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Short-term effects of caffeine intake on anterior chamber angle and intraocular pressure in low caffeine consumers

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Abstract

Background Acute caffeine consumption causes a transient increase in IOP; however, the mechanisms underlying this phenomenon remain unknown. This study aims to determine the structural changes in cornea and anterior chamber associated with caffeine ingestion.

Methods Seventeen healthy low caffeine consumers ingested a capsule of caffeine (~4 mg/kg) or placebo (300 mg of cornstarch) in a counterbalanced manner. We measured IOP by rebound tonometry and the anterior chamber depth (ACD), anterior chamber volume (ACV), anterior chamber angle (ACA) and central corneal thickness (CCT) with the Pentacam rotating Scheimpflug camera. Subjective feelings of arousal were also obtained. All the dependent variables were obtained before and 30, 60 and 90 min after caffeine/placebo intake.

Results Caffeine intake caused an acute IOP rise ($p = 0.005$, $\eta^2 = 0.403$) and a narrowing ACA ($p = 0.028$, $\eta^2 = 0.266$). However, our data did not reveal any effect on CCT, ACD and ACV after caffeine ingestion ($p = 0.798$, $p = 0.346$, $p = 0.175$, respectively). Participants reported greater levels of activation after ingesting caffeine in comparison to placebo ($p = 0.037$, $\eta^2 = 0.245$).

Conclusion The IOP rise associated with caffeine intake may be caused by an ACA reduction, which may add resistance to the outflow of aqueous humour. The current results may be of special relevance for subjects at high risk for glaucoma onset or progression and may help to understand the mechanisms underlying caffeine-induced ocular hypertension.

Keywords Caffeine · Intraocular pressure · Pentacam · Anterior chamber · Aqueous humour

Introduction

Approximately 80% of the world's population consumes a caffeinated product every day, being coffee and tea the primary sources [1]. According to the literature review performed by Grosso et al. [2], the consumption of caffeine has beneficial effects on a number of chronic diseases, including different type of cancers or neurological, cardiovascular, and metabolic diseases. Remarkably, the positive consequences of caffeine consumption for human health have been argued to be mediated by different biological mechanisms such as its action as an adenosine receptor antagonist, sympathomimetic agent or rising the catecholamine levels [3].

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Regarding vascular function, acute caffeine intake has demonstrated to increase vascular resistance, which consequently reduces blood flow [4]. In the ocular physiology, caffeine causes vasoconstriction in retinal arterioles and venules of the human eye [5], increases the resistive index of the ophthalmic artery, central retinal artery and posterior ciliary arteries [6] and reduces choroidal thickness [7, 8].

Additionally, the effects of caffeine on intraocular pressure (IOP) have been investigated by numerous researchers due to its possible relevance for glaucoma onset and progression [9], being high caffeine consumption a risk factor for glaucoma in susceptible individuals [10]. Most studies suggest that caffeine intake causes a transient IOP rise, with these effects occurring after a few minutes of caffeine ingestion and lasting for some hours [11, 12]. Of note, these IOP changes have showed to be highly dependent on habitual caffeine consumption, with low consumers showing a more abrupt IOP increase in comparison to high-caffeine consumers [13], as well as be mediated by the ocular health status, with glaucoma patients or

individuals with ocular hypertension suffering greater IOP fluctuations in comparison to normal individuals [12].

In relation to the ocular physiological biomechanisms that explain the IOP increases associated with caffeine, there is no consensus in the literature. Caffeine increases intracellular cyclic AMP levels by inhibiting phosphodiesterase in many tissues, including the eye tissues [14]. Cyclic AMP has shown to play an important role in the mediating action of catecholamines on aqueous humour dynamics, enhancing the production of aqueous humour by the cells of the ciliary body or inhibiting its drainage by losing the tone in the smooth muscle of the anterior angle [15]. On the other hand, Adams and Brubaker [16] did not found any difference in aqueous flow measured hourly from 1 to 4 h after caffeine intake. Other possible explanation could be that an increase in blood pressure would lead to a secondary IOP rise [17]. Only one study in rats has explored the morphological changes associated with caffeine-induced hypertension, observing the dilatation of the lateral cellular spaces of the non-pigmented ciliary epithelium with intact interdigitations among the cells [18].

The incorporation of new advances in ocular imaging techniques may aid in understanding the mechanisms underlying IOP changes. Among these instruments, the OCULUS Pentacam (Oculus Inc., Wetzlar, Germany) uses the Scheimpflug principle to acquire quantitative and qualitative data of the anterior and posterior surfaces of the cornea, anterior chamber depth, anterior chamber angle, iris and lens [19]. This apparatus has been previously used to study the relationship between the changes in anterior segment morphometry and the changes in IOP after surgical procedures [20] or as consequence of circadian variations [21]. In the present study, we aimed to assess the short-term effects of caffeine intake (~ 4 mg/kg) on IOP, as measured by rebound tonometry, and ocular anterior segment biometrics, as measured by the Pentacam, in low caffeine consumers (≤ 1 cup of caffeinated drink). We hypothesised that caffeine intake will rise in the IOP [13]; however, the lack of previous studies assessing the impact of caffeine consumption on the ocular anterior segment morphology does not allow us to establish a hypothesis in this regard. Our results may help to elucidate the physiological mechanisms involved in the IOP changes induced by caffeine.

Methods

Participants

We performed an a priori power analysis, using the GPower 3.1 software [22], for sample size estimation. For an assumed power of 0.80, alpha of 0.05 and effect size of 0.30, there was a required sample size of 17 participants. At this point, 19 low caffeine consumers (≤ 1 cup of coffee per day) were recruited to participate in this study. Participants with a history of ocular trauma, surgery or disease were excluded. All volunteers had no adverse symptoms associated with caffeine intake and were neither pregnant nor breast-feeding. Since smoking causes an acute rise in blood pressure, all smokers were also excluded. In addition, all participants were asked to abstain from alcohol and caffeine-based drinks 24 and 12 h before each experimental session, respectively, and to sleep at least 7 h the night prior to testing. We excluded one participant due to the lack of compliance with the inclusion criteria (insufficient sleeping), and another participant did not complete the experiment. Thus, data from 17 low caffeine consumers (mean age ± standard deviation: 27.4 ± 6.6 years) were considered for further analyses. This study was approved by the University of Granada Institutional Review Board (IRB approval: 438/CEIH/2017), and the experimental protocol followed the guidelines of the Declaration of Helsinki.

Instruments and measurements

In order to check that participants attended to laboratory under similar conditions, they reported their subjective levels of arousal before each experimental session (placebo and caffeine) using the Stanford Sleepiness scale which consists in a 7-point Likert, ranging from 1 "very active, alert or awake" to 7 "very sleepy" [23]. Additionally, they were asked to complete a visual analogue scale in order to evaluate the subjective level of activation before the experimental session, and after 30, 60 and 90 min after capsule ingestion. This numerical scale ranged from 1 "absolutely not activated" to 10 "extremely activated".

We measured IOP with a portable rebound tonometer (Icare Tonometer, TiolatOy, INC., Helsinki, Finland), which has been clinically validated [24]. Participants were asked to look at a distance target while six rapid consecutive measurements were taken against the central cornea. Subsequently, the tonometer displayed the average intraocular pressure reading and indicated whether differences between measurements were acceptable (only values with low standard deviations were included). Additionally, IOP values obtained by rebound tonometry have been demonstrated to be sensitive to CCT [25], and thus, these readings were corrected following the equation: $\text{IOP corrected} = \text{IOP reading} + 0.02\ (545 - \text{CCT})$ [26].

Anterior segment parameters were measured with the Pentacam, which has an excellent repeatability when using the corneal vertex as the reference point [27]. For it, the subject is positioned in a chin and forehead rest and is asked to fixate on a black fixation target. A rotating Scheimpflug camera rotates 360° around the optical axis [19], and just after completing a scan, the Pentacam software calculates the anterior chamber depth (ACD) from the corneal endothelium to the anterior surface of the lens, anterior chamber volume (ACV) obtained for a 12 mm diameter around the corneal

apex, anterior chamber angle (ACA) and central corneal thickness (CCT) centred at the corneal apex [21]. All scans satisfied the quality specification (register as "OK") of the instrument [27].

Procedure

Participants visited the laboratory on two different days, being both sessions scheduled at the same time (± 1 h) to avoid the influence of circadian variations [21]. In the first session, an individual test was held to verify that subjects met inclusion criteria, as well as to obtain information about their daily caffeine consumption and their anthropometric characteristics. The same eye from each participant was randomly selected for measure IOP and anatomical parameters in both experimental sessions. Participants received, in a counterbalanced order, a capsule of caffeine or placebo along with a cup of water (100 ml). Each placebo capsule was composed of 300 mg of corn-starch and the caffeine capsules (caffeine anhydrous) were dispensed in steps of 20 mg, being prepared based on participant's weight (~ 4 mg/kg). Both were prepared by a pharmacist laboratory (Acofarma distribución S.A., Madrid, Spain) and packaged identically in an opaque gelatine capsule to avoid identification of contents by shape, taste or colour. Aiming to accomplish the double-blind procedure, the capsules were coded and prepared by a third person. All the dependent variables (IOP, anterior segment and corneal parameters and perceived levels of activation) were obtained before and 30, 60 and 90 min after capsule ingestion. In each measurement moment, every patient was examined firstly with the Oculus Pentacam, and then with the tonometer, in order to not introduce bias in the evaluation. All measurements were obtained under constant environmental and illumination conditions.

Statistical analysis

Before any statistical analysis, the normal distribution of the data (Shapiro-Wilk test) and the homogeneity of variances (Levene's test) yielded no significant differences between groups ($p > 0.05$).

To ensure that participants visited the laboratory under similar levels of alertness/sleepiness in both experimental conditions (caffeine and placebo), SSS values were submitted to a paired two-tailed t test.

To assess the acute impact of caffeine on IOP, anterior segment and corneal parameters (ACD, ACV, ACA, CCT) and perceived levels of activation, we performed separate analyses of variance (ANOVAs) for each dependent variable, with the measurement moment (baseline, 30, 60 and 90 min) and caffeine consumption (caffeine and placebo) as within-participant factors.

For all analyses, an α of .05 was adopted to determine significance of main effects, and the Holm-Bonferroni correction was adopted for multiple comparisons. Standardized effect sizes were reported as partial η^2 and Cohen's d for F and t tests, respectively.

Results

Table 1 shows the descriptive values for all the variables assessed at the different measurement moments for both experimental conditions.

The level of sleepiness/alertness revealed no significant differences between both experimental sessions ($t_{16} = 0.825$, $P = .421$), with an average value of 2.06 ± 1.06 and 2.22 ± 1.17 in the caffeine and placebo conditions, respectively.

For the main analyses, the ANOVA on IOP yielded a significant effect for caffeine consumption ($F_{1,\ 16} = 10.815$, $P = .005$, $\eta^2 = 0.403$) and the interaction caffeine consumption × measurement moment ($F_{3,\ 48} = 18.057$, $P < .001$, $\eta^2 = 0.530$), whereas no effect was found for the measurement moment ($F_{3,\ 48} = 1.762$, $P = .167$). Subsequently, post hoc comparisons revealed that higher IOP values were obtained after 30 min (corrected $P = .040$, $d = 0.63$), 60 min (corrected $P = .004$, $d = 0.98$) and 90 min (corrected $P = .004$, $d = 1.18$) of caffeine intake when compared to the placebo condition (Fig. 1).

No effects were found on ACD for either caffeine consumption ($F_{1,\ 16} = 0.943$, $P = .346$), measurement moment ($F_{3,\ 48} = 1.071$, $P = .370$) or the interaction ($F_{3,\ 48} = 0.135$, $P = .939$). Similarly, ACV did not reach significant differences for caffeine consumption ($F_{1,\ 16} = 2.026$, $P = .175$), measurement moment ($F_{3,\ 48} = 1.884$, $P = .146$) and the interaction ($F_{3,\ 48} = 0.738$, $P = .535$).

The analysis of ACA revealed a significant effect for caffeine consumption ($F_{1,\ 16} = 5.813$, $P = .028$, $\eta^2 = 0.266$), whereas no effects were found for the measurement moment ($F_{3,\ 48} = 2.192$, $P = .101$) and the interaction ($F_{3,\ 48} = 2.180$, $P = .103$). Post hoc tests revealed that there were only significant differences after 90 min of caffeine ingestion (corrected $P = .020$, $d = 0.78$), with narrower angles in the caffeine condition when compared to the placebo (Fig. 2).

For CCT, there were no differences for any factor (caffeine consumption: $F_{1,\ 16} = 0.068$, $P = .798$; and measurement moment: $F_{3,\ 48} = 0.312$, $P = .312$), as well as the interaction ($F_{3,\ 48} = 0.668$, $P = .576$).

Lastly, perceived levels of activation showed significant differences for caffeine consumption ($F_{1,\ 16} = 5.193$, $P = .037$, $\eta^2 = 0.245$) and the measurement moment ($F_{3,\ 48} = 3.429$, $P = .024$, $\eta^2 = 0.176$), but no effect was observed for the interaction ($F_{3,\ 48} = 2.315$, $P = .088$). Post hoc tests

Table 1 Average ± standard deviation values for the subjective, intraocular pressure and anterior segment values at the different measurement moments in both experimental conditions

		Measurement moment			
		Baseline	After 30 min	After 60 min	After 90 min
Perceived level of activation (arbitrary units)	*Caffeine*	7.12 ± 1.80	7.42 ± 1.41	7.94 ± 1.39	8.06 ± 1.39
	Placebo	7.24 ± 1.60	7.18 ± 1.84	7.29 ± 1.74	7.35 ± 1.77
Intraocular pressure (mmHg)	*Caffeine*	15.59 ± 4.05	17.47 ± 4 .37	17.24 ± 4.11	17.65 ± 4.58
	Placebo	16.11 ± 4.17	15.65 ± 4.24	15.06 ± 4.16	14.59 ± 4.09
Anterior chamber depth (mm)	*Caffeine*	3.67 ± 0.32	3.67 ± 0.32	3.68 ± 0.33	3.67 ± 0.31
	Placebo	3.68 ± 0.33	3.68 ± 0.32	3.69 ± 0.32	3.69 ± 0.33
Anterior chamber volume (mm^3)	*Caffeine*	190.22 ± 32.17	185.49 ± 35.67	185.56 ± 36.43	186.84 ± 37.88
	Placebo	188.50 ± 37.88	187.08 ± 36.88	188.21 ± 37.55	187.06 ± 37.99
Anterior chamber angle (degree)	*Caffeine*	39.53 ± 5.46	38.86 ± 5.37	37.18 ± 4.52	37.11 ± 5.34
	Placebo	39.31 ± 5.55	39.44 ± 6.14	39.08 ± 6.24	39.78 ± 5.54
Central corneal thickness (μm)	*Caffeine*	557.71 ± 43.59	556.35 ± 42.71	558.88 ± 41.99	560.94 ± 43. 60
	Placebo	559.24 ± 46.05	558.00 ± 42.07	558.65 ± 41.29	559.06 ± 41.07

demonstrated greater perceived levels of activation after 60 min (corrected $P = .030$, $d = 0.79$) and 90 min (corrected $P = .020$, $d = 0.79$) of caffeine intake in comparison to the baseline value.

Discussion

In this study, we investigated the acute biometrics changes of the eye anterior pole and IOP following caffeine (~4 mg/kg) or placebo consumption. There is scientific evidence that caffeine intake causes a transient IOP rise [11–13]; however, no studies have determined the short-term effects of caffeine consumption on the ocular anterior segment morphology. Here, we observed a statistically significant IOP rise of ~2 mmHg after caffeine intake, as well as a reduction of the ACA of ~2.5°, which may add resistance to the outflow of aqueous humour, and thus, increases IOP levels. Our data revealed that caffeine ingestion had no effect on CCT, ACD and ACV. Additionally, participants reported greater levels of activation in the caffeine condition, confirming the arousing effect of caffeine shown in the related literature [28].

At the beginning of each experimental session, participants reported an analogous level of alertness/sleepiness (SSS), allowing us to confirm an appropriate experimental control. Previous studies had found that caffeine induces stimulant subjective effects on arousal and wakefulness [28]. Similarly, in our study, after caffeine but not placebo

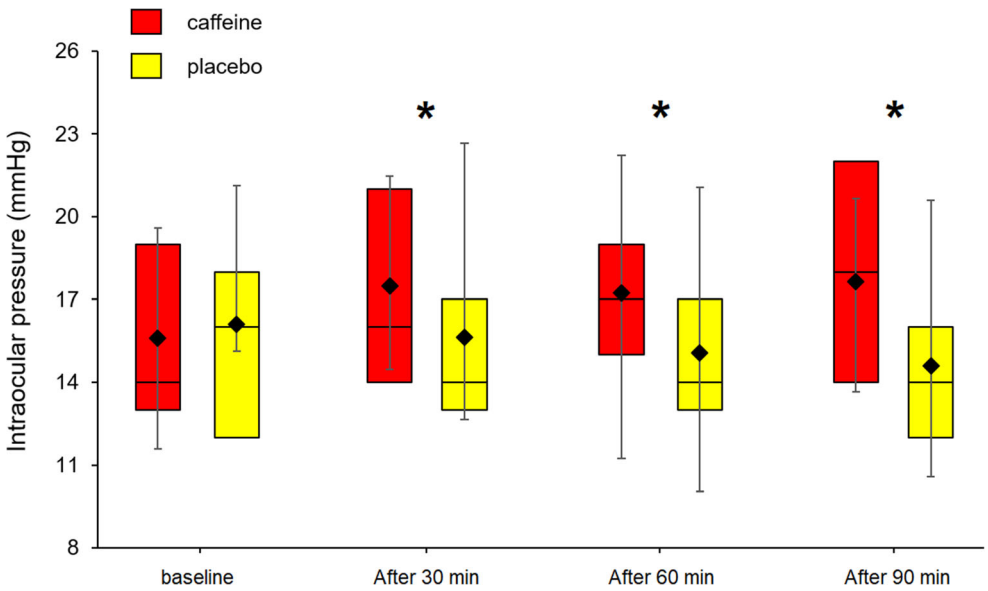

Fig. 1 Effects of caffeine consumption on intraocular pressure at the different points of measure. *Statistically significant differences between the experimental conditions (corrected p values < 0.05). The box plots represent 75th, 50th and 25th centiles. Horizontal lines and diamonds into the box represent median and mean values, respectively. The whiskers show the maximum and minimum values. All values are calculated across participants ($n = 17$)

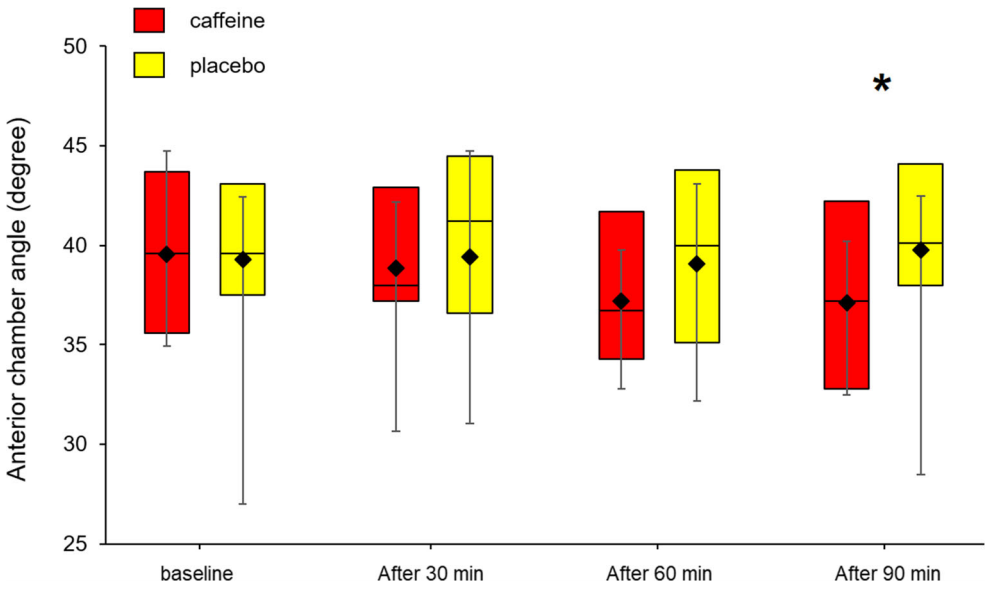

Fig. 2 Effects of caffeine consumption on anterior chamber angle at the different points of measure. *Statistically significant differences between the experimental conditions (corrected p values < 0.05). The box plots represent 75th, 50th and 25th centiles. Horizontal lines and diamonds into the box represent median and mean values, respectively. The whiskers show the maximum and minimum values. All values are calculated across participants ($n = 17$)

consumption, the subjective feelings of activation increased in comparison to baseline.

Acute caffeine consumption causes a transient increase in IOP [11], being this effect highly influenced by the ocular health status [12]. Remarkably, Vera and colleagues [13] recently found that the effects of caffeine intake on IOP are subject to tolerance as a result of habitual caffeine consumption in healthy individuals, with low caffeine consumers exhibiting a more accentuated IOP increment in comparison to high caffeine consumers. In this study, we included a representative sample of low caffeine consumers (≤ 1 cup of coffee per day), obtaining comparable results to those of Vera and colleagues since both studies have evidenced a moderate IOP rise after caffeine intake. On the contrary, a few studies did not find any IOP changes after caffeine consumption in healthy individuals. Nevertheless, it should be noted that these investigations did not differentiate between high and low caffeine consumers [8, 16], and there is evidence that habitual caffeine consumers have an attenuated physiological responsiveness to caffeine [3, 29].

It is well known that CCT influences IOP readings, namely thinner corneas cause lower readings while thicker corneas lead to higher IOP values [25]. Animal studies have shown that caffeine alters some structures of the eye, specifically a decrease in thickness of developing chicken corneas [30]. We did not observe any changes on CCT, and therefore, it does not seem to be associated with the IOP changes induced by caffeine intake. Also, the corneal biomechanical response has been strongly linked to central corneal thickness in non-glaucoma subjects and only moderately in glaucoma patients [31]. Therefore, biomechanical properties of the cornea associated with corneal viscoelasticity and resistance (e.g., corneal hysteresis or corneal resistance factor) should be considered when evaluating the effects of caffeine on IOP, since these indices have demonstrated to influence IOP measurements more than corneal thickness or curvature [32, 33], especially in glaucomatous patients [31]. Future studies should examine the biomechanics of the cornea after caffeine intake in order to clarify its possible effects on IOP.

Secretion and outflow of aqueous humour are the two crucial processes for regulating IOP levels [34]. Aqueous humour is produced in the ciliary processes from the epithelial layers and drained by passive flow via the trabecular outflow pathways (approximately 85% of aqueous outflow) and uveoscleral outflow route [35]. An impaired aqueous humour dynamics as a consequence of anatomical changes in the anterior chamber leads to an increment of IOP, which is a central aspect in the prevention and management of glaucoma [34]. Previous studies have suggested that the main cause of the IOP rise after caffeine intake is a heightened production of aqueous humour, possibly explained by changes in the non-pigmented ciliary epithelium or an increased blood pressure [14, 17, 18]. Here, assessing the biometrics dimensions of eye anterior pole, we observed a significant decrease of the ACA after caffeine consumption. However, there were no changes for ACD and ACV. Angle closure occurs by apposition or adhesion of the peripheral iris to the surface of the pigmented trabecular meshwork resulting in impaired aqueous outflow, and subsequently, causing ocular hypertension [36]. This study incorporates novel insights into the possible mechanisms (narrowing of the ACA) that may explain the IOP rise associated with acute caffeine consumption. Also, there is evidence that ACV is independently associated with narrow angles, with this relationship being more evident for women in comparison to men [37]. However, we found an effect of caffeine intake on ACA, but not on ACV in healthy young adults. It is plausible to speculate that the small changes in ACA caused by caffeine may not be sufficient to induce

significant changes in ACV. Future studies are guaranteed in this regard.

Notably, the ACA narrowing (~ 2.5°) and IOP rise (~ 2 mmHg) found in this study after caffeine consumption seems to be clinically modest; however, these changes may be more evident in individuals at risk of primary angle-closure glaucoma (angle closure without increase in IOP) or primary angle-closure patients (angle closure with increased IOP). Indeed, caffeine effects on IOP are more pronounced in patients with glaucoma or ocular hypertension than in normal individuals, possibly because healthy drainage systems have a better ability to drainage aqueous humour [12]. Of note, IOP changes of 1 mmHg have demonstrated to be associated with a 10% higher risk for both the development and progression of glaucoma [38], and thus, small IOP rises must be also taken into account. Moreover, the present outcomes should be tested in glaucoma patients or those at risk.

This study incorporates valuable information for understanding the mechanisms underlying the IOP rises provoked by caffeine ingestion. However, our results should be interpreted according to the following limitations. First, it is plausible that caffeine intake may alter the biomechanical properties of the cornea, which could be also associated with the IOP changes found in this study [31, 32]. Second, we found a decrease in the ACA after caffeine consumption; however, further studies, using high-frequency ultrasound biomicroscopy [39], are needed to explore the possible causes of angle narrowing after caffeine ingestion. Third, other limitations are associated with the inclusion of a relatively small sample of young healthy adults, and that we did not evaluate patients with glaucoma or ocular hypertension, as well as an older population. The results obtained in healthy young adults may vary between different cohorts, and thus, the external validity of these findings in glaucoma patients and older adults needs to be addressed in future investigations. Also, larger sample sizes would allow to explore the possible link between the changes observed in IOP and ocular anterior segment morphology after caffeine intake. In the same line, we consider of interest to assess the eye anterior segment biometrics changes in subjects who have a narrow anterior chamber angle in order to quantify the risk of induced angle closure as a consequence of caffeine intake. Lastly, there is a lack of longitudinal studies exploring the relationship between caffeine habits and glaucoma. It is our hope that future studies will deepen into this topic.

Conclusions

The results of this study show a significant IOP rise and ACA narrowing when consuming an acute dose of caffeine (~ 4 mg/kg) in a group of low caffeine consumers. We did not find any change in CCT, ACD, and ACV after caffeine intake. Our findings suggest that the IOP rises associated with caffeine intake may be caused by an ACA reduction, which limits aqueous humour outflow. These outcomes may be of special relevance for subjects at high risk for glaucoma onset or progression.

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Compliance with ethical standards

Conflict of interest Beatriz Redondo declares that she has no conflict of interest. Jesus Vera declares that he has no conflict of interest. Ruben Molina declares that he has no conflict of interest. Raimundo Jiménez declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of Granada Institutional Review Board (IRB approval: 438/CEIH/2017) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Heckman MA, Weil J, de Mejia EG (2010) Caffeine (1, 3, 7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. J Food Sci 75:77–87. https://doi.org/10.1111/j.1750-3841.2010.01561.x
2. Grosso G, Micek A, Godos J et al (2016) Coffee consumption and risk of all-cause, cardiovascular, and cancer mortality in smokers and non-smokers: a dose-response meta-analysis. Eur J Epidemiol 31:1191–1205. https://doi.org/10.1007/s10654-016-0202-2
3. Ferré S (2008) An update on the mechanisms of the psychostimulant effects of caffeine. J Neurochem 105:1067–1079. https://doi.org/10.1111/j.1471-4159.2007.05196.x
4. Nurminen ML, Niittynen L, Korpela R, Vapaatalo H (1999) Coffee, caffeine and blood pressure: a critical review. Eur J Clin Nutr 53:831–839. https://doi.org/10.1038/sj.ejcn.1600899
5. Terai N, Spoerl E, Pillunat LE, Stodtmeister R (2012) The effect of caffeine on retinal vessel diameter in young healthy subjects. Acta Ophthalmol 90:524–528. https://doi.org/10.1111/j.1755-3768.2012.02486.x
6. Özkan B, Yüksel N, Anik Y et al (2008) The effect of caffeine on retrobulbar hemodynamics. Curr Eye Res 33:804–809. https://doi.org/10.1080/02713680802344708
7. Vural AD, Kara N, Sayin N et al (2014) Choroidal thickness changes after a single administration of coffee in healthy subjects. Retina 34:1223–1228. https://doi.org/10.1097/IAE.0000000000000043
8. Dervişoğulları MS, Totan Y, Yüce A, Kulak AE (2016) Acute effects of caffeine on choroidal thickness and ocular pulse amplitude. Cutan Ocul Toxicol 35:281–286. https://doi.org/10.3109/15569527.2015.1104330
9. Hecht I, Achiron A, Man V, Burgansky-Eliash Z (2017) Modifiable factors in the management of glaucoma: a systematic review of current evidence. Graefes Arch Clin Exp Ophthalmol 255:789–796. https://doi.org/10.1007/s00417-016-3518-4
10. Kang JH, Willett WC, Rosner BA et al (2008) Caffeine consumption and the risk of primary open-angle glaucoma: a prospective

cohort study. Investig Ophthalmol Vis Sci 49:1924–1931. https://doi.org/10.1167/iovs.07-1425
11. Yoon JJ, Danesh-Meyer HV (2019) Caffeine and the eye. Surv Ophthalmol 64:334–344. https://doi.org/10.1016/j.survophthal.2018.10.005
12. Li M, Wang M, Guo W et al (2011) The effect of caffeine on intraocular pressure: a systematic review and meta-analysis. Graefes Arch Clin Exp Ophthalmol 249:435–442. https://doi.org/10.1007/s00417-010-1455-1
13. Vera J, Redondo B, Molina R et al (2019) Effects of caffeine on intraocular pressure are subject to tolerance: a comparative study between low and high caffeine consumers. Psychopharmacology 236:811–819
14. Kurata K, Fujimoto H, Tsukuda R et al (1998) Aqueous humor dynamics in beagle dogs with caffeine-induced ocular hypertension. J Vet Med Sci 60:737–739. https://doi.org/10.1292/jvms.60.737
15. Neufeld AH, Jampol LM, Sears ML (1972) Cyclic-AMP in the aqueous humor: the effects of adrenergic agents. Exp Eye Res 14:242–250. https://doi.org/10.1016/0014-4835(72)90009-7
16. Adams BA, Brubaker RF (1990) Caffeine has no clinically significant effect on aqueous humor flow in the normal human eye. Ophthalmology 97:1030–1031. https://doi.org/10.1016/S0161-6420(90)32468-5
17. Ajayi OB, Ukwade MT (2001) Caffeine and intraocular pressure in a Nigerian population. J Glaucoma 10:25–31 https://doi.org/10.1097/00061198-200102000-00006
18. Kurata K, Maeda M, Nishida E et al (1997) Relationship between caffeine induced ocular hypertension and ultrastructure changes of non pigmented ciliary epithelial cells in rats. J Toxicol Sci 22:447–454
19. Rabsilber TM, Khoramnia R, Auffarth GU (2006) Anterior chamber measurements using Pentacam rotating Scheimpflug camera. J Cataract Refract Surg 32:456–459. https://doi.org/10.1016/j.jcrs.2005.12.103
20. Dooley I, Charalampidou S, Malik A et al (2010) Changes in intraocular pressure and anterior segment morphometry after uneventful phacoemulsification cataract surgery. Eye 24:519–527. https://doi.org/10.1038/eye.2009.339
21. Read SA, Collins MJ, Iskander DR (2008) Diurnal variation of axial length, intraocular pressure, and anterior eye biometrics. Investig Ophthalmol Vis Sci 49:2911–2918. https://doi.org/10.1167/iovs.08-1833
22. Faul F, Erdfelder E, Lang A-G, Buchner A (2007) G*power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 39:175–191. https://doi.org/10.3758/BF03193146
23. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement W (1972) Quantification of sleepiness; a new approach. Psychophysiology 10:431–436
24. Pakrou N, Gray T, Mills R et al (2008) Clinical comparison of the Icare tonometer and Goldmann applanation tonometry. J Glaucoma 17:43–47. https://doi.org/10.1097/IJG.0b013e318133fb32
25. Doughty MJ, Zaman ML (2000) Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. Surv Ophthalmol 44:367–408. https://doi.org/10.1016/S0039-6257(00)00110-7
26. Smedowski A, Weglarz B, Tarnawska D et al (2014) Comparison of three intraocular pressure measurement methods including biomechanical properties of the cornea. Investig Ophthalmol Vis Sci 55:666–673. https://doi.org/10.1167/iovs.13-13172
27. Shankar H, Taranath D, Santhirathelagan CT, Pesudovs K (2008) Anterior segment biometry with the Pentacam: comprehensive assessment of repeatability of automated measurements. J Cataract Refract Surg 34:103–113. https://doi.org/10.1016/j.jcrs.2007.09.013
28. Glade MJ (2010) Caffeine-not just a stimulant. Nutrition 26:932–938. https://doi.org/10.1016/j.nut.2010.08.004
29. Grosso G, Godos J, Galvano F, Giovannucci EL (2017) Coffee, caffeine, and health outcomes: an umbrella review. Annu Rev Nutr 37:131–156. https://doi.org/10.1146/annurev-nutr-071816-064941
30. Monika KH, Dariusz T, Hieronim B (2010) Changes in thickness of each layer of developing chicken cornea after administration of caffeine. Folia Histochem Cytobiol 48:273–277. https://doi.org/10.2478/v10042-010-0043-x
31. Mangouritsas G, Morphis G, Mourtzoukos S, Feretis E (2009) Association between corneal hysteresis and central corneal thickness in glaucomatous and non-glaucomatous eyes. Acta Ophthalmol 87:901–905. https://doi.org/10.1111/j.1755-3768.2008.01370.x
32. Liu J, Roberts CJ (2005) Influence of corneal biomechanical properties on intraocular pressure measurement: quantitative analysis. J Cataract Refract Surgery 31:146–155
33. Elsheikh A, McMonnies CW, Whitford C, Boneham GC (2015) In vivo study of corneal responses to increased intraocular pressure loading. Eye Vis 2:1–10. https://doi.org/10.1186/s40662-015-0029-z
34. Weinreb RN, Aung T, Medeiros FA (2014) The pathophysiology and treatment of glaucoma. JAMA 311:1901–1911. https://doi.org/10.1001/jama.2014.3192
35. Tamm ER (2009) The trabecular meshwork outflow pathways: structural and functional aspects. Exp Eye Res 88:648–655. https://doi.org/10.1016/j.exer.2009.02.007
36. Nongpiur ME, Ku JYF, Aung T (2011) Angle closure glaucoma: a mechanistic review. Curr Opin Ophthalmol 22:96–101. https://doi.org/10.1097/ICU.0b013e32834372b9
37. Wu RY, Nongpiur ME, He MG et al (2011) Association of narrow angles with anterior chamber area and volume measured with anterior-segment optical coherence tomography. Arch Ophthalmol 129:569–574. https://doi.org/10.1001/archophthalmol.2011.68
38. Leske M, Heijl A, Hussein M et al (2003) Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol 121:48–56. https://doi.org/10.1097/00132578-200310000-00007
39. Dada T, Gadia R, Sharma A et al (2011) Ultrasound biomicroscopy in glaucoma. Surv Ophthalmol 56:433–450. https://doi.org/10.1016/j.survophthal.2011.04.004