover, in mucosal tissue, the protective mucin barrier appears to be largely influenced by local and circulating sex hormone levels, by modulating key mucin components [3][6][11]. This apical epithelial barrier is constituted by transmembrane mucins, carbohydrate-binding proteins named galectins and soluble mucins, which are highly expressed by the ocular surface [12][13][14][15].

Therefore, the effects of sex hormones are clinically seen in women after breast cancer surgery. In fact, those patients require complex care, since the rapid and necessary treatments lead to a drastic hormonal change, which is abrupt, severe, and unexpected by the patients. The hormonal changes critically subvert the hormonal assets, leading to psychological and physical effects such as a still not well-known systemic dryness. This breast cancer iatrogenic dryness (BCID) may be related: (1) to the functional hyperandrogenism, apparently similar to Polycystic Ovary Syndrome (PCOS), affecting young women; (2) to the pharmacologically induced menopause by aromatase inhibitors (AIs), which causes a two-fold increase in dryness symptoms compared to untreated women; and (3) to a long-term perioperative chemotherapy, which frequently is mandatory [16].

Recently, some authors focused on the association between dry eye syndrome and breast cancer patients, particularly those using AIs [17]. This could be attributed to the decreased aromatization of the A-cycle of steroids, which leads to the conversion of androgens into estrogens, decreasing the extra-ovarian estrogen production and causing sex hormone imbalance [17]. AIs are also increasingly used for the treatment of postmenopausal patients with estrogen/progesterone receptor-positive breast cancer, in subsequent metastatic settings, and as a tool of chemoprevention in women at increased risk of breast cancer [18]. Hence, a comprehensive assessment of one's sex hormone dynamics during cancer treatment and appropriate interventional measures may be essential in minimizing ocular and overall mucosal side effects.

This review aims to describe the impact of breast cancer surgery on women's hormonal setting, by understanding the relationship between physiological sex hormone dynamics and dry eye pathophysiology in similar sex hormone-dependent diseases.

2. The Role of Systemic Hormones Therapy on Ocular Surface

Several studies report the impact of sex hormones on the ocular surface, particularly in patients treated with systemic hormonal replacement therapy (SHRT), which has also been proposed as an interesting strategy to improve the ocular surface and tear functions in DES [19][20][21][22].

Schaumberg et al. [23] reported that women receiving SHRT with estrogen and estrogen plus medroxyprogesterone acetate were at increased risk of DES. A possible explanation for these conflicting conclusions is that the outcome of SHRT depends on estrogen dosage and the age of the individuals when therapy is first initiated. Estrogen may be only beneficial in younger women, as the typical age group of breast surgery recipients, whereas it may be detrimental and/or pro-inflammatory in older females [24]. Clinical evidence suggests that estrogen supplementation either improves dry eye symptoms and tear function or has minimal effects [25]. Despite the lack of a definitive effect of external estrogen, it is likely that changes in hormonal balance ultimately influence the function of various sebaceous glands, including meibomian glands.

3. Functional Hyperandrogenism on the Ocular Surface

When investigating the link between breast surgery and DES, the inherent issue at hand is a potential sex-steroid imbalance and the functional severe hyperandrogenism. However, it remains to be clarified how estrogen or androgen insufficiency or a complex interplay between them serves to increase or protect from dry eye disease. One way to examine this relationship between sex hormone imbalance and dry eye disease is to conduct observational studies in clinical situations where this takes place. Two such examples are patients suffering from polycystic ovary syndrome (PCOS) and patients undergoing menopause. In both conditions, patients experience a relative reduction in blood estrogen and progesterone.

3. PCOS

PCOS is the most common endocrine disorder in reproductive-age women. The clinical features of PCOS are hyperandrogenism, anovulation, and metabolic syndrome. Associated diseases include type 2 diabetes, obstructive sleep apnea, and depression. Risk factors include family history, obesity, and lack of physical exercise. The potential association between hyperandrogenism and dry eye in PCOS was first reported by Bonini et al. in 2007 [11]. In a prospective observational case series, the team demonstrated that 16 PCOS patients, with both clinical and biochemical signs of hyperandrogenism, had significantly higher rates of dry eye symptoms and objective signs compared to 46 patients with ultrasound-proven polycystic ovary without evidence of hyperandrogenism. The findings regarding the higher rates of symptomatic dry eye disease in PCOS patients than controls were subsequently confirmed by Yavas et al. in 2008, Coksuer et al. in 2011, and Gonen et al. in 2013, with all three studies reporting a higher prevalence of evaporative dry eye in PCOS patients [26][27][28]. Coksuer et al. and Gonen et al. further demonstrated that there were no significant differences in aqueous tear secretion, via Shirmer I test, between PCOS patients and controls [26][28]. A study by Yuksel et al. in 2015, comparing dry eye symptoms and signs in 35 PCOS patients with biochemically proven hyperandrogenism with 27 healthy controls, also found significantly lower TF-BUT in PCOS patients [29].

However, unlike other studies, Yuksei et al. found no significant differences between groups in terms of dry eye symptoms. A proposed underlying mechanism for the higher prevalence of evaporative-type dry eye in PCOS was suggested by Baser et al., who noted that the PCOS group had a significantly higher prevalence of MGD compared to controls [30]. However, it is important to note that the diagnostic criteria for MGD used for this study were based mostly on the presence of posterior blepharitis. No objective assessment or grading of meibomian gland expression and meibum content was reported for the study, making the confirmation of MGD relatively subjective. Another proposed mechanism was highlighted by a study by Asfuroğlu et al., who noted a correlation between subclinical systemic inflammation and dry eye severity in patients with PCOS, as determined by the blood neutrophil to lymphocyte ratio (NLR) and TF-BUT, respectively [19]. It is important to note, however, that while NLR may have proven prognostic utility in certain cancers and infections, its usefulness in otherwise healthy patients is not yet established.

Overall, looking at the data from published research, it appears that DES prevalence is high in PCOS patients, and is linked to hyperandrogenism. Furthermore, the type of dry eye that is most prevalent in this cohort is evaporative-type dry eye. However, the underlying mechanism will require further studies, particularly those looking into ocular surface inflammation measured by tear cytokines and impression cytology, as well as tear lipid content determined by lipidomic studies on expressed meibum. It is also important to consider the potential confounding factors and effects of diabetes and obstructive sleep apnea on dry eye prevalence and severity in PCOS patients. Such conditions are independently

known to increase the risk of dry eye disease. Nevertheless, the aggregated results on PCOS and dry eye provide a useful model to determine the potential effects of breast cancer treatment on dry eye symptoms and signs.

4. Discussion

In addition to fighting this terrible disease, patients must face several systemic side effects induced by iatrogenic menopause and by estrogen deprivation therapy, as well as perioperative chemotherapy, with important psychological implications. Among these, BCID and dry eye disease, in particular, are life-threatening complications that critically affect women's daily life, beyond their complex fighting against cancer. This status may be due to a loss or failure of immune regulatory mechanisms, which usually maintain homeostasis by para-inflammation [31][32], subsequent to the hormonal changes, such as in other ocular diseases [33][34]. The BCID pathogenesis is also associated with a systemic estrogen-level drop, and a consequent functional hyperandrogenism, as in case of PCOS, and, rarely, with an unexpected hypoandrogenism, as in case of physiological menopause. Thus, these women after breast surgery experience a severe chronic evaporative dry eye syndrome with mucus filaments and frequent intolerance to wearing contact lenses. Most of them suffer from moderate itching associated with the usual ocular discomfort caused by the dryness.

Such hormonal changes also occur in other phases of women's daily life, such as menopause and the menstrual cycle, as well as in other pathologic conditions such as PCOS and functional hyperandrogenism. In these conditions, an overall reduction in mucosal tissue lubrification and increased mucus production are related to a decrease in the tear aqueous component and an alteration in ocular surface mucin production [11]. Moreover, sex hormones may influence ocular surface-modulating immune response, leading to a low-grade subclinical inflammation, caused by the subverted para-inflammatory mechanisms that maintain ocular surface equilibrium. However, although sex hormone alteration may influence ocular surface status, PCOS and menopause studies have taught us that, rather than a specific activity of estrogens and androgens, it is above all the homeostatic balance between them that guarantees the normal function of the ocular surface. Therefore, an imbalance of sex hormones induces a dysregulation of the innate para-inflammatory response [33], which causes the failure of the ocular surface and overall mucosal dryness.

Despite the multifactorial nature of BCID, meibomian gland physiology is most likely the single major bridge between sex hormones and dry eye disease. Meibomian gland function is balanced between protective androgen effects and androgen-modulating effects of estrogens. Therefore, healthcare providers should be mindful, in the current state of research, that androgens are the main modulator of meibomian gland function and sex hormone-related dry eye. Assessment of androgen levels in dry eye disease patients should be prioritized for patients with sexual hormone imbalances, such as menopause. Before setting up sex hormone-altering treatments, physicians should ideally assess patients' risk factors for dry eye disease; however, these therapies are often necessary to relieve more severe pathologies and symptoms. Therefore, initiating estrogenic or anti-androgenic treatments may be inevitable, despite the high risk of dry eye disease. In these cases of induced dry eye disease, clinicians should first consider the aforementioned local androgen administration or estrogen-progesterone HRTs for postmenopausal women looking for treatment options. Breast cancer is the most common cancer among females and it has devasting consequences in patients' lives. Medical treatment and surgery related physical changes lead to a negative effect on one's body image, depression and anxiety, as well as partner issues related to physical and hormonal changes. For many women, the consequences of iatrogenic menopause or estrogen deprivation therapy have the greatest negative impact on sexual function [35].

However, the ethology of this clinical entity is still controversial, as well as the ocular signs and symptoms. Therefore, the BCID ocular management is still mainly focused on the ocular surface training by lid hygiene, warm compresses and lipophilic artificial tears, as well as by oral omega −3 and −6 supplementation. In fact, the early use of hormonal topical or systemic treatment has been not fully beneficial in improving dry eye disease, and it is still not completely safe in such post-cancer patients.

5. Conclusions

Breast cancer iatrogenic dryness is a systemic condition that is a consequence of the hormonal changes caused by necessary tumor treatments. The ocular involvement with severe dry eye, as well as the overall mucosal dryness, critically limits the daily life choice and activity of such women, therefore should be taken into account in the medical management of this large group of patients.

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