

Effects of Aerobic Exercise on Tear Secretion and Tear Film Stability in Dry Eye Patients

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Research article

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Abstract

Background: To study the effects of aerobic exercise (AE) on tear secretion and tear film stability in dry eye patients.

Methods: Firstly we observed Schirmer \square test and 6 tear compositions detected by ELISA in 34 eyes of dry eye patients and 34 eyes of normal subjects before and after AE. Then we observed 30 eyes of dry eye patients and 30 eyes of normal subjects before and after AE, the evaluated variables included tear meniscus height (TMH), first and average non-invasive tear breakup time (F-NITBUT and A-NITBUT), lipid layer thickness (LLT), number of incomplete and complete blinks, partial blink rate (PBR) and visual acuity.

Results: In dry eye group, compared with baseline, Schirmer \square test at 0 minutes after AE increased significantly ($P < 0.001$), F-NITBUT and A-NITBUT at every time point after AE prolonged significantly ($P < 0.001$, $P = 0.007$, $P = 0.036$; $P < 0.001$, $P = 0.001$, $P = 0.044$), number of incomplete blinks and PBR at 10 minutes after AE decreased significantly ($P < 0.001$; $P < 0.001$) while number of complete blinks increased significantly ($P < 0.001$), visual acuity at 10 and 20 minutes after AE improved significantly ($P = 0.017$, $P = 0.021$). The overall oxidative stress marker 8-hydroxy-2'-deoxyguanosine at 0 minutes after AE decreased significantly compared with baseline ($P = 0.040$).

Conclusion: AE promotes tear secretion and improves tear film stability in dry eye patients. AE may be a potential treatment for dry eye.

Trial registration: Chinese Clinical Trial Registry, ChiCTR2000038673. Registered 27 September 2020, <http://www.chictr.org.cn/showproj.aspx?proj=57282>

Background

Dry eye is a multifactorial ocular surface disease characterized by a loss of homeostasis of the tear film. The main pathophysiological mechanisms include tear film instability, hyperosmolarity and ocular surface inflammation and damage [1]. Dry eye has a significant impact on vision function and quality of life. Dry eye prevalence ranges from 5-50% globally, it increases with age [2] and the widespread use of visual display terminals [3]. Currently, drug therapy is the main treatment for dry eye. Drug therapy restores the microenvironment of the ocular surface by promoting tear secretion and anti-inflammatory treatment [4]. However, due to the complex etiology and poor consistency between signs and symptoms [5], the drugs have limited effects [6]. For moderate and severe dry eyes, drug treatment can only relieve some of the symptoms while it is not suitable for long-term use. Therefore, more new non-drug treatment strategies need to be explored.

Aerobic exercise (AE) is an effective treatment for many systemic diseases especially chronic diseases [7]. Currently, animal studies have shown that 8 weeks of AE increases tear secretion in diabetic mice [8]. A large population study found that lack of exercise was closely related to increased susceptibility to dry eye [3]. Ten weeks of exercise improves the subjective symptoms of dry eye patients [9]. The aim of this study was to determine the specific effects and possible mechanisms of AE on tear secretion and tear film stability.

Methods

Subjects

This research was implemented in accordance with the requirements of the Declaration of Helsinki and the protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Army Medical University. The clinical trial registration number is ChiCTR2000038673.

All subjects were 18-30 years old and agreed to participate in this study and signed an informed consent. The diagnostic criteria for dry eye was the average non-invasive tear breakup time (A-NITBUT) < 10s according to the Tear Film and Ocular Surface Society Dry Eye Workshop (DEWS) [10]. Subjects were excluded if they had allergic conjunctivitis, Sjögren's syndrome, lacrimal obstruction or other ocular surface diseases. Subjects were also excluded if they had dry eye treatment or used contact lenses within one month, if they had a history of eye trauma or surgery within one year or subjects with serious systemic diseases who were not suitable for strenuous exercise.

Study design

The test was divided into two parts in order to avoid the possible influences of Schirmer test on the subsequent measurements of signs associated with dry eye. In total, 34 eyes of 17 dry eye patients and 34 eyes of 17 normal subjects were observed before and at 0, 30 minutes after AE in part 1. The evaluated variables included Schirmer test and six tear compositions. A total of 30 eyes of 15 dry eye patients and 30 eyes of 15 normal subjects were observed in part 2. The evaluated variables included visual acuity before and at 0, 30, 60 minutes after AE, signs associated with dry eye before and at 10, 20, 40 minutes after AE including tear meniscus height (TMH), first non-invasive tear breakup time (F-NITBUT), A-NITBUT, tear film lipid layer thickness (LLT), incomplete and complete blinks and partial blink rate (PBR). All the subjects were required to fast throughout the test period because eating have an effect on tear secretion [11].

AE protocol

The AE protocol was defined as jogging for 30 minutes. The venue was outdoors, the ambient temperature was 25-27°C while the humidity was 50-60% during the test. According to the 6-20 Rating of Perceived Exertion Scale, the target heart rate was set to 64-76% of the maximum heart rate in order to achieve moderate exercise intensity [12]. The maximum heart rate was defined as 220 minus age [12]. The measuring time was between 18:00 and 19:00.

Test items

OSDI

The Ocular Surface Disease Index (OSDI) questionnaire was used to quantify the subjective symptoms of dry eye [13]. The symptoms and environmental triggers for dry eye in the past week were assessed. OSDI score ≥ 13 was considered positive. The score range was 0-100. The higher the score, the more severe the symptoms.

Schirmer test

The researcher wore gloves and placed the Schirmer test strip (35mm; DSA Exports, India, without fluorescent agent) at the outer 1/3 of the lateral eyelid margin without using anesthetics. Both eyes were tested simultaneously and the eyes remained closed during the procedure. The strip was removed after 5 minutes and the length of wetted part up to the indentation line was recorded. Each test was carried out in a quiet and dark environment.

Analysis of tear compositions

Schirmer test strips were used to collect the tears. The test strips were stored in a refrigerator at -80°C until testing. Amount of PBS buffer to be added to each strip was calculated by multiplying the wetted length of the Schirmer test strip (Schirmer test reading + about 5mm of the head of strip without scale) by 100 μ l. After homogenizing, the samples were centrifuged at 2-4°C for 15 minutes (2000 rpm). In total, 10 μ l of the supernatant was collected for analysis after precipitation. Six compositions of the tear were determined using ELISA kit (Jiangsu Meimian, China).

The compositions tested included dry eye diagnostic factor lactoferrin [14] and matrix metalloproteinase-9 (MMP-9) [15], dry eye inflammation marker IL-6 [16], oxidative stress marker 8-hydroxy-2'-deoxyguanosine (8OHdG) [17], (O-acyl)- ω -hydroxy fatty acids (OAHFA) which is closely related to tear film stability [18], and Mucin 5 subtype AC (MUC5AC) which is considered to be the most abundant secretory mucin in human tears [19]. The absorbance was measured at 450 nm with a multifunctional microplate reader (Labsystems Multiskan MS, Finland).

Measurements of signs associated with dry eye

Keratograph 5M (OCULUS, Wetzlar, Germany) was used to measure TMH, F-NITBUT and A-NITBUT. Each measurement was measured twice by the same ophthalmologist and average measurements was recorded. Images with unclear boundaries of the tear meniscus were deleted to avoid affecting image analysis. LipiView LVI-1001 (TearScience, Inc., Morrisville, North Carolina) was used to measure LLT and shot 20s video which automatically recorded incomplete and total blinking [20]. Number of complete blinks (number of total blinks minus incomplete blinks) and PBR (number of incomplete blinks / total blinks) were obtained using simple calculation.

Visual acuity

ETDRS chart was used to measure the best corrected visual acuity.

Statistical analysis

Statistical analyses were performed with SPSS version 20.0 software package (IBM Corp., Armonk, NY, USA). Data was expressed as median (25% interquartile, 75% interquartile) or mean \pm standard deviation. The Mann-Whitney U test was applied to compare the age and OSDI score between two groups. The Schirmer \square test, tear compositions, signs associated with dry eye and visual acuity at different time points were compared using two-way repeated measures analysis of variance. Bonferroni correction was used for multiple comparisons. The level of significance was set at $P < 0.05$.

Sample size

The sample size was calculated using PASS software (version 15.0, NCSS, LLC). According to the results of the A-NITBUT in preliminary experiment, the sample size was estimated by adopting the significance level (α) as 0.05, the desired power ($1-\beta$) as 0.85, the autocorrelation coefficient as 0.7 and the standard deviation of the population of 5.1. The estimated sample size was at least 29 eyes in each group.

Results

Age and gender distribution and OSDI score of each part were mentioned in Table 1. The heart rate of all subjects reached the target and none of those subjects experienced any discomfort or pain during the examination.

Table 1 Comparison of basic information between dry eye group and control group

χ^2 Male (eyes): Female (eyes)

		Dry eye	Control	<i>P value</i>
Part 1	NO. subjects (eyes)	17 (34)	17 (34)	/
	Male (eyes): Female (eyes)	12 (24): 5 (10)	12 (24): 5 (10)	1.000
	Age (years)	22.0 (21.0, 24.0)	21.0 (21.0, 23.3)	0.197
	OSDI score	22.7 (16.0, 32.2)	16.7 (7.3, 21.3)	0.031
Part 2	NO. subjects (eyes)	15 (30)	15 (30)	/
	Male (eyes): Female (eyes)	12 (24): 3 (6)	12 (24): 3 (6)	1.000
	Age (years)	22.0 (21.0, 23.3)	21.0 (21.0, 23.0)	0.721
	OSDI score	25.0 (20.0, 45.0)	13.6 (5.0, 25.0)	0.006

OSDI the ocular surface disease index

Changes of tear volume and tear compositions before and after AE

Tear volume was evaluated using Schirmer I test. The interaction between group and time had a significant difference in tear volume ($P = 0.006$). Tear volume was significantly different at each time point between two groups (Figure 1). In dry eye group, tear volume at 0 minutes after AE increased significantly compared to baseline ($P < 0.001$). Tear volume decreased significantly at 30 minutes after AE compared to 0 minutes after AE ($P < 0.001$) (Figure 1). In control group, there was no significant difference between each time point ($P > 0.05$).

The interaction of group and time had no significant difference on the six tear compositions ($P > 0.05$). The main effect of time had a significant difference on 8-OHdG ($P = 0.031$). 8-OHdG decreased significantly at 0 minutes after AE compared to baseline ($P = 0.040$). There were no significant changes in the other tear compositions before and after AE ($P > 0.05$) (Table 2).

Table 2 Comparison of tear compositions at each time point before (baseline) and after AE

		Baseline	0 min	30 min	<i>P value</i>		
					Group x Time	Group main effect	Time main effect
Lactoferrin (µg/ml)	Dry eye	111.63±15.14	115.72±15.46	114.88±13.06	0.535	0.038	0.706
	Control	120.04±16.92	120.24±16.50	118.46±16.26			
MMP-9 (µg/L)	Dry eye	1065.60±157.43	984.20±151.56	999.36±171.43	0.652	0.041	0.097
	Control	976.62±178.87	940.23±190.27	959.15±171.21			
IL-6 (ng/L)	Dry eye	19.52±2.01	18.50±1.96	18.96±2.16	0.286	0.069	0.377
	Control	18.42±1.82	18.44±2.07	18.60±2.30			
8-OHdG (ng/L)	Dry eye	105.43±10.74	98.00±11.74	98.23±13.03	0.142	0.229	0.031 ^a
	Control	99.32±12.84	95.65±11.08	100.16±12.20			
OAHFA (pg/ml)	Dry eye	365.13±43.50	369.71±38.53	365.75±36.82	0.918	0.879	0.792
	Control	362.77±35.43	366.95±40.08	368.28±42.66			
MUC5AC (µg/L)	Dry eye	93.54±8.17	93.65±9.24	94.34±8.24	0.412	0.019	0.492
	Control	98.89±9.81	95.35±7.78	96.26±8.13			

^a 8-OHdG was significantly different between baseline and 0 minutes after AE ($P = 0.040$)

MMP-9 matrix metalloproteinase-9, *8-OHdG* 8-hydroxy-2'-deoxyguanosine, *OAHFA* (O-acyl)- ω -hydroxy fatty acids, *MUC5AC* Mucin 5 subtype AC

Changes in signs associated with dry eye before and after AE

In dry eye group, F-NITBUT and A-NITBUT were significantly prolonged at 10, 20 and 40 minutes after AE compared to baseline ($P < 0.001$, $P = 0.007$, $P = 0.036$; $P < 0.001$, $P = 0.001$, $P = 0.044$). The number of incomplete blinks and PBR decreased significantly at 10 minutes after AE compared to baseline, 20 and 40 minutes after AE ($P < 0.001$, $P = 0.013$, $P = 0.022$; $P < 0.001$, $P = 0.002$, $P < 0.001$), while the number of complete blinks increased significantly ($P < 0.001$, $P = 0.002$, $P < 0.001$) (Table 3).

TMH, LLT and number of total blinks had no significant difference before and after AE ($P > 0.05$). The comparison between two groups were shown in Table 3.

Table 3 Comparison of signs associated with dry eye at each time point before (baseline) and after AE

		Baseline	10 min	20 min	40 min	<i>P value</i>		
						Group x Time	Group main effect	Time main effect
TMH (mm)	Dry eye	0.32±0.13	0.31±0.11	0.31±0.13	0.30±0.09	0.404	0.866	0.537
	Control	0.31±0.09	0.30±0.07	0.30±0.09	0.32±0.11			
F-NITBUT (s)	Dry eye	5.44±1.88	10.80±5.35 ^a	7.94±3.88 ^a	7.87±4.24 ^a	0.036	/	/
	Control	10.16±4.07 ^c	10.77±5.66	9.50±5.48	9.64±5.05			
A-NITBUT (s)	Dry eye	7.73±1.63	12.94±4.65 ^a	11.04±4.41 ^a	10.34±4.83 ^a	0.003	/	/
	Control	14.37±3.42 ^c	14.67±5.56	13.70±5.41 ^c	13.73±5.48 ^c			
LLT (nm)	Dry eye	52.37±22.05	48.27±18.85	50.17±17.55	45.23±16.40	0.424	0.003	0.086
	Control	63.43±20.71	56.93±21.00	57.43±18.17	59.27±15.27			
Number of incomplete blinks	Dry eye	4.30±3.41	1.60±1.45 ^b	3.17±2.25	3.47±3.20	□ 0.001	/	/
	Control	2.77±1.83 ^c	2.77±2.03 ^c	2.80±1.97	2.37±1.99 ^c			
Number of complete blinks	Dry eye	3.80±2.83	7.90±4.87 ^b	4.93±2.59	4.70±2.77	□ 0.001	/	/
	Control	4.33±2.40	4.13±2.91 ^c	3.87±2.73	3.60±2.14			
Number of total blinks	Dry eye	8.10±5.16	9.50±5.22	8.10±3.49	8.17±4.50	0.325	0.035	0.106
	Control	7.10±3.64	6.90±3.88	6.67±4.37	5.97±3.32			
PBR	Dry eye	0.52±0.23	0.18±0.16 ^b	0.37±0.24	0.41±0.29	0.008	/	/
	Control	0.41±0.24	0.40±0.27 ^c	0.37±0.24	0.37±0.28			

^a There was significant difference compared with baseline ($P < 0.05$)

^b There was significant difference compared with the other time points ($P < 0.05$)

^c There was significant difference between two groups at same time point ($P < 0.05$)

TMH tear meniscus height, F-NITBUT first non-invasive tear breakup time, A-NITBUT average non-invasive tear breakup time, LLT lipid layer thickness, PBR partial blink rate

Changes in visual acuity before and after AE

Visual acuity in dry eye group improved significantly at 0 and 30 minutes after AE compared to baseline ($P = 0.017$, $P = 0.021$). However, there was no significant change in control group before and after AE (Table 4).

Table 4 Comparison of visual acuity at each time point before (baseline) and after AE

	Baseline	0 min	30 min	60 min	<i>P</i> value		
					Group × Time	Group main effect	Time main effect
Dry eye	83.2±9.5	84.4±9.6 ^a	84.5±9.4 ^a	83.9±9.2	0.038	/	/
Control	83.7±6.3	83.5±6.3	83.4±5.7	84.0±5.6			

^a There was significant difference compared with baseline ($P < 0.05$)

Discussion

Studies of the effects of AE on dry eye mainly focused on the improvement of subjective symptoms in dry eye patients and the tear secretion in mice. In this study, AE promotes tear secretion and improves tear film stability in dry eye patients compared to normal subjects. There was an increase in tear secretion at 30 minutes after AE in dry eye patients. AE excites the sympathetic nerves but inhibits the parasympathetic nerves. Parasympathetic nerves dominates the lacrimal gland which secrete tears [21]. Therefore, the immediate impact of stimulation to the lacrimal gland by sympathetic excitement was likely to be limited. The sympathetic nerves in lacrimal gland are mainly located around the lacrimal gland acinar blood vessels [22], they can cause vasodilation and increase the secretion of electrolytes and water [23]. This might be the main cause of increased tear secretion in dry eye patients after AE. The lack of significant change in tear secretion in normal subjects might be due to the limited effect of AE on secretory function of healthy lacrimal glands. This suggested that patients with dry eye are more likely to benefit from AE.

In 2017, DEWS II emphasized the importance of tear film instability in the latest definition of dry eye [1]. The most commonly used tear film stability test clinically is tear breakup time. In dry eye group, F-NITBUT and A-NITBUT were significantly longer at all time points after AE compared to baseline levels. This might be due to the changes of blinking parameters. Blinking is a fast eyelid movement and plays an important role in the dynamic balance of the ocular surface and tear film [24]. Blinking can effectively promote tear secretion, and replenish the tear film with tear from the inferior tear meniscus [25]. Blinking also makes the lipid layer to be evenly distributed on ocular surface. The lipid layer secreted by the meibomian gland prevent evaporation of tear and stabilize the tear film [26]. When the blinking is incomplete, the orbicularis muscle and the muscle of Riolan apply less squeezing force, resulting in insufficient driving force required for meibum secretion [27]. Moreover, the lipid layer becomes unevenly distributed on ocular surface thus affecting tear film stability. Clinical studies showed that the number of incomplete blinks was negatively associated with tear breakup time in dry eye patients [28]. In this study, the number of incomplete blinks and PBR at 10 minutes after AE decreased significantly compared to baseline levels, while the number of complete blinks increased significantly. This was helpful with tear secretion and more even distribution of tear film on ocular surface thus prolonging the tear breakup time and improving the stability of tear film.

In addition, visual acuity in dry eye group improved after AE and maintained at least 30 minutes after AE. An intact and regular tear film is an important factor for high-quality retinal images. Dry eye patients with destabilized tear film show higher values of higher-order aberrations. This leads to excessive diopter variation before and after blinking

causing visual fluctuation [29]. Therefore, we speculated that the improvement of visual acuity in dry eye group after AE was related to the change of higher-order aberration caused by the improvement of tear film stability. To determine the effect of AE on visual acuity, higher-order aberration should be included in the observation, and influencing factors such as accommodative function and retinal function should be excluded.

Oxidative stress plays an important role in pathogenesis of dry eye and may be a potential treatment target for dry eye [30]. This study found that the oxidative stress marker 8OHdG was significantly reduced after AE. This was similar to the results in animal experiments that AE reduces 8OHdG in tears of diabetic mice (with decreased tear secretion) [8]. Therefore, AE reduces the oxidative stress response on ocular surface. There were no significant changes in the other 5 tear compositions before and after AE, which might be related to short study period, long-term exercise could be different. Furthermore, the Schirmer \square test without anesthetic mainly reflected the secretion of reflex tear, although the method of tear collection were consistent before and after AE, it was still possible to influence the results by diluting the basal tears.

There were also some limitations to this study. First, compared to the condition of constant temperature and humidity, the outdoor complex environment inevitably had an impact on results. However, the experiment reflected the true effects of outdoor exercise on dry eye in most people. Secondly, it is necessary to expand the sample size and rationalize the ratio of age and sex to obtain more comprehensive and reliable results. Finally, this study only observed the impact of AE just once on dry eye. Further observation is needed for the benefits of long-term regular AE on dry eye.

Conclusions

In conclusion, this study showed that AE promotes tear secretion and improves tear film stability in dry eye patients. This was demonstrated by the increase in Schirmer \square test, F-NITBUT, A-NITBUT, the number of complete blinks, the decrease in the number of incomplete blinks and PBR.

Abbreviations

AE: Aerobic exercise; TMH: Tear meniscus height; F-NITBUT: First non-invasive tear breakup time; A-NITBUT: Average non-invasive tear breakup time; LLT: Lipid layer thickness, PBR: Partial blink rate; DEWS \square : Dry Eye Workshop \square ; OSDI: The ocular surface disease index; 8OHdG: 8-hydroxy-2'-deoxyguanosine; OAHFA: (O-acyl)- ω -hydroxy fatty acids; MUC5AC: Mucin 5 subtype AC.

Declarations

Ethics approval and consent to participate

The research was implemented in accordance with the requirements of the Declaration of Helsinki. All participants provided written informed consent before entering the study. Approval for the present study was obtained from the Ethics Committee of the Second Affiliated Hospital of Army Medical University.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

R Y designed the study and supervised the experiment. C S and M Y performed the experiments and C S performed data acquisition and analysis. All authors (C S, Y H, X F C, H Z, W F, M Y and R Y) were involved in participating in drafting or revising the manuscript. All authors reviewed and approved the final manuscript.

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Statement for CONSORT guidelines

We indicate that our study adheres to CONSORT guidelines.

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