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ARTICLE

Dry eye signs and symptoms in patients on aromatase inhibitor therapy

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Abstract

Purpose The study aimed to test whether symptomatic dry eye in aromatase inhibitor (AI) patients is associated with the clinical features of evaporative dry eye.

Methods A cross-sectional, observational study of postmenopausal women treated with AI was conducted. Clinical information was gathered from their treating clinician. Ocular and treatment symptoms were assessed using validated questionnaires. Clinical assessments were performed to assess for dry eye. The primary outcome measure for this study was dry eye symptoms measured via questionnaire. The secondary outcome measures were clinical signs of dry eye and hormone levels.

Results A total of 25 women on AI were recruited. 64% of women reported symptoms of dry eye (ocular surface disease index ≥ 13). Higher tear osmolarity (323 vs 307 mOsm/L, $p = 0.002$) and increased meibomian gland dropout (4 vs 1, $p = 0.002$) were observed in patients with symptomatic dry eye when compared to asymptomatic patients. Multivariate logistic regression identified that longer duration of AI use and higher tear osmolarity increased the likelihood of a patient experiencing dry eye symptoms.

Conclusion Our study found increased tear osmolarity and meibomian gland drop out in women on AI with symptomatic dry eye. Longer duration of AI therapy and higher tear osmolarity may increase the risk of developing dry eye.

Introduction

One in every eight women is expected to develop breast cancer during her lifetime [1], and a large proportion of such cancers will likely be hormone-receptor-positive [2]. Aromatase inhibitors (AI) are the standard of care in postmenopausal women with oestrogen receptor-positive breast cancer and are widely used in the adjuvant and metastatic settings. In addition, they are increasingly being used as chemoprevention in postmenopausal women at high risk of developing breast cancer. In the foreseeable future, millions of women are likely to use AI [3].

Aromatase inhibitors almost entirely suppress oestrogen synthesis in postmenopausal women by inhibiting the aromatase enzyme. Multiple side effects, predominately related to oestrogen deficiency, have been described including dry eye disease [4–6]. Within the wider population, dry eye disease is the most common eye disorder, affecting up to 1 in 5 people and occurs more frequently in women and significantly impacts quality of life. The proportion of women treated with AI reporting dry eye symptoms ranges from 4 to 46% [4–7], but little is understood of the impact of AI on the ocular surface. It has been hypothesised that a lack of oestrogen for ocular surface tissues impacts their function resulting in dry eye [8–10]. Increasing our understanding of the pathogenesis may aid in the development of new therapies for dry eye.

The primary aim of this study was to test the hypothesis that symptomatic dry eye in AI therapy patients is associated with clinical features of evaporative dry eye. The secondary aim was to investigate whether sex hormone serum levels were associated with dry eye.

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Methods

This study was a cross-sectional, observational, single-visit study of postmenopausal women treated with AI. The study adhered to the tenets of Declaration of Helsinki and was approved by the South Eastern Sydney Local Health District Human Research Ethics Committee (HREC 14/325). Data were reported in line with the STROBE statement for observational data.

Study population

Postmenopausal women treated with AI were recruited from the Prince of Wales Hospital, Prince of Wales Private Hospital and Mater Hospital, Sydney, NSW, Australia. Clinical assessments were performed at the Save Sight Institute, The University of Sydney, Sydney, NSW, Australia. Informed consent was obtained from all participants.

Exclusion criteria were topical therapy for ocular conditions aside from dry eye, eye surgery within one month of the study visit, inability to read English, history of herpes simplex keratitis, recent eye infection in the last 3 months, history of corneal transplant, autoimmune disease (i.e. rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus), ocular cicatricial pemphigoid, Steven-Johnson syndrome, allergic disease, metastatic disease (stage 4), cyclin-dependent kinase inhibitors, participation in ongoing clinical trials and patients who have not had contact with their treating physician for over 1 year.

G Power (version 3.1.9.6) was used to calculate a sample size based on OSDI with a moderate effect for the difference in meibomian gland drop out between symptomatic and asymptomatic dry eye groups (effect size of 0.5). For 80% power at alpha = 0.05 and an effect of 0.5 [11], a sample size of 17 per group was required. However, power analysis from the data collected demonstrated that with 16 symptomatic and 9 asymptomatic dry eye patients, we had a power of 80% to detect an effect size of 0.89.

Clinical assessment

Demographic data (i.e. age and ethnicity), patients' medical history and medications, such as duration of AI use and previous breast cancer treatments were recorded by their treating oncologist. Waist circumference, weight and height were measured by an investigator at Save Sight Institute and used to calculate body mass index (BMI). Questionnaires were self-completed by the participants. The presence of dry eye symptoms was assessed using the Ocular Surface Disease Index (OSDI) and Standard Patient Evaluation of Eye Dryness (SPEED) questionnaires. The presence of endocrine symptoms due to AI treatment was assessed using the Functional Assessment of Cancer Therapy: For patients with Endocrine symptoms (FACT-ES) questionnaire.

All ophthalmic procedures were performed in a single visit. The clinical assessments were performed in both eyes, in the order from least to most invasive as based on the Dry Eye Workshop (DEWS): visual acuity (VA), non-invasive tear break up time (NIBUT), tear meniscus height (TMH), conjunctival inflammation, tear osmolarity, corneal staining, Schirmer I test, and meibography. The Oculus Keratograph 5 M (Oculus, Wetzlar, Germany) was used to assess NIBUT, TMH, conjunctival inflammation, corneal staining and meibography.

Specifically, NIBUT was assessed with the T scan function with patients instructed to blink three times and then keep their eyes open for as long as possible. The first and average break-up time were recorded. TMH was measured from the superior edge of the tear meniscus to the margin of the inferior eyelid, using the photographic and built-in ruler functions, in line with the centre of the patient's pupil and perpendicular to the eyelid margin. The R-scans software analysed the sclera-to-conjunctival blood vessel ratio using the JENVIS grading scale to report conjunctival inflammation. Sodium fluorescein strips (I-DEW FLO, London, UK) were moistened with saline and applied to the temporal inferior bulbar conjunctiva. Corneal staining was then assessed using the integrated JENVIS grading system.

Meibography was performed utilising the infra-red diodes on the Keratograph, allowing the upper and lower eyelids to be transilluminated and assessed. The upper and lower lid meiboscore was determined according to the manufacturer's grading system independently by two investigators.

Tear osmolarity was measured using the TearLab osmolarity system (TearLab, California, USA) with the patient asked to blink three times and tilt their head slightly back, with the eyes looking towards the ceiling. The tear meniscus was then contacted along the temporal aspect of the lower eyelid margin.

A single Schirmer paper strip (I-DEW FLO, London, UK) gently placed halfway between the middle and outer third of the inferior eyelid in each participant without anaesthesia for 5 min was used to measure tear volume.

Blood collection and serum analysis

Venous blood collection was performed either at a Douglass Hanly Moir Pathology centre, Sydney, Australia or New South Wales Heath Pathology (NSWHP) at the Prince of Wales Hospital, Australia. Serum concentrations of cholesterol, testosterone, dehydroepiandrosterone (DHEA), sex hormone-binding globulin (SHBG) and ultra-sensitive oestradiol were assessed at NSWHP.

Cholesterol was determined via an automated enzymatic, colourimetric assay using Roche Cobas C501 (Roche, Basel, Switzerland). Testosterone was determined using supported liquid extraction (SLE) and isotope labelled internal standard. Separation was performed using biphenyl column followed by detection by liquid chromatography-tandem mass spectrometry (LS-MS/MS) (QTRAP 6500) (AB Sciex, Victoria, Australia). DHEA was established using diethyl ether extraction and incubation with ^{125}I-DHEA tracer followed by competition Radioimmunoassay using the Dream5 Gamma Counter (LabLogic, Sheffield, United Kingdom). SHBG was determined via automated electrochemiluminescence sandwich principle using Roche e411 (Roche, Basel, Switzerland). Ultra-sensitive oestradiol assay was established using an SLE and isotope labelled internal standard. Separation was performed using a C18 column followed by detection by LS-MS/MS (QTRAP 6500).

Dry eye diagnosis

Patients were considered to have symptomatic dry eye if they had an OSDI score of ≥13 [12]. All other patients were patients were classified into the asymptomatic group.

Statistical analysis

All data analysis was performed using IBM SPSS Statistics (version 24 for MAC, IBM, USA). Comparative analysis of AI patients with symptomatic dry eye vs asymptomatic was performed. Data were tested for normality using Shapiro–Wilk tests. Independent sample *t*-test and Mann–Whitney U tests were performed on AI therapy patients with symptomatic dry eye vs asymptomatic.

Multivariate logistic regression analysis was performed on AI cohort to assess the likelihood of dry eye in these patients factoring in age, duration of AI therapy, BMI, FACT-ES score and clinical signs. Only clinical sign variables found to be significant (i.e. $p < 0.1$) in the univariate model were subsequently used as covariates in the logistic regression model.

Outcome measures

The primary outcome measure for this study was dry eye symptoms measured via OSDI. The secondary outcome measures were clinical signs of dry eye and serum sex hormones levels in AI patients.

Results

A total of 25 AI therapy patients were recruited across 2 sites. The mean age was 62 years (range 40–76 years). The majority of patients (84%) were of North-West European, two were Southern/Eastern European, and two Asian. There were 16 patients in the symptomatic dry eye group and 9 patients in the asymptomatic group (Table 1). In the symptomatic dry eye group, 7 (44%) patients were prescribed letrozole, 6 (38%) exemestane and 3 (19%). In the asymptomatic group, 8 (89%) were prescribed letrozole and 1 (11%) exemestane. There was no difference between the symptomatic and asymptomatic dry eye group in age, duration on AI, breast cancer treatment, BMI or waist circumference (Table 1).

Ocular surface signs and symptoms

A total of 50 eyes were included in the study. NIBUT, tear osmolarity and upper and total meibography were significantly higher in the symptomatic dry eye group vs asymptomatic ($p = 0.034$, $p = 0.002$, $p = 0.012$ and $p = 0.004$, respectively). There were insignificant differences in VA, TMH, conjunctival inflammation, corneal staining, Schirmer test and lower lid meibography (Table 2). Symptomatic dry eye patients had significantly higher SPEED scores than the asymptomatic group ($p < 0.001$). There was no difference in FACT-ES between both groups (Table 1).

Dry eye and serum sex hormones

Serum concentrations of cholesterol, testosterone, DHEA, SHBG and ultra-sensitive oestradiol levels were similar across both symptomatic dry eye and asymptomatic group (Table 1). All patients were within the normal range for postmenopausal women for serum sex hormones except for oestradiol [13]. 88% of patients in both symptomatic dry eye and asymptomatic group had oestradiol levels of <5 pmol/L.

Predictor of dry eye disease

Multivariate logistic regression was performed to determine the effects of age, duration on AI, BMI, FACT-ES and clinical signs on the likelihood that participants would experience dry eye symptoms. The logistic regression model was statistically significant $p = 0.005$. The model explained 64% (Nagelkerke R^2) of the variance in dry eye and correctly classified 83% of cases. Patients taking AI for longer durations were 1.12 times more likely to exhibit dry eye symptoms than those taking it for shorter durations. Increased tear osmolarity was associated with an increased likelihood of experiencing dry eye symptoms (Table 3).

Discussion

The study compares the clinical features of symptomatic vs asymptomatic dry eye in AI patients. Overall, the study

Table 1 Demographics, questionnaire scores and sex hormone serum levels of all AI patients included in the study. Classification of dry eye disease was based on OSDI score (i.e. ≥13).

	Total	Asymptomatic	Symptomatic	*p*
No. of patients, n (%)	25	9 (36)	16 (64)	
Age, years (mean, SD)	62.3 ± 10	61.3 ± 9.3	62.8 ± 10.6	0.730
AI duration, months (mean, SD)[a]	35.8 ± 26.4	26.87 ± 19.4	40.78 ± 29.04	0.304
Breast cancer treatment, n (%)				
Radiotherapy	18 (72)	6 (67)	12 (75)	0.656
Chemotherapy	24 (96)	7 (79)	12 (75)	0.876
Breast surgery	20 (80)	8 (89)	15 (94)	0.667
Biological therapy	4 (16)	2 (22)	2 (13)	0.524
BMI score	28.4 ± 10.8	27.45 ± 3.5	28.87 ± 13.36	0.759
BMI, n (%)				
Normal	10 (40)	2 (25)	8 (50)	0.394
Overweight	13 (52)	6 (75)	7 (44)	
Obese	2 (8)	1 (13)	1 (6)	
Waist circumference, cm (mean, SD)	80 ± 27	92.6 ± 11.6	72.7 ± 31.1	0.081
Questionnaires (mean, SD)				
OSDI	24.1 ± 18.1	6.2 ± 4.9	34.1 ± 14.6	**<0.001**
SPEED	9 ± 6	5.7 ± 5.0	11.0 ± 4.9	**0.015**
FACT-ES	147.9 ± 19.4	146.4 ± 18.9	148.7 ± 20.2	0.787
Serum levels (mean, SD)				
Cholesterol, mmol/L	5.3 ± 0.9	5.5 ± 0.7	5.1 ± 1.0	0.429
Testosterone, nmol/L	0.6 ± 0.5	0.5 ± 0.1	0.7 ± 0.6	0.202
DHEA, nmol/L[a]	9.6 ± 6.6	7.7 ± 4.8	10.7 ± 7.3	0.698
SHBG, nmol/L	66 ± 32.3	59.3 ± 19.6	69.4 ± 37.1	0.484
Estradiol, pmol/L (n, %)[b]				
<5	21 (88)	7 (88)	14 (88)	0.999
<10	2 (8)	1 (12)	1 (6)	
75	1 (4)	0	1 (6)	

One patient did not follow up with blood collection.

Key: *AI* Aromatase inhibitor, *SD* Standard deviation, *BMI* Body mass index, *OSDI* Ocular surface disease index, *SPEED* Standard patient evaluation of eye dryness, *FACT-ES* Functional Assessment of Cancer Therapy: For patients with Endocrine symptoms, *mmol/L* millimoles per litre, *nmol/L* nanomoles per litre, *pmol/L* picomoles per litre.

[a]Mann–Whitney U test.

[b]Fisher Exact Test.

Bold values shown significant difference i.e. $p < 0.05$.

showed that the proportion of women treated with AI who experienced dry eye symptoms was 64%. Higher tear osmolarity and increased meibomian gland dropout were also observed in patients with symptomatic dry eye and longer duration of AI use increased the likelihood of patients experience dry eye symptoms.

The association between dry eye and AI therapy has been previously reported by several studies [4–7]. A previous study from our group found the prevalence of dry eye to be significantly higher in AI therapy patients than healthy postmenopausal women (35% vs 18%) [6]. In our study, two-thirds of patients reported an OSDI score of ≥13. This was higher than previously reported studies, which reported 4–46% of AI patients experiencing dry eye symptoms [4–7]. The increased number of patients experiencing dry eye in our study is possibly due to the duration of AI use. In our cohort treatment ranged from 8 months to 10 years. While insignificant differences were seen between the symptomatic dry eye and asymptomatic group, logistic regression analysis showed patients taking AI for longer durations were more likely to experience dry eye symptoms. A study by Gibson found no association between AI therapy and dry eye [7]. However, the median duration of AI use was 1.3 years compared to our study of 2.2 years.

The DEWS recommended the use of tear osmolarity as a homeostasis marker for the diagnosis of dry eye [12] as tear osmolarity increases with disease severity [14]. Tear osmolarity is considered as normal at 302.2 ± 8.3 mOsm/L,

Table 2 Clinical signs of AI patients, classified according to asymptomatic or symptomatic dry eye group.

Clinical signs	Total	Asymptomatic	Symptomatic	*p*
Total no. of eyes	50	18	32	
Visual acuity (logMAR)[a]	0.03 ± 0.1	0.03 ± 0.1	0.03 ± 0.1	0.992
NIBUT—1st (secs)[a]	7.9 ± 5.6	6.1 ± 4.3	8.8 ± 6.0	0.063
NIBUT—Average (secs)[a]	11.0 ± 6.1	8.6 ± 5.5	12.4 ± 6.1	**0.034**
Tear meniscus (mm)	0.26 ± 0.1	0.24 ± 0.1	0.27 ± 0.1	0.405
Conjunctival Inflammation	1.5 ± 0.4	1.4 ± 0.4	1.5 ± 0.5	0.398
Tear osmolarity (mOsm/L)	317 ± 21	307 ± 10	323 ± 23	**0.002**
Corneal staining[a]	0 (0–1)	0 (0–1)	0 (0–1)	0.296
Schirmer score (mm)	16.0 ± 11.7	14.4 ± 12.3	16.8 ± 11.4	0.490
Meibography—Upper lid[a]	1 (0–1)	0 (0–1)	2 (1–2)	**0.012**
Meibography—Lower lid[a]	2 (1–3)	2 (1–3)	2 (1–3)	0.236
Meibography total score[a]	3 (2–4)	1 (1–3)	4 (2–4)	**0.002**

Key: *NIBUT* Non-invasive tear break up time, *secs* seconds, *mm* millimeter, *mOsm/L* Milliosmoles per litre.

[a]Mann–Whitney U test.

Bold values shown significant difference i.e. $p < 0.05$.

Table 3 Multivariate logistic regression analysis of factors associated with dry eye in AI patients.

	Odds ratio of DED	Binary logistic regression 95% Confidence Interval	*p*
Age	0.845	0.71–1.00	0.056
Duration on AI therapy	**1.120**	1.00–1.26	**0.050**
BMI score	1.080	0.93–1.26	0.332
FACT-ES	0.964	0.90–1.03	0.285
NIBUT—1st	0.886	0.50–1.57	0.679
NIBUT—Average	1.158	0.94–1.82	0.525
Tear osmolarity	**1.091**	1.01–1.18	**0.035**
Meibography—Upper	2.191	0.37–12.14	0.395
Meibography—Total score	1.291	0.43–3.9	0.653

Key: *DED* Dry eye disease, *AI* Aromatase inhibitor, *BMI* Body mass index, *FACT-ES* Functional Assessment of Cancer Therapy: For patients with Endocrine symptoms, *NIBUT* Non-invasive tear break-up time.

Bold values shown significant difference i.e. $p < 0.05$.

mild to moderate at 315.0 ± 11.4 mOsm/L and severe at 336.4 ± 22.3 mOsm/L. The average tear osmolarity in our entire cohort was 317 ± 21 mOsm/L and 323 ± 23 mOsm/L in those with symptomatic dry eye; both within the range of mild to moderate dry eye [15, 16]. Golebiowski and co-workers investigated the relationship between dry eye symptoms and signs in postmenopausal women. They identified that worse meibomian gland secretion quality and higher tear osmolarity were significant predictors of OSDI symptoms. In their cohort of patients, the mean tear osmolarity was 307 mOsm/L [17], this suggests AI patients may have higher tear osmolarity and hence more severe dry eye than healthy postmenopausal women.

It is known that dry eye signs and symptoms are poorly associated, hence, it is not unexpected that NIBUT was not reflected in AI patients with symptomatic dry eye vs asymptomatic. Our study found NIBUT to be significantly higher in the symptomatic compared to asymptomatic. Two possible explanation for the increase in NIBUT is first, the method of examination for NIBUT via the keratograph inevitably leads to mild reflex tearing due to forced eye-opening required during the assessment that can influence results [18]. Secondly, studies have shown patients with meibomian gland dysfunction (MGD) have mild tear film instability compared to aqueous deficient dry eye patients and increased tear secretion to compensate for the loss of meibomian glands [19–21]. This is supported in our study with the increased number of AI patients with meibomian gland dropout. Similar results were seen by Gibson et al., they compared dry eye signs in AI patients to healthy controls and found no significant difference in tear function or ocular surface staining. However, the meibomian gland expressibility score was worse in the AI group ($p = 0.003$). Since AI therapy inhibits oestrogen synthesis, it is plausible that AI therapy impairs meibomian gland function leading to MGD. Both these causes can affect the interpretation of NIBUT, Koh et al. proposed measuring TMH for accuracy before measuring a non-invasive assessment of tear film stability (i.e. NIBUT) [18].

The female sex is a significant risk factor for the development of dye eye [22]. Existing literature suggests the prevalence is largely attributed to sex hormones [22]. Previous studies have shown higher serum oestrogen levels to

be associated with increased tear osmolarity, reduced tear secretion and stability and MGD [17, 23]. Within our study group, serum sex hormones were not associated with reports of dry eye symptoms. Our patients were within normal ranges for all serum analysis for postmenopausal women except for oestradiol. Normal levels of oestradiol for postmenopausal women ranges between 7 and 78 pmol/L [24]. In our study, 88% of our patients had low oestradiol levels of <5 pmol/L, which is typical for patients on AI therapy [13]. Our study also found no significant difference was seen between symptomatic and asymptomatic group. It should be noted that the mean OSDI score in the asymptomatic group was 6.2 ± 4.9 and all asymptomatic patients reported having minor symptoms of dry eye (OSDI range 2.1–12.5). As all patients in our study reported having dry eye symptoms, this suggests that oestrogen may play a local role through its effect on meibum secretion [17].

Sex steroid receptors are present on the meibomian glands, which are responsible for producing the oil component of tears that prevent evaporation [8]. Androgen binding results in synthesis and secretion of lipids from the glands, while oestrogen causes a decrease in production. The balance between oestrogen and androgen is important for ocular surface homeostasis [25]. However, the exact relationship between serum sex hormones levels and clinical signs and symptoms of dry eye remains unclear. Ablamowicz et al. reported increased levels of oestrogen and testosterone in the dry eye group compared to normal, although the difference was not significant [26]. Gagliano et al. on the other hand found that postmenopausal women with severe evaporative dry eye had lower levels of oestradiol and testosterone [23]. Our study found no significant difference in serum sex hormones in AI patients with symptomatic compared to asymptomatic dry eye. The inconsistencies between studies are likely due to the site of production of oestrogen. In the postmenopausal setting, oestrogen is produced in the target tissues from inactive precursors, whereas in the premenopausal period, they are predominantly produced in the adrenal or reproductive organs. In postmenopausal women, oestrogen exerts activity directly into the tissue they are synthesised in with little diffusion into the blood circulation [27]. Hence, the interpretation of serum oestrogen levels may be limited. The development of a technique to measure sex hormones in tears may prove more useful.

Our study has some limitations, such as small sample size and selection bias. As participation was voluntary, those experiencing dry eye may have been more likely to participate. As a result, our study identified a high level of AI patients with symptomatic dry eye. Nevertheless, our findings were consistent with previous studies investigating the relationship between dry eye and AI therapy. Future studies should consider conducting a longitudinal study, recruiting patients from the initial stage of treatment of AI therapy and assessing patients at various time points throughout their treatment, to determine if there is a cumulative-dose response. An age-matched comparison to normal healthy patients may also identify contributing factors.

With millions of women expected to develop breast cancer during their lifetime, the use of AI therapy is likely to increase. The association between dry eye and AI therapy is relevant for not only oncologists but also optometrists, ophthalmologists and general practitioners. Dry eye can significantly impact a patients' quality of life and treatment compliance with AI therapy. However, there are effective and simple interventions available, if the disease is diagnosed early. Health care professionals can screen AI patients for dry eye using the OSDI questionnaire to identify those who could benefit from an ophthalmic review. Women on AI therapy for breast cancer with dry eye symptoms may not be aware they have dry eye nor seek eyecare [6]. Screening patients on AI therapy with meibography and tear osmolarity may assist identification of dry eye in this group. With increasing access to diagnostic devices for dry eye such screening could be conducted by oncology teams to enable referral to eyecare professionals.

In conclusion, our study found a higher prevalence of dry eye in women on AI, and higher tear osmolarity and increased meibomian gland dropout in AI patients with symptomatic dry eye. The likelihood of a patient experiencing dry eye symptoms increased with longer duration of AI use and higher tear osmolarity. Our study suggests that meibomian gland function may be impacted by AI use and women undergoing such treatment should be monitored for dry eye throughout their treatment. Although serum sex hormones were not associated with reports of dry eye symptoms in our study group, oestrogen may play a role through its effect on the meibomian gland. Laboratory testing on sex hormones in tears may provide more meaningful data.

Summary

What was known before

- A side effect of AIs is dry eye Dry eye can significant impact a patient's quality of life

What this study adds

- Aromatase inhibitor patients with dry eye have higher tear osmolarity and meibomian gland drop out Longer duration of AI therapy may increase the risk of a patient developing severe dry eye

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Author contributions PK was responsible for designing the study protocol, obtaining ethics approval, writing the protocol, patient recruitment, performing clinical assessments, data collection and analysing data, interpreting results and writing the paper. TG was responsible for performing clinical assessment on patients. FB was responsible for providing feedback on the study protocol, patient recruitment, data collection and providing feedback on the paper. SO and BF were responsible for patient recruitment, data collection and providing feedback on paper. SLW was responsible for designing the study protocol, interpreting results and providing feedback on the paper.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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