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Hormone replacement therapy benefits meibomian gland dysfunction in perimenopausal women

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Abstract

Meibomian gland dysfunction (MGD) is believed to be the leading cause of dry eye (DE) disease worldwide. The connection between aging and MGD has long been recognized. However, few studies have addressed the relationship between MGD and hormone replacement therapy (HRT) in perimenopausal women, and not have examined the prevalence of MGD in perimenopausal women. The purpose of this study was to address and evaluate the possible relationship between MGD and HRT in perimenopausal women.

The results suggest that perimenopausal women have a high prevalence of DE related to perimenopausal symptoms. The study also shows that perimenopausal women who use HRT can gain benefits for DE as well as for perimenopausal symptoms. Physicians caring for women who are experiencing DE related to perimenopausal symptoms should consider HRT.

Abbreviations: CFS = corneal fluorescein staining, HRT = hormone replacement therapy, MGD = meibomian gland dysfunction, NITBUT = noninvasive tear break-up time test, SIt = Schirmer I test.

Keywords: dry eye, hormone replacement therapy, meibomian gland dysfunction, perimenopause, women

1. Introduction

Dry eye (DE) is a prevalent eye disorder affecting approximately 25% to 30% of patients in the adult population.[1–3] The prevalence of DE increases with the age process, and its prevalence has been shown to be higher in females than in males.[1] The main cause of DE includes aqueous tear deficiency, excessive evaporation, and inflammation.[4] The evaporative subtype is primarily caused by meibomian gland dysfunction (MGD), with age being a risk factor. MGD is a relatively new area of study in ophthalmological research, and therefore it has not been extensively studied to date.[5] However, MGD is believed to be the leading cause of DE disease worldwide.[6] It is estimated that MGD is a contributing factor for over two-thirds of all DE cases.[7] In 1 study, MGD accounted for 78% of DE patients.[8] In Asian populations of adults more than 40 years of age, the incidence of MGD is estimated to be 46.2% to 69.3%.[9]

Previous studies indicated that the tear production and stability were reduced in postmenopausal women and that hormone replacement therapy (HRT) could recover Schirmer I test (SIt) values to within the normal range.[10–12] However, contradictory results also exist. Some studies reported a greater DE incidence in women on HRT compared to those not receiving the treatment.[13,14] However, MGD was not specifically addressed in these previous studies. Previous epidemiologic investigation has been limited by the lack of agreement regarding a definition or a standardized, clinician-based assessment that characterizes MGD. The degree of prevalence of MGD in perimenopausal women is still unknown. Although the association of aging with MGD disease has long been recognized, very few studies have addressed the potential relationship between MGD and HRT in perimenopausal women, and not one has examined the prevalence of MGD in perimenopausal women. The purpose of this study was to evaluate the possible relationship between MGD and HRT in perimenopausal women.

2. Methods

2.1. Study population

This research followed the tenets of the Declaration of Helsinki and informed consent was obtained from the subjects after an explanation of the nature and possible consequences of the study. The study was performed between January 1, 2010 and June 1, 2015. The Study Protocol was accepted by the Ethics Committee at the Affiliated Second Hospital, School of Medicine, Zhejiang University in Hangzhou, China and the Hangzhou Maternity Hospital in Hangzhou, China. Each enrolled woman gave a written informed consent for participation in the study. Perimenopausal women without previous HRT from the Obstetrics and Gynecology Department of Hangzhou Maternity Hospital were invited to the Eye Center, Affiliated Second Hospital, School of Medicine, Zhejiang University, to undergo the DE examination. The exclusion criteria included all patients who suffered from diseases related to DE, such as diabetes

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Table 1

Perimenopause symptoms questionnaire.

Domain	No	Occasionally	Incontinuous	Continuous
Sleep disturbance	0	1	2	3
Depressed mood	0	1	2	3
Sexual problems	0	1	2	3
Fatigue	0	1	2	3
Bone and joint pain	0	1	2	3
Headache	0	1	2	3
Palpitations	0	1	2	3
Skin creeps	0	1	2	3
Urinary symptoms	0	1	2	3
Dizziness	0	1	2	3

mellitus, Sjogren syndrome, and Stevens–Johnson syndrome. All participants were free of cancer, liver disease, renal disease, stroke, transient cerebral ischemia, myocardial infarction, peptic ulcer, or gout. Women using anticoagulants, corticosteroids, or vitamin A, vitamin E, or beta carotene were also excluded. Although the number of women who reported was smaller than those invited, the results were analyzed.

2.2. Reproductive endocrinology

At baseline, participants reported demographic information including age, race, educational level, civil, and employment status, as well as a detailed medical history and information on lifestyle factors. Perimenopausal women made their own determinations to the use or not use HRT at baseline. HRT women accepted estrogen–progestogen combinations of complex packing estradiol tablets/estradiol and dydrogesterone (Abbott Healthcare Products BV, Weesp, Netherlands). The drug was administered p.o. once daily. A course of therapy was defined as 28 consecutive treatment days. For the 1st 14 days, the daily oral a white tablet (containing estradiol 1 mg) was administered orally, follow by daily oral administration of a gray tablet (containing 1 mg estradiol and dydrogesterone 10 mg) for the remaining 14 days.

The perimenopausal symptoms were obtained from a questionnaire survey. We used a modified criterion based on previous reports,[15] and its questions covered depressed mood, disturbed sleep, sexual problems, and related factors at baseline. Each item was rated from 0 to 3 according to frequency of occurrence: (0 = none; 1 = occasional symptoms; 2 = mild intermittent symptoms; and 3 = recurring obvious symptoms) (Table 1).

2.3. Eye examinations

The eye doctors involved were blind as to which participants were using HRT and which were not. The patients were evaluated through a slit lamp examination, and DE tests were performed as in our previous study: the subjective symptom score, noninvasive tear break-up time test (NITBUT), corneal fluorescein staining (CFS), and SIt.[18] The examination process was completed by the same doctor, and the results were recorded.

2.4. MGD examination

To evaluate MGD, we used a modified criterion based on previous reports,[16,17] which had been used in our previous studies[18] (Fig. 1). The changes of limbus palpebralis and meibomian glands orifices were noted: hyperemia, thickened, obtuse, neovessels, eczema-like appearance, keratinization, irregular shape of eyelid margin, and meibomian glands orifices that vanished. The scores of the palpebral margin were as follows: 0 = no change or imperceptible changes; 1 = mild changes; 2 = moderate variations; and 3 = serious variation. The scores of secretion characteristics were as follows: 0 = lipid clear and transparent; 1 = lipid dirty; 2 = lipid dirty with scraps; and 3 = lipid thick like toothpaste. The upper eyelid and lower eyelid score sum was the final score. The difficulty of lipid excretion using the squeeze test was evaluated. The application of pressure to the central area of the eyelid and 5 meibomian gland orifices within that area was observed and marked: 0 = expression can be observed from all glands; 1 = expression of 3 to 4 gland ducts can be observed; 2 = expression of 1 to 2 gland ducts can be observed; and 3 = no secretion can be observed. The upper eyelid and lower eyelid scores were added together to give the final score. The diagnostic criteria of the MGD included a composite score of more than 2 items which totaled 2 or more points, with or without morphological changes of the eyelid margin.

2.5. Dry-eye examination

(a) SIt: After the application of a topical anesthesia, a filter paper strip (35 mm × 5 mm) was put into the lower eyelid conjunctival sac, and the lengths of the wetted parts were recorded after 5 minutes, and lengths shorter than 10 mm were considered abnormal.
(b) NITBUT: The patient was asked to close her eyes after fluorescein staining, and the time was measured until the 1rst tear film rupture spot appeared. The average value was recorded from 3 measurements, and finally, less than 10 seconds was considered abnormal.
(c) CFS: The score of CFS was based on previous reports[19] and our previous studies.[20] The cornea was equally divided into the upper, middle, and lower 3 sections, and the score of each section was recorded after staining as follows: 0 = no punctate staining; 1 = less than half staining; 2 = more than half staining; 3 = whole staining; and cumulative score for each quadrant (0–9 score). Corneal staining was evaluated at each visit.

2.6. Subjective symptoms

We used a modified questionnaire based on previous reports,[19] which also had been used in our previous studies.[20] The results were obtained from the questionnaire survey, and items regarding foreign body sensation, photophobia, itching, aching, dryness, heavy sensation, blurred vision, fatigue, discomfortableness, ocular discharge, and lacrimation were listed. Each item, according to the frequency of occurrence, was rated from 0 to 3 as follows: 0 = none; 1 = occasional symptoms; 2 = mild intermittent symptoms; and 3 = recurring obvious symptoms, with a possible total of 0 to 33. Table 2 displays these symptoms.

2.7. Dry eye diagnostic criteria

The diagnostic criteria for DE were as follows[21]: if NITBUT ≤ 5 seconds, then both (a) and subjective symptoms could be diagnosed; if 5 seconds ≤ NITBUT ≤ 10 seconds, then (a) + (b) + subjective symptoms could be diagnosed; or if (a) + (c) +

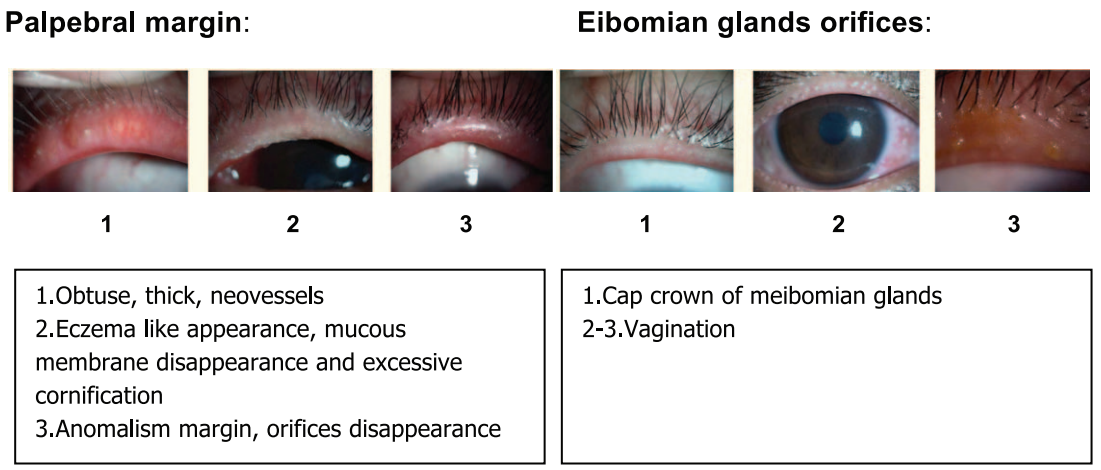

Figure 1. The standard criterion we used to evaluate the degree of meibomian gland dysfunction (MGD).

subjective symptoms could be diagnosed, then DE could be diagnosed.

2.8. MGD Treatment

Routine treatment of MGD and evaporated DE were performed on all patients (apply warm, wet compresses, and artificial tears eye drops).[22] Physical massage and expression of meibomian glands for therapeutic purposes were done after the application of a hot eyelid compress. Traction was applied on the lateral canthus by the massage implementer to immobilize the upper and lower eyelids, followed by compression of the eyelids with the finger of the opposite hand moving from the nasal canthus laterally to the lateral canthus with uniform mobility. Compression was implemented after topical anesthesia was administered. Metal tarsal plate forceps with round square ends were used to forcefully squeeze the lids from the zone of the fornix to the palpebral margin and from the nasal canthus laterally to the lateral canthus. Warm and wet compresses were continued once daily by the patient at home and the squeezing procedure was done once a week by a physician at the hospital. The abovementioned tests were administered to analyze the influence of the treatment on MGD after 15 days, 1 month, and 3 months of treatment.

2.9. Statistical analysis

The SPSS version 18.0 (SPSS, Inc., Chicago, IL) program package was used for statistical analysis. Results are reported as the mean ± standard deviation. In 1 group, the matched-pairs design t test was used, and between groups, a completely random designed 1 factor analysis of variance (ANOVA) was used. Spearman correlations were used to assess the pairwise association among perimenopausal symptoms, DE symptoms, and the results of HRT on perimenopausal and DE symptoms. P values lower than 0.05 were considered statistically significant.

Table 2

Dry eye questionnaire.

Symptom	No	Occasionally	Incontinuous	Continuous
Foreign bodies sensation	0	1	2	3
Photophobia	0	1	2	3
Itching	0	1	2	3
Aching	0	1	2	3
Dryness	0	1	2	3
Heavy sensation	0	1	2	3
Blurred vision	0	1	2	3
Fatigue	0	1	2	3
Discomfortableness	0	1	2	3
Ocular discharge	0	1	2	3
Lacrimation	0	1	2	3

3. Results

Of the 592 perimenopausal women invited to participate in the study, 76 were excluded because they did not present for follow-up at the appointed time after their 1st examination. The statistical analysis included 516 perimenopausal women. The mean age was 48.82 ± 4.26 years (range 35–59 years) (Table 3). Among these patients, there were 486 women (94.3%) with different degrees of perimenopausal symptoms.

Table 4 shows the comparison of perimenopausal symptoms between HRT and non-HRT users in perimenopausal women at baseline. There were no significant differences between HRT and non-HRT users in perimenopausal women in baseline characteristics.

HRT was used by 113 perimenopausal women in this study. HRT had a clear role in the treatment of a variety of perimenopausal symptoms (Table 5). Statistically significant differences were noticed in common perimenopausal symptoms in the HRT group after 1 month of treatments ($t = 12.28$, $P = 0.000$), and this difference remained statistically significant at 3 months ($t = 10.89$, $P = 0.000$) and 6 months ($t = 10.11$, $P = 0.000$). There was no significant difference in perimenopausal women who did not accept HRT at 1 month ($t = 1.61$, $P = 0.108$), 3 months ($t = 1.59$, $P = 0.113$), and 6 months ($t = 1.79$, $P = 0.074$).

Table 3

Sample characteristics.

Characteristic	N, %
Age, years (mean)	48.82 ± 4.26
Ethnicity (Chinese)	516
Education	
≤High school	167 (32.4%)
>High school	349 (67.6%)
Marital status	
Married/cohabitating	497 (96.3%)
Single	19 (3.7%)
Perimenopause symptoms	
Yes	486 (94.2%)
No	30 (5.8%)
Dry eye symptoms	
Yes	471 (91.3%)
No	45 (8.7%)
Hormone therapy	
Yes	113 (21.9%)
No	403 (78.1%)

Table 4

Compare the score of perimenopause symptoms and DE symptoms between HRT and non-HRT users in perimenopause women at baseline.

Baseline characteristics	HRT	Non-HRT	t	*P*
Perimenopause scores	17.6 ± 10.7	17.4 ± 9.3	1.136	0.186
DE scores	15.71 ± 3.4	15.63 ± 2.9	0.678	0.497
NITBUT, seconds	2.97 ± 0.76	3.01 ± 0.89	0.613	0.589
Lid meiboscore (0–6)	4.67 ± 1.15	4.73 ± 1.23	0.627	0.575
Excretion difficulty (0–6)	4.64 ± 1.13	4.76 ± 0.99	0.815	0.422
CFS (0–9)	2.94 ± 1.03	3.05 ± 0.91	0.804	0.463
Eyelid abnormality (0–6)	1.79 ± 1.14	1.75 ± 1.29	0.596	0.695
Slt, mm	7.34 ± 1.36	7.09 ± 1.65	1.357	0.152

P = the results of each stage after treatment and before treatment were compared respectively. CFS = corneal fluorescein staining, DE = dry eye, HRT = hormone replacement therapy, NITBUT = noninvasive tear break-up time test, Slt = Schirmer I test.

DE disease was found in 471 patients (91.3%) and included 448 patients (86.8%) who suffered from MGD. The degree of the DE symptoms was related to the degree of perimenopausal symptoms ($r = 0.679$, $P = 0.000$). The use of HRT was also significant in the treatment of DE in perimenopausal women. It was encouraging to find that improvement in the aforementioned symptoms was greater in the HRT group than in the non-HRT group after treatment, especially in symptom scores, lid meiboscore, excretion difficulty, and CFS. Statistically significant differences were noticed in common DE symptoms scores in the HRT group after 1 month of treatments ($t = 10.61$, $P = 0.000$), and this difference remained statistically significant at 3 months ($t = 11.24$, $P = 0.000$) and 6 months ($t = 10.87$, $P = 0.000$). There was also significant difference in perimenopausal women who did not accept HRT at 1 month ($t = 2.82$, $P = 0.005$), 3 months ($t = 2.53$, $P = 0.012$), but not 6 months ($t = 1.61$, $P = 0.108$). Both groups had great improvements in meibomian gland excretion difficulty. However, the paired sample *t* test demonstrated no significant difference for SIt and eyelid abnormality. We also found the improvement of DE symptoms was significantly related to the improvement of the perimenopausal symptoms ($r = 0.736$, $P = 0.000$). In the non-HRT group, no significant difference was found for NITBUT, SIt, CFS, eyelid abnormality, or ability and quality of the meibum expression. The detailed therapeutic effect on DE was shown in Table 6.

4. Discussion

In this study, perimenopausal women had a higher prevalence of DE (91.3%) than shown in the previous prevalence reports of DE in postmenopausal women.[1–9] Our results suggest that there is a high incidence of DE when women are during menopause and the perimenopausal period. Menopause in aging women may contribute to DE onset or worsening as a consequence of an overall hormonal imbalance.[23] The ocular surface is a morphofunctional unit comprising eyelid margin, tear film, cornea, and conjunctiva. Increasing evidence indicates that these structures are under sex hormone control, and relevant diseases such as DE are often caused by alterations in circulation or local steroid hormone levels.[24] Current understanding of sex hormone influences on the immune system suggests that estrogen may modulate a cascade of inflammatory events, which underlie DE.[25]

MGD appears to be a prevalent problem and potentially damaging to the patient's sense of well-being. In this study, a

Table 5

Compare the score of perimenopause symptoms and dry eye symptoms between HRT and non-HRT users in perimenopause women.

Symptom scores	Baseline (mean ± SD)		After treatment (mean ± SD)			Paired difference		
			1 m	3 m	6 m	1 m vs baseline	3 m vs baseline	6 m vs baseline
Perimenopause	HRT	17.6 ± 10.7	8.3 ± 8. 9	8.7 ± 6.8	8.5 ± 7.4	t = 12.28, P = 0.000	t = 10.89, P = 0.000	t = 10.11, P = 0.000
	Non-HRT	17.4 ± 9.3	17.0 ± 8.6	17.1 ± 7.8	16.7 ± 8.0	t = 1.61, P = 0.108	t = 1.59, P = 0.113	t = 1.79, P = 0.074
DE	HRT	15.71 ± 8.4	8.2 ± 9.7	7.9 ± 8.9	8.1 ± 10.3	t = 10.61, P = 0.000	t = 11.24, P = 0.000	t = 10.87, P = 0.000
	Non-HRT	15.63 ± 8.9	12.5 ± 9.3	13.7 ± 9.6	15.4 ± 10.2	t = 2.82, P = 0.005	t = 2.53, P = 0.012	t = 1.61, P = 0.108

DE = dry eye, HRT = hormone replacement therapy, SD = standard deviation.

higher prevalence of MGD was found in perimenopausal women, and MGD was shown to have a strong positive correlation with perimenopausal symptoms. In this study, the symptoms of sleep disturbance, depressed mood, and sexual problems occurred in most perimenopausal women. These perimenopausal symptoms may lead to MGD through a decrease in various factors such as hormonal imbalance, absence of blinking, and neural regulation defects. Hormonal imbalance in perimenopausal women may also lead to the development of MGD. Basic research suggests that sex hormone levels may influence the lacrimal and meibomian glands.[23] Androgens have been shown to regulate meibomian gland gene expression and lipid production.[26–28] The decline in androgens with age results in impaired lipid synthesis in meibomian gland cells, contributing to MGD in old age.[28,29] Laboratory and preliminary clinical studies also suggest that androgens have a beneficial influence on lacrimal and meibomian gland function.[23]

Perimenopausal symptoms such as disturbed sleep, depressed mood, and fatigue may lead to the absence of blinking because of poor rest. Proper blinking is important in lipid layer maintenance through augmentation of meibomian gland lipid expression and lipid spreading across the tear film. With perimenopausal symptoms in women, as in visual display terminal syndrome, both the blink rate and the number of complete blinks are decreased. Various studies have shown that aliquots of meibum are jetted directly from some glands into the tear film lipid layer,[30,31] and because of this, it is generally accepted that blinking plays a role in the delivery of meibomian lipids to the tear film lipid layer. Fenga et al[32] reported a clinical study of 70 visual display terminal users and found that 52 (74.3%) had MGD. The absence of blinking might contribute to the development of MGD.[18,33,34] However, the relationship between the blink reflex and perimenopausal symptoms still needs further investigation.

In this study, it was shown that perimenopausal women who use HRT could improve the symptoms of DE. The relationship of HRT and decreased DE was consistent after initiation of therapy. Perimenopausal women who never used HRT had DE syndrome improvement at 1 month after MGD treatment. This treatment was not consistent at 3 and 6 months. Previous studies reported a higher DE incidence in women on HRT compared to those not receiving the treatment.[13,14] However, our study indicated that DE, especially MGD, was more prevalent in perimenopausal women, and HRT could resolve NIBUT and MGD to a certain degree. The differing results may come from differences in patient inclusion criteria and different focus fields of DE.

In summary, the present study suggests that perimenopausal women have a high prevalence of DE and MGD and that this is related to perimenopausal symptoms. The study also shows that perimenopausal women who use HRT can experience beneficial effects that can counteract the effects of DE and MGD compared with women who did not use HRT. Physicians caring for women who have DE and MGD related to perimenopausal symptoms should consider the use of HRT for their patients.

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Table 6

Results of the association of HRT with DE among perimenopause women.

DE evaluation	Baseline (mean ± SD)		After treatment (mean ± SD)			Paired difference		
			1 m	3 m	6 m	1 m vs baseline	3 m vs baseline	6 m vs baseline
NITBUT, seconds	HRT	2.97 ± 0.76	4.77 ± 1.13	5.14 ± 0.97	5. 01 ± 0.89	t = 2.65, P = 0.008	t = 3.51, P = 0.000	t = 3.15, P = 0.000
	Non-HRT	3.01 ± 0.89	3.32 ± 0.98	3.06 ± 1.02	2.71 ± 0.93	t = 0.61, P = 0.484	t = 0.68, P = 0.437	t = 1.62, P = 0.106
Lid meiboscore (0–6)	HRT	4.67 ± 1.15	2.59 ± 0.81	2.21 ± 0.75	2. 12 ± 0.69	t = 2.41, P = 0.017	t = 2.64, P = 0.008	t = 2.92, P = 0.003
	Non-HRT	4.73 ± 1.23	4.16 ± 0.94	4.51 ± 1.04	4.71 ± 0.72	t = 0.641, P = 0.688	t = 0.82, P = 0.308	t = 0.31, P = 1.032
Excretion difficulty (0–6)	HRT	4.64 ± 1.13	3.16 ± 0.78	2.59 ± 0.76	2.31 ± 0.83	t = 2.16, P = 0.037	t = 2.68, P = 0.007	t = 3.01, P = 0.001
	Non-HRT	4.76 ± 0.99	3.09 ± 1.05	2.66 ± 0.84	2.29 ± 0.75	t = 2.36, P = 0.018	t = 2.69, P = 0.006	t = 2.94, P = 0.002
CFS (0–9)	HRT	2.94 ± 1.03	1.81 ± 0.85	1. 31 ± 0.69	1.01 ± 0.42	t = 2.01, P = 0.028	t = 2.69, P = 0.007	t = 2.97, P = 0.002
	Non-HRT	3.05 ± 0.91	2.59 ± 0.77	2.71 ± 0.62	2.85 ± 0.61	t = 1.69, P = 0.112	t = 1.32, P = 0.218	t = 0.97, P = 0.311
Eyelid abnormality (0–6)	HRT	1.79 ± 1.14	1.62 ± 0.89	1.57 ± 0.75	1. 51 ± 0.89	t = 0.21, P = 0.925	t = 0.54, P = 0.326	t = 0.51, P = 0.318
	Non-HRT	1.75 ± 1.29	1.66 ± 0.94	1.69 ± 1.06	1.81 ± 0.94	t = 0.39, P = 0.734	t = 0.31, P = 0.758	t = 0.29, P = 0.739
Slt, mm	HRT	7.34 ± 1.36	7.47 ± 2.09	6.98 ± 1.99	7. 61 ± 1.18	t = 0.59, P = 0.628	t = 0.91, P = 0.405	t = 1.21, P = 0.308
	Non-HRT	7.09 ± 1.65	7.61 ± 1.49	7.91 ± 1.34	7.52 ± 1.46	t = 0.66, P = 0.523	t = 0.51, P = 0.609	t = 0.87 P = 0.314

P = the results of each stage after treatment and before treatment were compared, respectively. CFS = corneal fluorescein staining, DE = dry eye, HRT = hormone replacement therapy, NITBUT = noninvasive tear break-up time test, SD = standard deviation, Slt = Schirmer I test.

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