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ASSOCIATION BETWEEN GLAUCOMA PREVALENCE AND SUPPLEMENTATION WITH CALCIUM, IRON AND CAFFEINE

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ABSTRACT **PURPOSE.** To investigate the relationship between supplementary consumption of the oxidants calcium and iron and caffeine and the prevalence of glaucoma. **METHODS.** This cross-sectional study included 3833 participants 40 years of age, who reported a presence or absence of glaucoma. Participants were interviewed regarding the use of dietary supplements and antacids during the preceding 30-day period. Data pertaining to the supplementary intake of calcium, iron and caffeine was aggregated and divided into quintiles. Information regarding the presence or absence of glaucoma and demographics, comorbidities, and health-related behavior was obtained via interview. **RESULTS.** Participants who consumed 800 mg/d of supplementary calcium or 18 mg/d of supplementary iron had significantly higher odds of having been diagnosed with glaucoma than did those who had not consumed supplementary calcium or iron, after adjustment for potential confounders. Concurrent consumption of both calcium and iron above these levels was associated with still greater odds of having been diagnosed with glaucoma. Compared with participants whose cumulatively updated total caffeine consumption was <125 mg/day, participants who consumed ≥500 mg/day had a trend toward increased risk of glaucoma. **CONCLUSIONS**. These results suggest that there may be a threshold intake of iron, calcium and caffeine above which there is an increased risk of development of glaucoma. Prospective longitudinal studies are needed, to assess whether oxidant intake is a risk factor for development and progression of glaucoma.

KEYWORDS : Calcium, Caffeine, Glaucoma, Iron

INTRODUCTION

Glaucoma is a chronic and irreversible optic neuropathy, characterized by the progressive loss of retinal ganglion cells[1,2]. The only confirmed modifiable risk factor for glaucoma is intraocular pressure (IOP); consequently, the goal of all current medical and surgical therapies for this disease is to reduce IOP. The identification of modifiable risk factors other than IOP may provide additional therapeutic targets that would be valuable in the management of patients, particularly those who continue to show substantial progression despite significant lowering of IOP.

Caffeine (l,3,7-trimethylxanthine), a methylxanthine, is a ubiquitous ingredient in several popular, internationally consumed beverages such as coffee, tea, and colaflavored drinks. Caffeine is widely consumed throughout the world. There have been conflicting reports about the effects of caffeine on IOP; however, most studies indicate a transient increase in IOP of 2 mmHg for a 2-hour period[3]. Kang and colleagues conducted the first prospective study to examine the relationship between caffeine consumption and risk of developing POAG[4]. It suggested that caffeine may have a possible adverse effect on subjects with an inherent susceptibility to glaucoma.

A body of research has focused on elucidating the role of oxidative stress in the pathogenesis of neuronal death as well as aqueous humor outflow [5], with particular interest in the role that oxidants such as calcium and iron may play in disease pathogenesis. Iron is a potent oxidant that accumulates with aging and catalyzes the creation of highly reactive hydroxyl radicals, which can cause oxidative damage to DNA and adjacent lipids and proteins. In vitro studies have suggested that iron regulation plays a role in glaucoma's pathogenesis both in retinal ganglion [6] and trabecular meshwork (TM) [7] cells. Dysregulation of calcium homeostasis has also been implicated in some neurodegenerative diseases[8], including glaucoma[9]. One study found that human TM cells from donors with glaucoma were defective in mitochondrial function, resulting in abnormal sensitivity to calcium-induced stress[10]. Impaired calcium regulation and calcium overload have been found in lamina cribrosa cells of donors with glaucoma [11], and intriguing yet controversial evidence suggests that treatment of glaucoma patients with a calcium channel blocker may slow loss of visual fields[12].

These previous animal and preliminary human studies have offered potential roles that calcium, iron and caffeine may play in the pathogenesis of glaucoma. However, there have been no epidemiologic studies investigating the relationship of calcium, iron and caffeine consumption with glaucoma. Hence, the aim of the present study was to evaluate the association between glaucoma and the consumption of calcium, iron and caffeine through dietary supplements.

METHODOLOGY

Patients were recruited from Medical College, India. All patients verbally consented to participate in the study before entry. Inclusion criteria for the glaucoma patients consisted of participants who replied to a mailed health questionnaire. From participants with self-reported glaucoma, we obtained permission to retrieve medical information to confirm the diagnosis. s. We sent the diagnosing eye care provider a request to complete a glaucoma questionnaire about maximum IOP, optic nerve features, status of filtration apparatus, and presence of exfoliation material or other secondary causes for elevated IOP. In lieu of completing the questionnaire, eye care providers could send complete medical records. We also requested all visual field (VF) reports supporting the glaucoma diagnosis. A glaucoma specialist (LRP) evaluated the questionnaire and medical record information as well as the VF data in a standardized manner masked to dietary data.

There were 3833 participants of glaucoma aged 40 years diagnosed during the study period. The eye care providers confirmed this diagnosis in 66% of women and 56% of men. The primary predictor variables were intake of caffeine, calcium and iron from dietary supplements and antacids.

Measurement of Caffeine, Calcium and Iron Consumption

Participants indicated their average intake of a serving of food or beverage over the year. Participants were asked about consumption of caffeinated coffee (in cups), caffeinated tea (in cups), and chocolate (in 1-ounce servings). The questionnaire provided nine response possibilities for intake frequency for each item ranging from "never or less than once per month" to "6 or more times per day." Average daily calcium and iron intake from all antacids and dietary supplements for each participant were categorized into five quintiles of intake with an additional no-intake category. The highest two quintiles of iron intake were combined into one category because the number of participants taking exactly 18 mg/d of iron exceeded 20% of the population taking supplemental iron; therefore, 18 mg/d represented both the 60th and the 80th percentiles of iron intake, and we could not readily

discriminate between the top two quintiles.

Statistical Analysis

We compared the distribution of possible confounding variables between participants with and without self-reported glaucoma using design-adjusted Rao-Scott Pearson-type 2 and Wald tests for categorical and continuous variables, respectively. The excluded confounders were spherical equivalent on objective refraction; BMI; the comorbid eye condition of macular degeneration; comorbid medical conditions including kidney failure, stroke, CHF, diabetes, CHD, MI, thyroid disease, liver disease, emphysema, and chronic bronchitis; and treatment for anemia in the past 3 months.

RESULTS

TABLE1. Characteristics According To Caffeine Intake in the Population

Characteristic	0 to 124 mg/day	125 to 249 mg/day	250 to 374 mg/day	375 to 499 mg/day	500 mg/day
% of total person-time					
Women	19.3	23.6	22.4	16.4	18.3
Men	40.7	21.7	15.8	10.2	11.6
Caffeinated coffee, cups/d					
Women	0.1	0.8	1.9	2.6	4.2
Men	0.2	0.9	1.9	2.7	3.9
Tea, cups/d					
Women	0.4	0.9	0.8	0.8	0.7
Men	0.3	0.6	0.6	0.5	0.5
Family history of glaucoma, %					
Women	13.9	14.1	13.5	13.2	12.5
Men	11.3	12.3	11.8	11.4	10.5

TABLE 2. Supplement Use among Participants with and without Glaucoma

Supplemental Nutrient Intake	No Glaucoma		Glaucoma		p value
Calcium	%	SE	%	SE	0.066
No intake	49.5	1.8	44.7	4.1	
1st Quartile >0 - <100 mg/d	11.1	0.7	12.1	2.1	
2nd Quartile ≥100 - < 200 mg/d	11.1	1.2	7.0	2.0	
3rd Quintile ≥ 200 - < 375 mg/d	8.5	0.7	8.5	2.6	
4th Quintile ≥375 - < 800 mg/d	10.9	0.9	12.3	1.9	
5th Quintile ≥ 800 mg/d	9.0	0.7	15.5	2.5	
Iron					
No intake	9.0	1.4	78.2	3.3	0.0226
1st Quintile, >0 - < 6 mg/d	4.4	0.6	3.2	1.3	
2nd Quintile ≥ 6 - < 15 mg/d	4.6	0.6	3.2	1.4	
3rd Quintile ≥15 - < 18 mg/d	9.9	0.7	9.0	1.7	
4th and 5th Quintiles ≥ 18 mg/d	2.2	0.3	6.4	1.9	

The results showed that the overall mean caffeine consumption was 232 mg/day. It showed that mean 4.9 cups 500 mg/day caffeine was consumed by women and 3.9 cups 500 mg/day caffeine was consumed by men. 12.5% women with caffeine intake of 500 mg/day had family history of glaucoma, whereas 10.5% men had family history of glaucoma.

Differences in calcium and iron intake by glaucoma status are presented in Table 2. Average daily calcium and iron intake from all antacids and dietary supplements for each participant were categorized into five quintiles of intake with an additional no-intake category. Intake of supplemental calcium differed between those with and without glaucoma, but the difference did not reach statistical significance in this unadjusted comparison (P 0.066). Intake of supplemental iron differed significantly between those with and without glaucoma, with a higher proportion of participants with glaucoma consuming iron in the highest two quintiles compared with those without glaucoma (6.4% vs. 2.2%, respectively, P 0.0226). The highest two quintiles of iron intake were combined into one category because the number of participants taking exactly 18 mg/d of iron exceeded 20% of the population taking supplemental iron; therefore, 18 mg/d represented both the 60th and the 80th percentiles of iron intake, and we could not readily discriminate between the top two quintiles.

DISCUSSION

The population– based sample of adults 40 years of age and older found that participants who consumed 800 mg/d of supplementary calcium or 18 mg/d of supplementary iron had significantly higher odds of self-reported glaucoma than those who reported no supplemental intake, after adjustment for potential confounders. These nutrient intake levels were equivalent to the highest quintile of calcium intake and the highest two quintiles of iron intake in this population. Concurrent consumption of both calcium and iron at these levels was associated with even greater odds of glaucoma. We did not, however, find a clear dose–response relationship between quintiles of supplementary calcium or iron intake and self-reported glaucoma. Rather, the relationship appeared to suggest a threshold level of oxidant consumption above which there is substantially increased risk of glaucoma. While the concurrent consumption of calcium and iron below threshold levels did not increase the odds of glaucoma, suggesting that there is no significant additive effect of oxidant supplementation below 800 mg/d of calcium and 18 mg/d of iron, the consumption of both oxidants above these threshold levels resulted in even greater odds of glaucoma. It is noteworthy that the threshold levels deemed to be associated with glaucoma risk in this population-based study are considerably lower than the tolerable upper intake levels of calcium (2000 mg/d for those aged ≥ 51 years)[13] and iron (45 mg/d for those aged ≥ 19 years)[14] established by the Institute of Medicine for total nutrient intake.

It can be hypothesized that the detrimental health effects of supplementary iron intake may be because it is a potent oxidant that accumulates in the body with age. Consumption of supplementary iron has recently been associated with increased total mortality among elderly women[15]. The role of calcium homeostasis in glaucoma and other neurodegenerative diseases, as well as aging, has also been studied. Influx and intracellular accumulation of high levels of calcium is known to trigger cell death through caspase-dependent degradation[16].

The association between caffeine consumption was modified by a family history of glaucoma, where the increased risk with greater caffeine or caffeinated coffee consumption was stronger among those who might have been more genetically susceptible to developing glaucoma.

We acknowledge that our study conclusions are limited by the reliance on a self-report of a prior diagnosis of glaucoma that may be subject to recall bias and disease misclassification.In summary, we found that after adjustment for confounding demographic factors, comorbidities, and health-related behaviors, consumption of supplementary calcium ≥ 800 mg/d or supplementary iron ≥ 18 mg/d was associated with significantly greater odds of self-reported glaucoma than was no supplementary consumption of these oxidants. We also found that heavier caffeinated coffee consumption was associated with increased risk of glaucoma. There may be a threshold level above which consumption of calcium or iron influences glaucoma, whereas consumption of these oxidants at lower levels has no such effect. The more than sevenfold greater odds of a glaucoma diagnosis in those with high levels of calcium and iron supplementation strongly suggest

an important association that warrants further study. In addition to epidemiologic confirmation of our findings, further research is needed to determine whether calcium and iron intake may increase the risk of glaucoma progression and to elucidate the potential mechanisms by which consumption of these oxidants may influence glaucoma pathogenesis.

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