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DRY EYE SIGNS AND SYMPTOMS IN AROMATASE INHIBITOR TREATMENT AND THE RELATIONSHIP WITH PAIN

Short title: AIs and Dry eyes

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ABSTRACT

Purpose: Aromatase inhibitors (AIs) limit the synthesis of oestrogen in peripheral tissues thus lowering levels of oestrogen. The primary aim was to evaluate whether women treated with AIs have altered dry eye symptoms and signs. A sub-aim was to investigate whether symptoms of dry eye in postmenopausal women were associated with symptoms of non-eye pain, ocular pain and self-rated pain perception.

Methods: This cross-sectional, observational, single visit study recruited 56 postmenopausal women (mean age 64.1+7.9 years) and 52 undergoing AI treatment (mean age 66.6+9.0). Ocular symptoms (OSDI, MGD14) and pain questionnaires (PSQ, OPAS) were administered and signs of dry eye and meibomian gland dysfunction were evaluated.

Results: Almost half of each group reported dry eye symptoms, defined as OSDI>12 (48% control, 46% AI). The PSQ score was significantly higher in the AI group (p=0.04). Neither frequency or severity of dry eye (or MGD) symptoms scores were significantly different between groups. In the AI group, meibomian gland expressibility score was worse (p=0.003); there were no differences in any other signs. Higher OSDI scores were associated with higher OPAS eye-pain scores (r=0.49, p<0.001), but not OPAS non-eye pain (r=0.09, p=0.35). Pain perception (PSQ) showed a moderate positive association with OPAS eye-pain (r=0.30, p=0.003).

Conclusions: In this study elevated ocular symptoms were observed in both the AI treated and the untreated groups, with no difference between the groups. Women undergoing AI

treatment for early stage breast cancer had worse meibum expressibility score and increased pain perception compared to an untreated group of women.

KEYWORDS

Aromatase inhibitors, breast cancer, dry eye, meibomian gland dysfunction, oestrogen, pain

ABBREVIATIONS

AI: Aromatase inhibitor; BMI: Body Mass Index; DED: Dry eye disease; IOP: intra ocular pressure; IOSS: Instant Ocular Symptom Survey; MGD: meibomian gland dysfunction; NIBUT: Non-invasive tear break up time; OPAS: Ocular Pain Assessment Survey; OSDI: Ocular Surface Disease Index; PRT: Phenol Red Thread; PSQ: Pain Sensitivity Questionnaire; QOL: Quality of life; UNSW: University of New South Wales.

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INTRODUCTION

Dry eye disease (DED) occurs more frequently in women than men.[1,2] Sex, gender and hormones play an important role in dry eye disease and regulation of the ocular surface, as reviewed in the TFOS DEWS II report.[2] Androgens appear to have a positive effect on tear production and the ocular surface in humans.[3–5] However the role of oestrogen is not well understood[2,6] and there is conflict in the literature regarding its effect on the tear film and ocular surface. [2,6,7]

Post-menopause, ovarian secretion of oestrogens ceases and it is estimated that 100% of oestrogens are synthesised locally in peripheral tissues by intracrinology.[6,8] Aromatase inhibitors (AIs) limit the synthesis of oestrogen from the oestrogen precursor androstenedione[9] in peripheral tissues thus lowering levels of oestrogen. By investigating postmenopausal women treated with AIs it may be possible to observe the effects of absence of oestrogen on tear production and thus DED and meibomian gland dysfunction (MGD).

Previous investigations of dry eye symptoms in postmenopausal women undergoing treatment with AIs showed a two-fold increase in symptoms compared to untreated women.[10–12] It can be hypothesised that reduced oestrogen availability to ocular surface tissues impacts the function and/or morphology of the tear producing glands and thus results in DED and MGD. However, the effect of aromatase inhibitors on clinical dry eye signs has not yet been investigated.

The primary aim of this study was to investigate whether treatment with aromatase inhibitors impacts clinical signs of DED and /or MGD. This study also aimed to investigate whether the associations between symptoms of DED and AIs found by previous studies could be replicated, with the addition of specific questionnaires to also assess symptoms of MGD and pain.

Dry eye symptoms and ocular signs are often poorly associated.[13] Pain perception/sensitivity may help to explain the lack of association between dry eye signs and symptoms.[14,15] Sex and gender appear to affect pain reporting, in systemic pain and in DED.[2] Therefore, two pain questionnaires were included in this study (Pain Sensitivity Questionnaire [PSQ] and Ocular Pain Assessment Survey [OPAS]) to achieve the secondary aim, to investigate whether higher symptoms of dry eye were associated with higher symptoms of general body pain (OPAS), ocular pain (OPAS) and self-rated pain perception (PSQ).

High pain sensitivity and low pain tolerance, measured with heat stimuli applied to the arm, have been shown to be associated with symptoms of dry eye.[15] This suggests people with symptomatic dry eye may be more sensitive to pain and vice versa. Therefore, another objective was to investigate whether associations between dry eye symptoms and signs were impacted by self-rated pain perception.

METHODS

STUDY DESIGN

This was a cross-sectional, observational, single visit study of postmenopausal women treated with AIs and postmenopausal women not undergoing any hormone-based treatment.

The research followed the tenets of the Declaration of Helsinki and informed consent was obtained from the participants after explanation of the nature of the study and prior to starting the study. The research was approved by the Human Research Ethics Committees of St Vincent's Hospital Sydney and the University of New South Wales.

PARTICIPANT SELECTION

Women aged 50 years and over with a minimum of 12 months postmenopause (determined as permanent menstrual cessation of at least 12 months)[16,17] and treated with AIs, were recruited from The Kinghorn Cancer Centre, St Vincent's Hospital, Sydney (October 2017 - May 2018). The control group comprised of postmenopausal women, not taking hormone therapy (including hormone replacement therapy [HRT] or AIs), recruited from the University of New South Wales (UNSW) Optometry Clinic in Sydney and nearby community (September 2017 - June 2018). Women in the control group were enrolled to correspond to the age ranges, and average ages (mean and median), of the women enrolled in the treatment group to avoid age as a confounding factor. On the visit day, women in the treatment group were seen when they attended for their oncology appointment; the control group attended the optometry clinic purely to take part in the research (their attendance was in response to the recruitment advertisement, although some participants had previously attended the optometry clinic for routine eye exams).

Exclusion criteria were: hormone treatment within the preceding 12 months, (other than AI in the treatment group); diagnosis with Sjögren Syndrome (revised European Classification criteria[18]) or other autoimmune disease; concurrent chemotherapy treatment in the AI group or history of chemotherapy in the control group; recent (1 month) ocular or refractive surgery; ocular or systemic conditions and/or treatment (topical/systemic) deemed likely to significantly impact the ocular surface (including current use of anti-acne medication, eye drops to control intra-ocular-pressure (IOP), corticosteroids, immunosuppressants).

G Power (version 3.0) was used to calculate a sample size based on OSDI[19] with a moderate effect for the difference in OSDI symptoms between the AI and non AI groups (effect size of 0.5). For 80% power at alpha =0.05 and effect of 0.5, a sample size of 51 per group was required. Up to an additional 10% of participants were recruited into each group to account for potential missed data.

PROCEDURES

All procedures were conducted in a single visit during clinic hours (8am to 5pm). The clinical procedures were performed on the right eye only, in the order from least to most invasive (grading scales provided in Supplementary Table 1).

Questions regarding general health and medication, including duration of AI use and any prior history of chemotherapy were conducted verbally. Weight and height were self-reported and used to calculate body mass index (BMI). Questionnaires were completed by the participant on an iPad in the following order: Ocular Surface Disease Index (OSDI)[20,21] and MGD Questionnaire (MGD-14)[22] to assess ocular surface symptoms, PSQ[23] to assess self-rated pain perception, OPAS to assess ocular surface pain, the OPAS non-ocular pain

component to assess non-eye pain, [24] and the Instant Ocular Symptoms Survey (IOSS)[25] to assess dry eye symptoms at that moment.

The PSQ assesses self-rated pain perception based on imagined scenarios experienced in daily life. [26] Scenarios are graded on a scale of 0-10 (no pain-most severe pain imaginable), for example: “Q2. Imagine you burn your tongue on a very hot drink.” Therefore, patients do not need to be suffering from pain, of any type, to be able to score the imagined pain in the scenarios presented in the questions. The PSQ was associated with experimentally obtained pain intensity ratings in healthy individuals.[26] The PSQ provides three scores: the overall pain “perception” score (PSQ-total), scores for “pain perception” to scenarios with mild (PSQ-minor) and moderate (PSQ-moderate) pain. [23] The OPAS was specifically designed to measure intensity of ocular pain of any origin and provides scores for non-eye pain.[24]

Slit lamp bio-microscopy was carried out to assess the general ocular surface and eyelid health.

Non-invasive tear break up time (NIBUT) was evaluated using a slit lamp mounted tearscope with grid attachment (Easy Tear View +, Easytear s.r.l. Trento, Italy). NIBUT was recorded as the mean of three readings at the timepoint when the grid pattern reflected in the tear film first distorted.

Tear volume was measured using a Phenol Red Thread (PRT), (Tianjin Jingming New Technological Development Co. Ltd. Tianjin, China).[27]

Integrity of the cornea and conjunctiva were assessed using vital dye staining (Sodium Fluorescein strip [Contacare Ophthalmics & Diagnostics, Gujarat, India] and Lissamine Green

strip [Biovison Limited, Dunstabel, UK]) and the Modified Oxford grading scale.[28] The ophthalmic strips were moistened with saline, shaken to remove excess solution and applied to the temporal inferior bulbar conjunctiva. Following the initial application of lissamine green, Marx line was assessed and graded.[29]

Prior to stain application, the number of capped meibomian glands were counted and lower eyelid telangiectasia was graded as 0 (no telangiectasia) to 3 (>5 telangiectasia)[30–32] Expressibility of meibum was assessed using the Meibomian Gland Evaluator (Tear Science Inc, Morrisville, NC) (Supplementary figure 1) and graded according to published scales.[27,33–35]

STATISTICAL ANALYSIS

All data analysis was performed using IBM SPSS Statistics (version 24). Data were tested for normality using Shapiro-Wilk tests. Independent samples t–tests and Mann-Whitney U tests were used to compare variables between groups. Fisher Exact tests were used to compare dry eye symptoms between groups. Partial correlations were used to examine associations between variables, controlling for AI use and PSQ. A p=value of <0.05 was considered to be statistically significant. AI data was assessed in isolation to examine the effect of chemotherapy on variables.

MAIN OUTCOME MEASURES

The primary outcome measure for this study was dry eye symptoms, measured with the OSDI. The secondary outcome measures were clinical signs of dry eye and/or MGD and pain questionnaire scores.

RESULTS

A total of 109 participants were enrolled. One participant from the control group was excluded from analysis because she had started taking eye drops to control intra ocular pressure (IOP) between the screening and the study visit. Therefore 108 participants were included in the analysis, 56 in the control group and 52 in the AI group (Table 1). In the AI group, 38 women were taking letrozole (73 %), 7 anastrozole (13.5 %) and 7 exemestane (13.5 %). There was no significant difference between the control and AI groups in age, BMI or ethnicity (Table 1). All variables showed non-parametric distribution, other than age and PSQ scores.

Table 1. Demographics of test (AI) and control groups.
Aromatase Inhibitor (AI), Body mass index (BMI), inter quartile range (IQR), standard deviation (SD).

	Control (n=56)	**AI (n=52)**	**p**
Age (mean, SD, range [years])	64.1 ± 7.9 (50.5-80.6)	66.6 ± 9.0 (51.9-93.5)	0.18
AI duration (median, IQR[years])		1.3 [3.0]	
BMI	26.9 ± 6.5	26.8 ± 5.9	0.33
Ethnicity			
Caucasian	51 (91%)	47 (90%)	0.81
Asian	3 (5%)	2 (4%)	
Other	2 (4%)	3 (6%)	

OCULAR SURFACE SYMPTOMS AND PAIN

Six participants in the AI group did not complete the questionnaires because they needed to leave the clinic for transportation reasons. Although these patients could have affected the study outcomes, by the exclusion of these patients' symptom data, this is unlikely as their clinical data was not distinct from the remainder of the participants.46% of the AI and 48%

of the control participants reported dry eye symptoms, as defined by an OSDI score >12 (Figure 1).[36] There was no significant difference between groups in distribution of OSDI scores (p=0.84). There was no significant difference in OSDI, MGD-14 or IOSS scores between the AI and control groups, (Table 2). Pain perception measured using the PSQ was significantly higher in the AI group than the control group for moderate pain scenarios (p=0.045) and total pain (p=0.04) (Table 2 and Figure 2). There were no significant differences between groups in any of the OPAS score domains (Table 2).

Table 2. Group averages for dry eye and pain questionnaires scores.
Key: 2 weeks (2w), Instant Ocular Symptoms Survey (IOSS), Meibomian Gland Dysfunction (MGD-14: 14 questions), Ocular Pain Assessment Survey (OPAS), Ocular Surface Disease Index (OSDI), Pain Sensitivity Questionnaire (PSQ), Quality of Life (QOL), 24 hours (24h).

Questionnaire	**Control (n=56)**		**AI (n=46)**		**p**
	Median [IQR]	**Range**	**Median [IQR]**	**Range**	
Dry eye symptom scores					
OSDI (0-100)	9.8 [18.0]	0.0-68.8	10.9 [13.5]	0.0-72.9	0.84
MGD-14 (0-126)	11.0 [25]	0-96	14.0 [19.3]	0-115	0.63
IOSS (0-10)	2.0 [2.8]	0-8	1.5 [2.0]	0-6	0.21
Pain scores					
OPAS					
total(0-200)	7 [17.0]	0-103	12 [20.6]	0-111	0.30
non-eye pain					
severity (0-20)	2.0 [7.0]	0-16	3.5 [9.3]	0-20	0.35
QOL (0-60)	3.0 [8.0]	0-47	4.0 [13.3]	0-52	0.74
eye pain					
severity 24h (0-30)	0.0 [0.8]	0-16	0.0 [0.0]	0-13	0.37
severity 2w (0-30)	0.0 [1.8]	0-16	0.0 [0.3]	0-19	0.59
QOL (0-60)	0.0 [1.8]	0-27	0.0 [1.0]	0-26	0.80
aggravating factors (0-20)	1.0 [4.8]	0-17	1.0 [3.3]	0-18	0.95
associated factors (0-40)	1.0 [4.0]	0-29	0.0 [7.0]	0-35	0.82
Pain perception scores	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**	
PSQ					
total (1-170)	58.0 ± 21.8	16-117	67.3 ± 23.7	29-132	***0.04***
minor pain (0-70)	21.3 ± 11.1	6-52	25.1 ± 12.1	9-63	0.09
moderate pain (0-70)	36.8 ± 11.8	10-65	42.2 ± 13.1	17-70	***0.045***

OCULAR SURFACE AND MGD SIGNS

Meibomian gland expressibility score was worse in the AI group (p=0.003) (Figure 2, Table 3; see also supplementary data Figure 2). There were no significant differences between the AI and control groups in tear function, ocular surface staining or other MGD signs (Table 3).

Table 3. Group averages for clinical signs of dry eye and MGD.
Key: meibomian gland (MG), non-invasive tear break up time (NIBUT), phenol red thread (PRT).

Dry eye and MGD signs	**Control (n=56)**		**AI (n=52)**		**p**
	Mean ± SD or Median [IQR]	**Range**	**Mean ± SD or Median [IQR]**	**Range**	
Corneal Staining (0-5)	0.0 [0.0]	0-1	0.0 [0.0]	0-3	0.91
Conjunctival staining (0-5)	2.1 ± 1.2	0-4	2.2 ± 1.0	0-4	0.84
Tear Function					
NIBUT (seconds)	8.7 ± 4.1	2.9-24.7	9.3 ± 3.0	4.3-18.1	0.39
PRT (mm)	11.5 ± 7.6	3-35	12.6 ± 6.8	1-30	0.22
MGD					
Capping	0.0 [1.0]	0-8	0.0 [2.0]	0-12	0.18
Marx Line (0-9)	3.8 ± 2.7	0-9	3.5 ± 2.2	0-9	0.73
MG expressibility (0-3)	0 [1]	0-3	1 [1]	0-2	***0.003****
Telangiectasia (0-3)	2.5 ± 0.8	0-3	2.7 ± 0.7	0-3	0.052

ASSOCIATIONS

There was good association between OSDI, MGD-14, IOSS and OPAS eye pain scores (Table 4). OPAS non-eye pain was weakly associated only with the IOSS score. Increased PSQ score was weakly associated with increased OPAS eye, OPAS non-eye and MGD-14. Partial correlations showed that neither AI use nor pain sensitivity (PSQ) had any effect on these relationships.

The only significant association between dry eye signs and ocular surface symptoms or pain was that between reduced NIBUT and increased MGD-14 score(r=-0.24, p=0.02 [controlling

for PSQ r=-0.21 p=0.04, controlling for AI r=-0.24, p=0.015). There was no association between AI duration and any of the variables examined.

Table 4. Summary of significant associations between signs and symptoms of dry eye, MGD and pain sensitivity in postmenopausal women when controlling for AI treatment: rho (p value) shown.
Key: Ocular Surface Disease Index (OSDI), Meibomian Gland Dysfunction (MGD-14 Question), Instant Ocular Symptom Survey (IOSS), Ocular Pain Assessment Survey (OPAS eye: sum of eye pain severity in 24 hours, 2 weeks and effect on quality of life), Pain Sensitivity Questionnaire (PSQ).

	OSDI	MGD-14	IOSS	OPAS eye	OPAS non-eye
OSDI					
MGD-14	***0.75 (<0.001)***				
IOSS	***0.56 (<0.001)***	***0.68 (<0.001)***			
OPAS eye	***0.49 (<0.001)***	***0.69 (<0.001)***	***0.57 (<0.001)***		
OPAS non-eye	0.09 (0.35)	0.14 (0.16)	***0.20 (0.04)***	0.09 (0.36)	
PSQ total	0.09 (0.38)	***0.25 (0.01)***	0.18 (0.07)	***0.30 (0.003)***	***0.23 (0.02)***

EFFECT OF CHEMOTHERAPY

17 of the 52 (33%) participants in the AI group had a history of prior chemotherapy. These participants were significantly younger (61.9 ± 6.3 years) than those without a history of chemotherapy (70.0 ± 9.3 years) (p=0.01). The median duration of AI use was significantly shorter in participants with a history of chemotherapy (0.6 years, IQR 3.5, range 0.2-25.0 years) compared to those without a history of chemotherapy (1.8 years, IQR 3.0, range 0.2-7.0 years) (p<0.001).

There were no significant differences between the two groups for any of the symptoms scores, clinical signs of dry eye or MGD (Supplementary Table 2).

DISCUSSION

The primary aim of this research was to investigate the effects of reduced oestrogen synthesis on dry eye symptoms and signs, in postmenopausal women. No difference in dry

eye symptoms scores were found between women treated with AIs compared to untreated women, however pain perception scores, measured with the PSQ, were significantly higher in the treated group. Meibum was not as clear or as easily expressed in the AI treated group.

In this cross-sectional study, the frequency of dry eye in both AI treated and untreated women was higher than that previously reported for the general population.[1] Almost half of the participants in this study reported dry eye symptoms with an OSDI score > 12 and approximately a quarter had an OSDI score > 22 (indicating moderate or severe dry eye symptoms). [20,21] Inglis et al. also used an OSDI score > 12 to diagnose dry eye symptoms in women in Australia.[12]

The present study did not find dry eye symptoms to be different between postmenopausal women undergoing treatment with AIs and untreated women of the same age. This contrasts with three previous studies which report symptoms of dry eye to be twice as common in women treated with AIs. Notably, the proportion of women treated with AIs who reported dry eye symptoms in this study (46%) is comparable to that reported by Inglis et al. (35%).[12] However, Inglis et al. report a substantially lower occurrence of dry rye symptoms in their untreated group (18%) recruited from a mammography screening clinic in the same catchment area. [12] A retrospective chart review conducted by Turaka et al. of dry eye symptoms in patients presenting to a US cornea service showed that 29% of women treated with AIs reported the symptom of ocular irritation or foreign body sensation, compared to 9.5% of untreated women.[10] A much lower rate of dry eye symptoms (4% in AI treated women and 2% in untreated women) was reported in a world-wide study of the

efficacy and safety of AI for breast cancer recurrence, which relied on voluntary self-reporting of symptoms.[11]

To our knowledge, this is the first study to investigate the effects of AI treatment on ocular surface signs. Significantly worse meibomian gland expressibility was observed in the AI group. Since AI treatment inhibits oestrogen synthesis, this suggests that reduced oestrogen levels impair meibomian gland function.

Our values were comparable to those found by Arita et al. in two different studies, which use the same meibum grading method as used in this study; [34,35] Arita et al. used a similar age group to our study, however they included males and females. Golebioiwski et al.[16]and Ablamowicz et al.[37] also looked at the effect of oestrogens on meibomian glands in postmenopausal women and, using a different grading scale to the one used here, they found values for expressibility and quality to be comparable to the present study. Three of these studies (those by Arita et al. and Ablamowicz et al.) evaluated differences in meibum score between two groups of participants with different dry eye or MGD status: all three studies found a difference in score of one grade, which is comparable to the difference found between AI and non-AI treated women in this study.[34,35,37]

As dry eye signs and symptoms are known to be poorly associated it is not surprising that the difference in meibomian gland expressibility score was not reflected in differences in symptoms. [14,15] NIBUT was not reduced in the AI group in the presence of worse meibomian gland expressibility score suggesting changes in meibum appearance may precede an impact of tear stability. Other clinical signs were not different between AI and untreated women.

The duration of AI use varied from 6 weeks to in excess of ten years. No significant association was found between AI duration and any signs and symptoms of dry eye. This suggests that once maximum oestrogen suppression is achieved, at about 3-7 days of AI use,[38] the extent of the effect of AIs on dry eye remains stable. In contrast, Inglis et al. found longer AI treatment duration to be weakly associated with higher OSDI scores.[12] The average duration for AI use in the study by Inglis et al. (2.5 years [range 1 month-8 years]) was longer than in this study (± 28.6 months, range 4-84) and Turaka et al. found the mean length of treatment before dry eye symptoms were self-reported was 14 months.

This study found no effect of a history of chemotherapy on any signs or symptoms or dry eye, which is consistent with results found by Inglis et al. who assessed effect of chemotherapy on symptoms.[12] Chemotherapy is reported to increase dry eye in patients while they are undergoing treatment,[39–41] but the long-term effects and "wash-out" period are unclear.[41]

Using heat stimuli, Vehof et al. found high pain sensitivity to be associated with symptomatic DED, which implies consideration of pain management is important when treating dry eye, in addition to treating the ocular surface.[15] The PSQ has previously shown association with experimentally obtained pain intensity ratings in healthy individuals. [26] In this study, we investigated the association between PSQ and symptomatic DED. We found self-reported pain perception measured with the PSQ was not associated with OSDI scores, which is in contrast to increased pain sensitivity measured with heat stimuli associated with increased eye symptoms.[15] Measuring pain sensitivity rather than pain perception appears to have an effect on the association with dry eye symptoms.

All three dry eye questionnaires were moderately associated with the eye-pain section of the OPAS. Although they each ask different questions, all the questionnaires which asked about ocular surface symptoms were highly associated. Whilst there was strong association between eye symptoms questionnaires, neither the IOSS nor the OSDI were associated with self-rated pain perception measured using the PSQ. PSQ scores were significantly associated with MGD-14 score, OPAS eye-pain and OPAS non-eye pain.

To investigate whether pain perception may in part explain the lack of association between dry eye signs and symptoms, associations between symptoms and signs were assessed with and without controlling for PSQ scores. Associations between dry eye signs and symptoms were actually weaker in this study when controlling for pain perception. Pain perception does not appear to account for the lack of association between symptoms and signs of dry eye.

In order to test causation, the optimal study design would be a longitudinal study which used baseline data prior to treatment and assessed patients at various time points whilst undergoing treatment. However, a longitudinal study of this same cohort has logistical complications. Recruitment of the AI cohort was difficult due to the stringent exclusion criteria and enrolment in a longitudinal study would be more challenging due to the increased requirements from participants, who are undergoing treatment for cancer. Many of the participants in this clinical study came to Sydney especially for their oncology appointments so timing study visits on schedule to coincide with participants' return visits would be challenging. Some weeks only one or two eligible patients presented to the clinic, with no guarantee that they would be willing/able to participate in the study; this was a

limitation also encountered by Inglis et al. [12] Given the large time and cost investment required for such a longitudinal study in this group, we believe that a cross-sectional design in the first instance is most appropriate.

The high level of dry eye symptoms reported in the control group may be a result of some selection bias in recruitment of the control group. Untreated participants were recruited from the community and UNSW optometry clinic, and it is possible that women symptomatic for dry eye self-selected into the study. This limitation can be overcome in future studies by consecutive recruitment of patients from other clinics in the same catchment area.

A potential limitation of this study is that participants who experienced side-effects with AI use, including dry eye symptoms, may have already discontinued treatment, and thus were not included in our sample. Future longitudinal studies, in which every patient put onto AI treatment is subject to evaluation after a few weeks of treatment, would address this potential bias.

In this study, to grade meibum, we used a 4 point grading scale used by previous studies to explore differences between normal and MGD participants as well as between MGD and aqueous deficient dry eye participants.[33,34] Alternative methods for grading meibomian gland function have also been published, including evaluating number of glands expressing meibum and objective tests, such as meibography, with gland drop out evaluated using image analysis. Unlike diagnostic tests such as the OSDI and tear osmolarity, meibomian gland grading tests do not have universally accepted cut off values for a positive diagnosis,

therefore understanding the clinical significance between grades is open to interpretation by clinicians and would rely on other clinical signs and symptoms to influence management.

In conclusion, in this study elevated ocular symptoms were observed in both the AI treated and the untreated groups, with no difference between the groups. Women undergoing AI treatment for early stage breast cancer had worse meibum expressibility score and increased pain perception compared to an untreated group of women. Meibomian gland function appears to be negatively affected by AI use and should be evaluated in women undergoing treatment.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

FIGURE LEGENDS

Figure 1. Frequency of occurrence of dry eye symptoms (measured with the OSDI) for postmenopausal women treated with aromatase inhibitors and an age-matched untreated control group.

There was no significant difference in frequency of occurrence between the two groups.

Key: dry eye (DE), moderate (mod), Ocular Surface Disease Index (OSDI).

Figure 2. A) pain sensitivity questionnaire (PSQ) total score and B) meibomian gland expressibility score.

Postmenopausal women undergoing treatment with aromatase inhibitor (AI) and an age-matched untreated control group.

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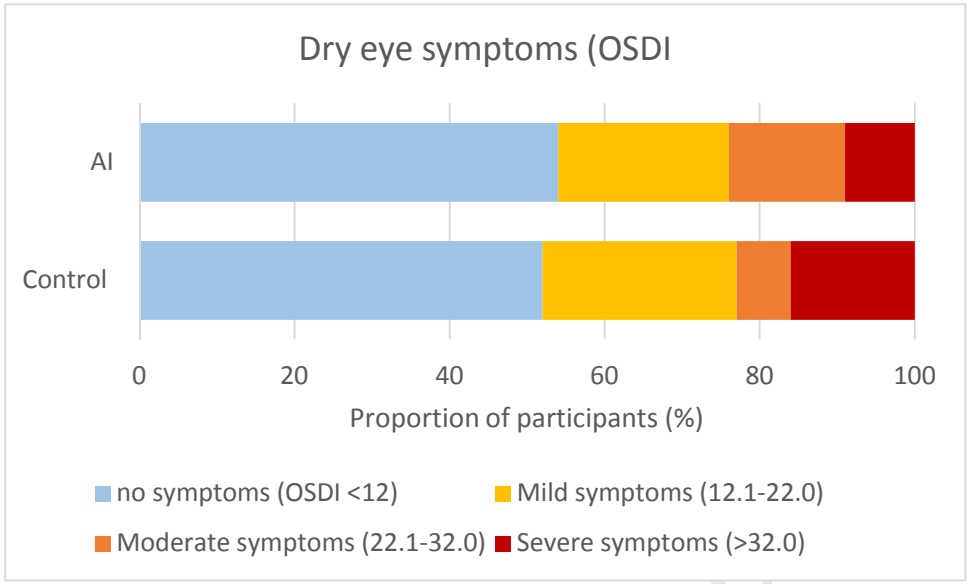
Figure 1



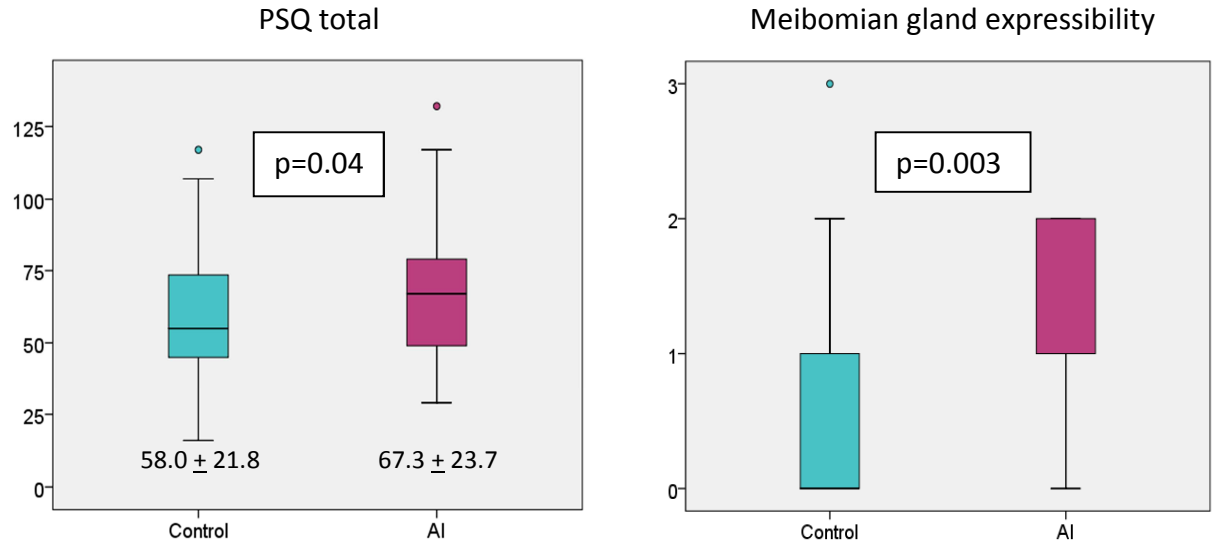


Figure 2