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The Effect of Caffeine on Tear Secretion

Kwaku Antwi Osei*, Godwin Ovenseri-Ogbomo†, Samuel Kyei‡, and Michael Ntodie*

ABSTRACT

Purpose. Caffeine, probably the most widely consumed psychoactive substance, is claimed to have conflicting effects on some tear film dynamics. This study sought to investigate the effect of orally ingested caffeine on tear secretion.

Methods. In an examiner-masked, placebo-controlled, crossover experimental model, the effect of caffeine intake on tear secretion was studied in 41 healthy volunteers aged 20 to 26 years (mean, 23.0 ± 2.1 years). Participants were randomly assigned into two groups, A and B, to receive two different treatments in two sessions. Subjects in group A were exposed to 5.0 mg/kg body weight of caffeine dissolved in 200 mL of water on their first visit, whereas those in group B were exposed to 200 mL of water. On the second visit, however, the order of treatment was reversed. Schirmer 1 scores were measured repeatedly at 45, 90, 135, and 180 minutes after treatment. The baseline Schirmer 1 scores were compared with posttreatment scores.

Results. Schirmer 1 scores increased after caffeine intake. The increase was statistically significant at 45 and 90 minutes ($p < 0.05$) after caffeine intake. Age, body mass, and blood pressure had no correlation with Schirmer 1 scores (Spearman correlation test, $p > 0.05$). There was no influence of gender in caffeine's effect on tear secretion ($F = 0.994$, $p = 0.399$).

Conclusions. From our study, orally ingested caffeine appears to stimulate tear secretion in healthy non–dry eye subjects. (Optom Vis Sci 2014;91:171–177)

Key Words: caffeine, tears, lacrimal gland, Schirmer 1 test, dry eye

Caffeine, 1,3,7-trimethylxanthine, is a naturally occurring compound in more than 60 plants and belongs to a family of chemical substances called xanthine alkaloids. It is probably the most frequently consumed pharmacologically active psychoactive substance in the world.[1] Common sources of caffeine include coffee, tea, soft drinks, chocolate, and energy drinks.[1,2] Approximately 80% of the world's population consumes caffeine on a daily basis,[3] and in North America, 90% of adults consume it daily.[1,3] In North America, coffee (60 to 75%) and tea (15 to 30%) are the major sources of caffeine in the adult diet, whereas caffeinated soft drinks and chocolate are the major sources in the diet of children.[2] Coffee is the primary source of caffeine in the diet of adults in some European countries, such as Finland, Sweden, Switzerland, and Denmark.[2] Limited data are however found on the rate of consumption in Africa.

The probable influence of caffeine intake on tear secretion and dry eye has been the subject of a number of studies and claims.[4–8] Dry eye results from inadequate tear secretion or an unstable tear film. It presents with symptoms such as burning sensation, foreign body sensation, mild to moderate decreased vision, and excessive tearing. If poorly managed, it results in ocular surface abnormalities like punctate epithelial keratopathy and corneal ulcers. Patients with severe dry eye are at a greater risk of ocular infections because of deficits in defense proteins like lysozyme, lactoferrin, and immunoglobulin A.[9,10] Dry eye affects quality of life, impacts the economic burden to patients, and reduces work productivity.[11–13]

Measures of tear secretion are highly variable. Clinically, tear secretion is assessed by quantitative measures such as the Schirmer test, phenol red thread test, and tear film fluorophotometry.[14]

Seemingly conflicting claims have been made regarding the effect of caffeine on dry eye and lacrimal function; whereas some claims are that caffeine intake may be associated with reduced tear function,[4–6] others claim caffeine use may be associated with improved lacrimal function and hence protective against dry eye.[7,8] These conflicting findings and claims clearly give a body of evidence that underscores the uncertainty in the effect of caffeine on tear secretion. Further studies are thus warranted on the effect of caffeine on tear film function. This study seeks to further investigate the effect of caffeine on tear secretion using pure caffeine treatment in an examiner-masked, placebo-controlled, crossover model in healthy non–dry eye subjects.

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The outcome of this research might stimulate interest for further studies involving a dry eye population.

METHODS

Study Design

The research was an examiner-masked, placebo-controlled, crossover experimental study. The subjects were exposed to caffeine and water in two different sessions. The researcher performing the Schirmer 1 test was masked to the treatment that had been administered to the subjects in a bid to eliminate any possible researcher bias. However, it was not possible to mask the subjects to the treatments because of caffeine's characteristic bitter taste.

Inclusion and Exclusion Criteria

Subjects included in the study were emmetropes with unaided visual acuity of 20/20 or better in both eyes. They had a baseline Schirmer 1 score of 10 mm or greater in both eyes, with the scores being comparable in each eye. In the context of this study, two scores were considered comparable if the difference between the scores was 3 mm or less. The subjects also had tear breakup times of 15 seconds or greater in both eyes.

Smokers and alcohol consumers were excluded from the study because smoking and alcohol consumption affect caffeine's pharmacokinetics by affecting its elimination half-life.[2,15] Subjects on any topical or systemic medication and those with any ocular or known systemic pathology were also excluded.

Setting

The study was carried out at the Optometry Clinic, University of Cape Coast. The clinic serves the eye care needs of the university community as well as people from Cape Coast and its environs. It also serves as a teaching facility for Doctor of Optometry clinical students.

Study Participants

A total of 41 subjects participated in the study. Participants were volunteers recruited from the Department of Optometry, University of Cape Coast. Sixty-two subjects volunteered to take part in the study after details of the research including its methodology had been duly explained to them. After giving their informed consent, the subjects had a comprehensive ocular health assessment and systemic health review. Eight did not qualify and two withdrew consent before randomization. Of the 52 remaining individuals, six withdrew consent before receiving the first treatment and five were withdrawn before receiving the second treatment. Of the five subjects, three were withdrawn because their baseline Schirmer 1 scores before receiving the second treatment were significantly different from their baseline scores before receiving the first treatment. The remaining two were withdrawn because they were indisposed.

Ethical Consideration

The study was conducted in accordance with the tenets of Declaration of Helsinki. A proposal on the research was submitted to and approved by the institutional review board of the University of Cape Coast, Ghana, before the study commenced. The research protocol was also clearly explained to the participants, and the participants' consents were obtained before the study commenced. All the clinical procedures performed were within the scope of optometric practice in Ghana.

Procedures

The body mass and blood pressure of eligible participants were measured after they had provided written informed consent, and then they were randomly assigned to two groups, A and B. All participants were advised to refrain from any caffeine-containing beverage for 1 week before receiving the first treatment and also do the same until they receive the second treatment to prevent any carryover effect of caffeine. The baseline Schirmer 1 scores were measured after which the subjects were exposed to a treatment. On their first visit, group A participants were exposed to 5.0 mg/kg body weight of pure anhydrous caffeine (Herb Store USA, Walnut, CA) dissolved in 200 mL of water whereas group B participants were exposed to 200 mL of water. The dose administered is equivalent to four cups of brewed coffee, five cans of American Bull energy drink, or six tablets of Excedrin in an 80-kg person. The order of treatment was reversed on the second visit, with group A participants receiving 200 mL water while those in group B received 5.0 mg/kg body weight of caffeine in 200 mL of water. Sufficient time (3 days) was allowed before participants received the second treatment to eliminate any potential carryover effect. Three days (72 hours) was selected as washout phase because, with caffeine's estimated half-life of 2.5 to 6 hours,[16–18] it was anticipated that the concentration of caffeine in the blood would fall to a pharmacologically insignificant level by the third day, with reference to the highest administered caffeine dose (450 mg in the 90-kg participant).

After any treatment, Schirmer 1 test was measured repeatedly after 45, 90, 135, and 180 minutes. The Schirmer 1 test was performed with TearFlo strips (HUB Pharmaceuticals, LLC, Rancho Cucamonga, CA). The test was performed with the subject in the upright seated position after instillation of one drop of tetracaine 0.5% (Alcon, Forth Worth, TX). The conjunctival sac was dried with cotton-tipped applicator after the administration of the anesthetic to absorb any reflex tearing, which might result from irritation by the anesthetic. Three minutes was allowed for any reactive hyperemia and reflex tearing to subside. The lower eyelid was gently pulled and the folded notched end of the Schirmer strip was placed over the lower lid margin at its lateral third. The subject was instructed to close the eyes gently for 5 minutes. The strip was removed after 5 minutes, unless the entire length got wet before the stipulated time. The amount of wetting was read off from the millimeter scale. The procedure was carried out thrice, and the average of two consistent scores was considered the Schirmer 1 score.

Data Analysis

The results from the data sheet were captured and analyzed using the Statistical Package for Social Science (version 16.0, SPSS, Chicago, IL). Descriptive statistics, independent *t* tests, repeated-measures analysis of variance (ANOVA), and *post hoc*

multiple comparisons were used for data analysis. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Demographic Characteristics of Subjects

Forty-one healthy subjects aged 20 to 26 years (mean, 23.0 ± 2.1 years) completed all two sessions of the study. Twenty-two (53.7%) were men, and 19 (46.3%) were women. The men had a mean age of 23.3 ± 2.2 years, mean body mass of 66.6 ± 11.1 kg, mean systolic pressure of 117.7 ± 5.1 mm Hg, and mean diastolic pressure of 77.5 ± 4.0 mm Hg. The women had a mean age of 22.7 ± 1.9 years, mean body mass of 58.2 ± 9.1 kg, mean systolic pressure of 116.1 ± 5.4 mm Hg, and mean diastolic pressure of 76.8 ± 5.1 mm Hg.

Mean age, mean systolic pressure, and mean diastolic pressure were not statistically different between men and women (independent *t* test, $p > 0.05$); however, the mean body mass was statistically greater for males (independent *t* test, $p = 0.015$).

Normality of Measured Variables

Normality of measured variables was tested using the Shapiro-Wilk test of normality. The mean Schirmer 1 scores measured before and after caffeine intake were all normally distributed; however, variables such as age, body mass, systolic pressure, and diastolic pressure of study participants were not normally distributed. Table 1 summarizes the results of Shapiro-Wilk test of normality.

The Effect of Caffeine on Schirmer 1 Scores

The mean baseline Schirmer 1 score was 17.9 ± 4.6 mm before exposure to caffeine. The scores measured after caffeine treatments were 20.9 ± 5.2, 20.7 ± 5.8, 19.8 ± 5.0, and 18.1 ± 5.8 mm after 45, 90, 135, and 180 minutes, respectively. These represent percentage increases in tear secretion of 16.59, 15.47, 10.84, and 1.17% at the respective time points.

TABLE 1.
Results of Shapiro-Wilk test of normality

Variable	Statistic	p
Age	0.903	0.002
Body mass	0.921	0.007
Systolic pressure	0.716	0.000
Diastolic pressure	0.843	0.000
Baseline Schirmer 1 score (caffeine)	0.964	0.222
Schirmer 1 score at 45 min (caffeine)	0.964	0.225
Schirmer 1 score at 90 min (caffeine)	0.976	0.537
Schirmer 1 score at 135 min (caffeine)	0.983	0.776
Schirmer 1 score at 180 min (caffeine)	0.984	0.826
Baseline Schirmer 1 score (water)	0.918	0.006
Schirmer 1 score at 45 min (water)	0.897	0.001
Schirmer 1 score at 90 min (water)	0.916	0.005
Schirmer 1 score at 135 min (water)	0.947	0.057
Schirmer 1 score at 180 min (water)	0.936	0.023

TABLE 2.
Post hoc test (with Bonferroni adjustment) to determine the effect of caffeine on tear secretion

			95% CI for difference	
Pair	Mean difference	p	lower bound	Upper bound
1	2.963	0.000	1.214	4.713
2	2.768	0.021	0.269	5.268
3	1.939	0.074	−0.104	3.982
4	1.976	0.207	−0.462	4.413

1 = 45 min – Baseline; 2 = 90 min – Baseline; 3 = 135 min – Baseline; 4 = 180 min – Baseline.

The effect of caffeine on Schirmer 1 scores was analyzed using repeated-measures ANOVA. Using repeated-measures ANOVA with a Greenhouse-Geisser correction, the mean Schirmer 1 scores were found to be statistically significantly different at the various time points with caffeine intake ($F = 4.919$, $p = 0.003$).

Post hoc test with Bonferroni correction revealed that there was an increase in Schirmer 1 score from pre–caffeine intake to 45 minutes after caffeine intake (17.9 ± 4.6 mm vs. 20.9 ± 5.3 mm, respectively), which was statistically significant ($p > 0.0001$). Another statistically significant increase in Schirmer 1 score was found between baseline and 90 minutes after caffeine intake (17.9 ± 4.6 mm vs. 20.7 ± 5.8 mm, respectively; $p = 0.021$). There was an increase in Schirmer 1 scores at 135 minutes and 180 minutes, but these were not statistically significant ($p > 0.05$). Table 2 represents the results of the Bonferroni *post hoc* test.

The influence of gender in caffeine's effect on Schirmer 1 scores was also assessed. There was no statistically significant gender influence in caffeine's effect on Schirmer 1 scores ($F = 0.994$, $p = 0.399$).

The Effect of Water on Schirmer 1 Scores

The mean baseline Schirmer 1 score was 18.1 ± 4.9 mm before exposure to water. The scores measured after water treatments were 18.6 ± 6.2, 18.5 ± 6.2, 18.0 ± 5.5, and 18.3 ± 5.6 mm after 45, 90, 135, and 180 minutes, respectively. These represent percentage increases in Schirmer 1 scores of 2.76, 2.15, 0.55, and 0.83%, respectively.

The effect of water on Schirmer 1 scores was similarly analyzed with repeated-measures ANOVA. Using repeated-measures ANOVA with a Greenhouse-Geisser correction, the mean Schirmer 1 scores were found not to be statistically significantly different at the various time points with water intake ($F = 0.839$, $p = 0.434$). Fig. 1 represents the pattern of change in Schirmer 1 scores with caffeine and water intake.

Association Between Measured Variables

Test of correlation was performed to determine if there is any association between the measured variables. The Spearman correlation test was used to analyze any association of age, body mass, systolic pressure, and diastolic pressure with the Schirmer 1 scores measured at the various time points with caffeine intake. The analysis revealed no statistically significant correlation between

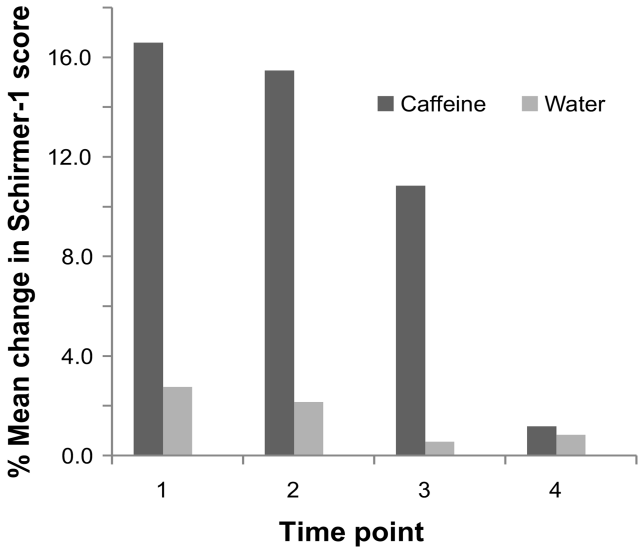

FIGURE 1.

Mean change in Schirmer 1 scores after caffeine and water treatments: 1 = (45 min – Baseline); 2 = (90 min – Baseline); 3 = (135 min – Baseline); 4 = (180 min – Baseline).

the measured variables. Table 3 summarizes the results of the Spearman correlation test.

DISCUSSION

This study sought to investigate the effect of orally ingested pure caffeine on tear secretion. The main outcome measure of the study was Schirmer 1 test score.

The Schirmer 1 test as a clinical measure of tear secretion has been shown to have some limitations such as low repeatability and high variability of test scores.[19–21] Also, the test has low sensitivity,[22–24] and there is disagreement over the cutoff limits for normals.[24] Because there's no single test battery considered gold standard for dry eye,[24] the Schirmer 1 test is still used in the assessment of dry eye and in the screening for potential contact lens wear despite the uncertainty over its validity. It is easy to perform, and it does not require expensive instrumentation.

A number of measures were taken to minimize the effects of the inherent limitations of the Schirmer 1 test and to justify its use in the study. The Schirmer 1 test when performed without anesthesia reflects such data as reflex tear secretion, lacrimal meniscus volume, and basal tear secretion.[25] We minimized the effect of lacrimal meniscus volume and reflex secretion by performing the test with topical anesthesia and blotting residual tears from the cul-de-sac after instillation of the anesthetic. The test when performed under topical anesthesia also yields more objective and reliable results.[26] Also, by performing the test with the eyes closed, we minimized variability and enhanced reproducibility of the test.[27] Furthermore, each participant received the two treatments at approximately the same time of the day so as to minimize the effect of any possible diurnal variation in tear secretion.[28] In addition to these, the baseline Schirmer 1 score for each participant was measured before exposure to either treatment. Participants were eligible to receive the second treatment only if the two baseline scores were comparable. By this, we ensured that participants had somewhat consistent tear secretion.

Only one eye (right) was involved in the study because all subjects had comparable baseline Schirmer 1 scores in both eyes, and hence results from the analysis could be extrapolated to the uninvolved (left) eye.

Participants in the study weighed 44 to 90 kg, and each received 5.0 mg/kg body weight of caffeine as one of two forms of treatments. Thus, each participant received 220- to 450-mg dose of caffeine depending on body weight. Participants stayed off any known caffeine-containing beverage or drink for 1 week before receiving any treatment to ensure that any caffeine that might have been consumed previously would be eliminated to prevent any possible carryover effect. With 4 days being sufficient enough to make a person caffeine naive,[29] a 1-week washout phase is expected to rid the body of any traces of caffeine.

The results from this study show an increase in tear secretion after ingesting 5.0 mg/kg body weight of caffeine. The Schirmer 1 scores obtained after caffeine treatments were higher than the baseline score. The increase was statistically significant after 45 minutes and 90 minutes after caffeine consumption. This significant effect of caffeine at 45 minutes and 90 minutes is expected because maximum plasma concentration of caffeine after ingestion is reached around this time period (30 to 90 minutes),[2,30–32] so any effect is expected to peak around this time.

Although not significant, there was an increased tear secretion at 135 and 180 minutes after caffeine intake. This is consistent

TABLE 3.

Spearman correlation analysis to determine the association of age, body mass, systolic pressure, and diastolic pressure with Schirmer 1 scores (with caffeine intake) at the various time points

		ST_0	ST_45	ST_90	ST_135	ST_180
Age	Spearman correlation	0.047	0.024	−0.077	0.011	0.100
	p (2-tailed)	0.768	0.879	0.631	0.948	0.532
Mass	Spearman correlation	0.221	0.052	0.230	0.234	0.277
	p (2-tailed)	0.164	0.746	0.149	0.141	0.080
SP	Spearman correlation	0.076	−0.026	−0.167	−0.036	0.040
	p (2-tailed)	0.636	0.871	0.297	0.821	0.803
DP	Spearman correlation	0.044	0.035	−0.114	−0.070	0.070
	p (2-tailed)	0.783	0.826	0.476	0.663	0.663

DP, diastolic pressure; SP, systolic pressure; ST_0, Schirmer 1 score before caffeine intake; ST_45, Schirmer 1 score at 45 minutes after caffeine intake; ST_90, Schirmer 1 score at 90 minutes after caffeine intake; ST_135, Schirmer 1 score at 135 minutes after caffeine intake; ST_180, Schirmer 1 score at 180 minutes after caffeine intake.

with caffeine's estimated elimination half-life of 2.5 to 6 hours.[17,18] A possible explanation for this insignificant increase in tear secretion at these two time points could be elucidated from caffeine's half-life data. With a half-life of 2.5 to 6 hours, caffeine is expected to fall in concentration 135 minutes (≈2.5 hours) after consumption. Thus, at these two time points, there will still be caffeine in the plasma but its physiological effects might be reduced.

The exact mechanisms for the observed stimulatory effect of caffeine on tear secretion have not been well elucidated; however, we postulate a number of potential mechanisms.

Caffeine, being a nonselective competitive adenosine antagonist,[2,30,32] increases the level of acetylcholine,[33,34] the neurotransmitter for the parasympathetic pathway. Acetylcholine acts on the main lacrimal gland via the 1,4,5-inositol triphosphate/Ca^{2+}/diacylglycerol-dependent signal transduction pathway in which it stimulates a muscarinic receptor and a G protein, leading to a rise of intracellular calcium concentration and the activation of Ca^{2+}/calmodulin protein kinases that phosphorylate specific proteins to activate ion channels in the apical and basilateral membranes. This results in secretion of electrolyte, water, and protein, and hence, the stimulation of tear secretion.[33]

Like other methylxanthines, caffeine's inhibition of 3,5-cyclic nucleotide phosphodiesterase (cAMP-PDE)[2] could also explain its stimulatory effect on the tear gland. This cAMP-PDE enzymatically degrades cAMP into non–cyclic adenosine monophosphate; thus inhibition of phosphodiesterase increases the biological half-life of cAMP. The cAMP stimulates secretion from the main and accessory lacrimal glands.[33,35,36]

Our findings are in sharp contrast with those found by Amaechi and Savia[4] in their work to study the effect of caffeine on tear formation in 30 young healthy subjects in Owerri, Imo state, Nigeria, using a pretest and posttest experimental design. The participants were exposed to 150 mL cup of coffee (equivalent of 250 mg of caffeine) each after which the Schirmer 1 test was repeated at hourly intervals during a 4-hour period, with resulting scores of 19.67, 13.73, 15.50, and 16.18 mm after 1, 2, 3, and 4 hours, representing a percentage reduction of 12.58, 38.98, 31.11, and 28.09%, respectively. This reduction in tear formation was found to be statistically significant (paired sample *t* test, $p < 0.05$).

The reason for this contrast is not far-fetched. Subjects in the work of Amaechi and Savia[4] consumed coffee that does not contain only caffeine but other physiologically active substances like chlorogenic acid,[37,38] caffeic acid,[39,40] citric acid,[41,42] and acetaldehyde.[15] There could be a possible confounding influence from these substances that the researchers failed to control. Although there are no data to support any inhibitory effect any of these substances have on lacrimal gland secretion, one cannot completely rule out any possible influence. Coffee is not analogous to caffeine; therefore, attributing the supposed inhibitory effect of coffee solely to the caffeine content seems implausible.

Our findings are in agreement with those observed by Arita et al.,[8] although the parameters studied in the two studies are not the same. Arita et al.[8] investigated the effect of caffeine on tear volume using a double-masked, placebo-controlled, crossover design involving 78 volunteers. Subjects participated in two sessions in which they received capsules containing either placebo or caffeine. The caffeine capsules were given to the subjects to keep the caffeine volume per body weight within 5.0 to 7.0 mg/kg. After caffeine intake, tear meniscus height was measured at 60 and 120 minutes after caffeine intake. Tear volume was found to increase after caffeine consumption. The net increase in tear meniscus height was 0.08 mm (95% confidence interval, 0.05 to 0.10) greater when participants were given caffeine than when given placebo ($p < 0.0001$).

We measured tear secretion in our study, whereas Arita et al.[8] measured tear volume. Although tear meniscus height and Schirmer 1 score are different parameters of tear film dynamics, we speculate that the two parameters could have a link because volume of tears in the inferior conjunctival sac could depend on the amount of tears secreted; reduced tear secretion will result in reduced tear volume and *vice versa*.

Our findings also support an earlier observation by Moss and Klein[8] in the Beaver Dam study to examine the risk factors for the prevalence of dry eye syndrome in a population-based cohort. The researchers found caffeine use to be one of the factors associated with a lower prevalence of dry eye. Dry eye prevalence was found to be 13.0% among caffeine users, whereas it was 16.6% among non–caffeine users. This seemingly protective effect of caffeine against dry eye is in line with our findings.

Drinking water is often recommended as a possible augmentation to dry eye therapy. However, from our findings, water seems not to have any impact on tear secretion. The basis for this recommendation thus ought to be investigated.

Our study has some limitations. A major limitation to the study is with our sample selection. The participants are not representative of the general population, the sample size was small, and participants had normal tear secretion and were drawn from a limited age range. Also, there was exclusion of smokers and alcohol users whose habits affect caffeine's half-life.[2,43]

In view of these, it will not be plausible to extrapolate the findings to the general population because we are unsure if caffeine will yield similar effects with the inclusion of older subjects, dry eye subjects, smokers, and alcohol users.

Another limitation is the use of the Schirmer 1 test. As discussed earlier, the test has some limitations[18–23] and as such has fallen from favor in dry eye research.

In addition to these, tolerance to caffeine might have influenced our results because caffeine tolerance is known to affect some physiological effects of caffeine such as diuretic effect and the effect on parotid gland secretion.[44,45] We could not ascertain the level of tolerance in our subjects because there was no limit on caffeine use as entry criterion, although participants refrained from caffeine-containing beverages before receiving an intervention.

In summary, acknowledging the limitations of the study, we found that orally ingested caffeine seems to stimulate tear secretion in healthy non–dry eye subjects. We also found that water has no impact on tear secretion. We recommend replicate studies using a large sample–sized dry eye subjects with varying social habits to ascertain if similar findings will be revealed. Such studies will be exploratory for possible enhancement of current treatment modalities for dry eye.

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