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LITERATURE REVIEW

EFFECT OF CAFFEINE CONSUMPTION ON INTRAOCULAR PRESSURE AND RISK OF GLAUCOMA: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: *Glaucoma is one of the leading causes of blindness worldwide with intraocular pressure (IOP) as its main risk factor. Several studies have investigated the association between IOP and caffeine consumption with mixed results. This study aims to review whether caffeine consumption increases IOP thus, increases the risk of glaucoma.*

Methods: *A comprehensive literature search was performed in 4 databases, including Pubmed, Proquest, ScienceDirect, and Cochrane. Last search was conducted on March 20, 2023. We include human studies investigating caffeine impact on IOP and/or glaucoma risk published in English with full text available from 2013 to 2023. The risk of bias was assessed with RoB 2.0 for crossover studies, NIH for cross-sectional and case-control studies. We present our results according to PRISMA guidelines.*

Discussion: *A total of 130.012 participants from 7 different studies were included in this review. Three crossover, 3 cross-sectional, and 1 case-control study were evaluated. This study involved a multi-racial population although Caucasian predominated. Five out of 7 studies exhibited a significant association (all p values <0.05) between caffeine consumption and increased risk of developing glaucoma.*

Conclusion: *Caffeine consumption generally shows a significant impact on developing risk of glaucoma and has been shown to increase IOP in acute settings, reported up to 90 minutes after consumption/ingestion. Limitations of this study include a small number of crossover participants and a high variability of participants (young healthy individuals and glaucoma patients). Further research is advised to investigate the association between caffeine consumption in a longer follow-up time and a more specific population.*

Keywords: *Caffeine, Coffee, Intraocular Pressure, Glaucoma, Ocular Hypertension*

INTRODUCTION

Glaucoma is a complex eye disease characterized by progressive damage to the optic nerve and visual field loss. It has become one of the leading causes of blindness worldwide. There are several different types of glaucoma, including primary open-angle glaucoma (POAG), primary angle-closure glaucoma (PACG), and secondary glaucoma. POAG is the most common type of glaucoma and is characterized by a gradual increase in IOP due to blockage of the drainage channels in the eye, which leads to optic nerve damage and visual field loss. PACG, on the other hand, is characterized by a sudden increase in IOP due to the closure of the drainage angle in the eye, which can lead to acute symptoms such as severe eye pain and

vision loss. Secondary glaucoma can occur as a result of other eye diseases or conditions such as uveitis or trauma. As seen on the mechanism of each type of glaucoma, elevated intraocular pressure (IOP) is the most significant risk factor, which can damage the optic nerve and lead to irreversible vision loss if left untreated.[1]

As caffeine has shown its impact on increasing blood pressure, recent studies have suggested that caffeine intake may also be associated with increased IOP which leads to the development and progression of glaucoma. The exact mechanism by which caffeine affects intraocular pressure and the pathogenesis of glaucoma is not yet fully understood. One possible mechanism is that caffeine may increase intraocular pressure by stimulating the production of aqueous humor, the fluid that nourishes the eye. This increase in pressure can damage the optic nerve and lead to glaucoma. Additionally, caffeine has been shown to decrease the flow of blood to the eye, which may further contribute to the development of glaucoma. Furthermore, caffeine has been found to have an impact on various biological pathways that may influence the development and progression of glaucoma. For example, caffeine intake has been shown to increase levels of cortisol, a stress hormone that has been associated with an increased risk of glaucoma. Caffeine may also affect the regulation of nitric oxide, a molecule involved in the control of intraocular pressure.[2]

While some studies have found a positive correlation between caffeine consumption and increased risk of glaucoma, others have also reported conflicting results. Since prevention of development and progression of glaucoma are critical to avoid the risk of irreversible vision loss and blindness, understanding the preventable risk factors such as caffeine consumption is essential to improve the diagnosis and management of this sight-threatening condition. Given the widespread use of caffeine-containing beverages and foods, understanding the potential impact of caffeine on glaucoma is a significant public health importance. In this systematic review, we aim to synthesize the available evidence on the association between caffeine intake with IOP and glaucoma, and to provide a comprehensive analysis of the findings. The results of this review may have implications for clinical practice, public health recommendations, and future research in the field.

METHODS

This systematic review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[3] We conducted a comprehensive literature search across four databases, including Pubmed, Proquest, ScienceDirect, and Cochrane, using the following keywords: Caffeine OR Coffee AND Intraocular Pressure OR Glaucoma OR Ocular

Hypertension. Search was performed using adaptive search according to each database and MESH terms if available. The search was restricted to English articles published between 2013 to 2023, with the most recent search conducted on March 20, 2023. Article results from the databases then imported to Rayyan, a web-tool with artificial intelligence designed for systematic review.[4]

Inclusion and exclusion criteria were employed. Inclusion criteria included (1) Human studies (2) Studies involving caffeine intake (3) Studies describing the effect of caffeine on increased intraocular pressure and/or the risk of developing glaucoma. The exclusion criteria include (1) Studies that are not available in English (2) Studies that do not provide access to complete papers (3) review articles. The main outcome assessed in the included studies are IOP measurements and association to glaucoma prevalence.

After retrieving the articles from the search results, four authors independently reviewed them to determine their eligibility for inclusion. The risk of bias assessment was carried out by 4 independent reviewers in each study. Different assessment tools were determined for each type of research. The risk of bias was assessed with RoB 2.0 for crossover studies and NIH for cross-sectional and case-control studies. Evaluation of bias was performed at the study level, and any disagreements were resolved through discussion between the authors.

The process of data extraction involved first and second reviewers, who systematically collected information from the included articles. This information encompassed various aspects, including: (1) the author and year of publication of each study (2) Study design (3) Patients (4) Mean Age (5) Exposure (6) Control (7) Outcome. Subsequently, a thorough examination and verification of the extracted data were conducted by two additional reviewers, referred to as the third and fourth reviewers.

RESULTS

Following the removal of duplicates using the Rayyan automation tool and subsequent manual confirmation, each reviewer independently screened the abstracts with a blinded review process. Subsequently, the blind was turned off allowing discussion and resolution of conflicts between reviewers, aiming to achieve a consensus for the final analysis and data extraction. A total of 7 studies and 130.012 participants met the inclusion criteria (Figure 1).

Risk of bias for all crossover studies was low, while the risk of bias for the cross-sectional and case-control studies were fair. The characteristics of the studies are presented in Table 1. Among the evaluated studies were three crossover studies, three cross-sectional

studies, and one case-control study. Although the study included a multi-racial population, Caucasians were predominant.

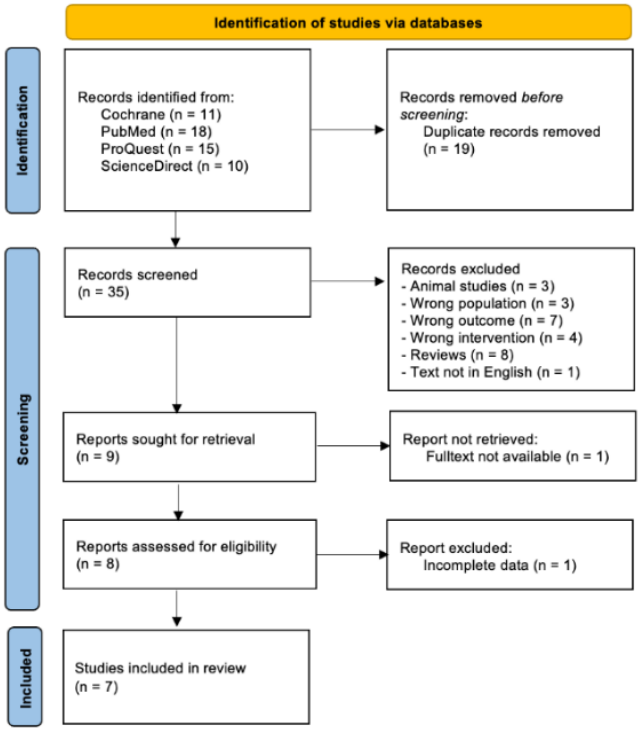

Figure 1. Study Selection Process

The effect of caffeine consumption was examined in healthy adults with both low and high caffeine consumption levels and in glaucoma patients. In healthy individuals, caffeine consumption at a dose of 4 mg/kg resulted in an acute increase in intraocular pressure (IOP) compared to placebo.[5–7] Furthermore, within the group of healthy individuals, a study comparing low-caffeine consumers to high-caffeine consumers found that the increase in IOP was more pronounced in the low-caffeine group influenced by tolerance level.[6] Caffeine consumption also has demonstrated an effect on patients with open-angle glaucoma (OAG). Two included studies, one cross-sectional and one case-control, revealed a significant association between coffee consumption and OAG.[8,9] Hun Bae, et al. suggested that coffee consumption may affect the risk of OAG, particularly in men compared to women.[8] However, two of the cross-sectional studies included in the analysis reported no significant association between caffeine consumption and either IOP or glaucoma ($p > 0.05$).[10,11] Although, a sub analysis Kim et al reported in individuals with high IOP genetic predispositions, consuming higher doses of caffeine was associated with a 0.35-mmHg higher IOP and a 3.90-fold higher glaucoma prevalence.[11]

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Table 1. Characteristic and Outcomes of the Studies Included

Study (Year)	Settings	Study Design	Patients	Mean Age	Exposure	Control	Outcomes
Jiménez et al. (2020)	Spain	Placebo - controlled, double - blind, crossover study	22 healthy low caffeine consumers (≤ 1 cup/day)	22.4 years	Caffeine (~4 mg/kg)	Placebo (300 mg of corn starch)	**Caffeine intake caused an acute IOP rise ($p < 0.005$)**
Vera et al. (2018)	Spain	Placebo - controlled, double - blind, crossover study	40 university students (21 low- and 19 high - caffeine consumers)	22.1 years	Caffeine (~4 mg/kg)	Placebo (300 mg of corn starch)	**Caffeine intake caused an acute IOP rise particularly in low-caffeine consumers and in 90 minutes after ingestion ($p < 0.001$)**
Redondo et al. (2019)	Spain	Placebo - controlled, double - blind, crossover study	17 healthy low caffeine consumers (≤ 1 cup/day)	27.4 years	Caffeine (~4 mg/kg)	Placebo (300 mg of corn starch)	**Caffeine intake caused an acute IOP rise ($p = 0.005$)**
Wu et al. (2017)	Korean National Health and Nutrition Examination Survey (NHANES) Database in 2005 - 2006	Retrospective Cross - sectional	1.678 (84 glaucoma, 1593 non - glaucoma)	55.8 years (62.8 yrs for glaucoma, 55.4 yrs for non-glaucoma)	Consumption of various caffeinated beverages in the past 12 months including coffee, tea, and soft drinks: < 1 cup, 1-6 cups, and > 6 cups per week	-	No statistically significant association between consumption of coffee, tea and soft drinks, and glaucoma ($p > 0.05$). Consumption of at least one cup of hot tea daily had 74% decreased odds of having glaucoma compared with those who did not consume hot tea (adjusted OR=0.26, 95% CI 0.09 to 0.72, P=0.004). No statistically significant association existed for decaffeinated hot tea and glaucoma.
Bae et al. (2020)	Korean National Health and Nutrition Examination Survey	Cross - sectional	6.681 (323 glaucoma, 6358 non - glaucoma)	49.9 years for glaucoma, 41.8 years	Consumption of various caffeinated beverages in the past 12 months	-	**Participants who drank coffee had a higher risk of having OAG ([OR] 2.40; 95% [CI] 1.22–4.72; $p = 0.011$). In sex-stratified analyses, the robust association of coffee consumption with**

Study (Year)	Settings	Study Design	Patients	Mean Age	Exposure	Control	Outcomes
	(KNHANES) Database in 2010 - 2011			for non - glaucoma	including coffee, tea, and soft drinks: none, 6-11 cups/year, 1 cup/month, 2-3 cups/month, 1 cup/week, 2 cups/day, > 2 cups/day		**OAG was observed in men (OR, 3.98; 95% CI, 1.71–9.25; p = 0.001) but not in women. The OR comparing those who consumed coffee with those who did not consume coffee was 2.06 (95% CI, 1.11–3.82).**No significant association between tea consumption and OAG. Coffee consumption was not significantly associated with elevation of IOP.
Kim et al. (2021)	UK Biobank Database in 2006 - 2010	Cross - sectional	121.374 patients	56.8 years	Habitual tea and coffee consumption: nondrinkers (0 cup/day), low consumption (≤ 1 cup/day), and high consumption (> 1 cup/day)	-	No significant association between habitual tea and coffee consumption and IOP and glaucoma (p > 0.1). Greater caffeine intake was associated weakly with lower IOP (P=0.01). **Subanalysis in individuals with high IOP genetic predispositions, consuming higher dose of caffeine was associated with a 0.35-mmHg higher IOP (P = 0.01) and a 3.90-fold higher glaucoma prevalence (P = 0.0003).**
Mylona et al. (2019)	Outpatient services, Department of Ophthalmology, Aristotle University of Thessaloniki, Greece	Case - control	100 POAG patients, 100 healthy patients	68.63 years for POAG, 69.4 years for controls	Coffee consumption in POAG: 0-3/month, 1-6/week, 1-6/day	Coffee consumption in healthy patients: 0-3/month, 1-6/week, 1-6/day	**POAG patients had higher coffee consumption (p < 0.001)**

Significant results are written in bold

DISCUSSION

Within this review, all experimental crossover studies examining the impact of caffeine consumption on the rise of IOP in acute settings consistently yielded positive outcomes.[5–7] These findings are consistent with several studies reporting an IOP increase after administration of caffeine capsules compared to placebo. [12,13] Although the exact mechanism of IOP rise is not fully understood, several physiological processes may take part regarding these results. In animal studies, caffeine found to have an impact on epithelial cells of the ciliary body, promoting the production of aqueous humor, also reducing the tone of the smooth muscle cells in the chamber angle, causing the narrowing of fenestrae responsible for draining the aqueous humor, therefore increasing the resistance to its outflow.[14,15] This phenomenon also identified in human study by Redondo et al, where anterior chamber angle reduction after caffeine consumption has been causing an impair of the aqueous humor outflow.[7]

There are several suggested pathophysiological effects of caffeine on the risk of developing glaucoma. The meta-analysis of randomized controlled trials by Cai et al indicated that coffee intake is associated with elevated serum levels of triglycerides and low-density lipoprotein cholesterol, which increase the risk factors for development of glaucoma.[16] An experimental study also supports evidence regarding the ability of caffeine to elevate blood pressure resulting in an increase of total peripheral resistance that can lead to risk of developing glaucoma.[17] Moreover, caffeine is reported to have an impact on the posterior segment by reducing choroidal thickness, attributed to the vasoconstrictive property of caffeine on the choroid vascular structures.[18] Another possible mechanism is increasing plasma and aqueous levels of homocysteine, which is associated with development of pseudoexfoliation glaucoma and OAG.[19] Notably, these effects are observed to be attenuated in individuals who habitually consume caffeine.[20]

Our study revealed an adverse impact between coffee consumption and primary open-angle glaucoma primarily in men, while no significant association was found in women. The underlying reasons for this gender discrepancy are not yet fully understood but may be linked to physiological variances and differing hormone levels. Previous research has also highlighted disparities in OAG prevalence and risk factors between men and women, potentially influenced by factors such as serum glutamate levels, estrogen-progesterone levels, and tissue responses to glaucomatous insults. Estrogen-related effects, such as intraocular pressure reduction or neuroprotection, have been proposed as potential mechanisms explaining the sex-specific

association. Interestingly, Kang et al. observed a significant positive relationship between caffeine intake and OAG risk in women, particularly those with high IOP.[11,21,22]

However, in a non-acute setting, the relationship between caffeine consumption with IOP and glaucoma-remained debatable. Li et al. reported minimal effects of caffeine on IOP in individuals without ocular abnormalities but noted significant elevation in IOP among patients with ocular hypertension or glaucoma.[23] Although a prospective cohort study by Kang et al. found no overall association between regular coffee consumption and OAG risk, subgroup analyses revealed a significant relationship between caffeine intake and the risk of OAG with elevated IOP in individuals with a family history of glaucoma.[22] It is considered that individuals with glaucoma may have heightened resistance to aqueous outflow compared to healthy individuals, explaining the IOP elevation following coffee consumption in individuals with OAG.[23] This may explain the investigated findings in the included studies that in individuals with high IOP genetic predispositions, consuming higher dose of caffeine was associated with a 0.35-mmHg higher IOP and a 3.90-fold higher glaucoma prevalence.[11]

Moreover, caffeine consumption from coffee or tea was weakly associated with decreased IOP and decreased risk of developing glaucoma in one of our included studies. These data are aligned with a Japanese study adjusting for multiple covariates found that male habitual coffee consumers had lower IOP compared to abstainers.[24] It is considered that individual with more habitual coffee consumption had a heightened tolerance level thus resulting in a decrease of caffeine effects. Additionally, The antioxidant compounds in coffee have been suggested as potential modifiers of blood pressure changes induced by caffeine consumption, which could partially explain the reduced responsiveness to caffeine observed in habitual consumers.[25] While tea, on the other hand, contains phytochemicals and flavonoids, which has been associated with anti-inflammatory, anticarcinogenic, antioxidant, and neuroprotective properties.[17] Flavonoids may play a protective role in individuals without glaucoma by promoting vasodilation, and caffeinated teas exhibit higher antioxidant capacity compared to decaffeinated teas.[26,27]

Conflicting results between studies may stem from differences in the study population and follow-up time. Additional studies are warranted to unravel the underlying pathophysiology and clarify these relationships.

This research has a few limitations that should be considered. Firstly, the number of samples included in crossover studies is limited, which may impact the generalizability of the findings. Additionally, the specific effects of caffeine on intraocular pressure (IOP) after a 90-

minute period have not been extensively studied, leaving gaps in our understanding of the long-term impact of caffeine on IOP. Another limitation is the high variability in the characteristics of the study samples, including both healthy individuals and those with glaucoma, which may introduce confounding factors. Furthermore, the limited representation of different ethnicities in the study population and the lack of assessment of the dose effect of caffeine on IOP may restrict the applicability of the results to diverse populations.

CONCLUSION

This review indicated that caffeine consumption has a significant impact on the risk of developing glaucoma and an acute effect on intraocular pressure (IOP), up to 90 minutes after consumption. This transient elevation emphasizes the need to consider caffeine intake when managing glaucoma or conducting an IOP assessment. It is important to note individual variations in caffeine response and other factors that may interact with caffeine consumption to influence glaucoma risk. Future research should focus on understanding the underlying mechanisms, long-term effects of chronic caffeine consumption, and more specific population characteristics in different ethnicities. This knowledge will inform clinical decision-making and interventions for individuals at risk of or diagnosed with glaucoma.

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