Dietary Nitrate Intake and Primary Open-Angle Glaucoma

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Jae Hee Kang

40.1 Introduction

It has been reported that low BMI is associated with lower CSF pressure, which then translates into higher translaminar cribrosa pressure gradient, a risk factor for glaucoma [1]. Previously, in our epidemiologic studies, we have reported that low BMI was a possible risk factor for POAG. To better understand this association and because POAG is a heterogeneous condition, we previously evaluated the relation between BMI and POAG subtypes based on pattern of visual field loss. We observed that low BMI is more strongly associated with primary open-angle glaucoma where the loss of vision tends to focus on the paracentral region rather than the peripheral vision. Every 10-unit increase in BMI was associated with a 33% lower risk of primary open-angle glaucoma with early paracentral loss, whereas it was not associated with peripheral loss [2, 3]. So we have hypothesized that the paracentral fibers, particularly the inferior, are in the "macular vulnerability zone," as the fovea lies below the disc, and accompanying blood vessels make more acute arcuate turns, creating shear forces that could compromise local blood flow [4, 5].

NO signaling may be important in POAG. Changes in blood flow to the eye differ by POAG case and control status after a NO synthase inhibitor is administered [6]. Also, polymorphisms in *NOS3* (OMIM 163729) were related to POAG [7] as well as lower NO production [8]. Recently, new glaucoma drugs that have nitric oxide as a component have been introduced; however, nitrates from the diet can also increase nitric oxide. Nitrate from diet can be reduced to nitrite by oral/gut bacteria [9] and converted to NO (Fig. 40.1). A few servings of green leafy vegetables yield more nitrate than from the L-arginine NO pathway [10]. A list of vegetables by nitrate content [11] is shown in (Fig. 40.2).

Thus, we evaluated dietary nitrate and POAG risk in a large long-term longitudinal study of female nurses and male health professionals.

40.2 Objective

We investigated the relation between intake of nitrates from diet and risk of POAG [12].

40.3 Study Population and Design

Design: Prospective cohort study from the Nurses' Health Study (NHS; 1984–2012) and Health Professionals Follow-up Study (HPFS; 1986–2012).

Participants: 63,893 women in NHS and 41,094 men in HPFS (1) who were at least 40 years of age, (2) without prevalent glaucoma, (3) had eye exams, and (4) had complete dietary nitrate data (from 1984 in NHS and from 1986 in HPFS).

Outcome: Confirmed incident POAG (n = 1483) and POAG subtypes classified by the predominant visual field loss pattern and intraocular pressure (IOP) at diagnosis.

Exposure: Dietary nitrate intake updated every 2–4 years.

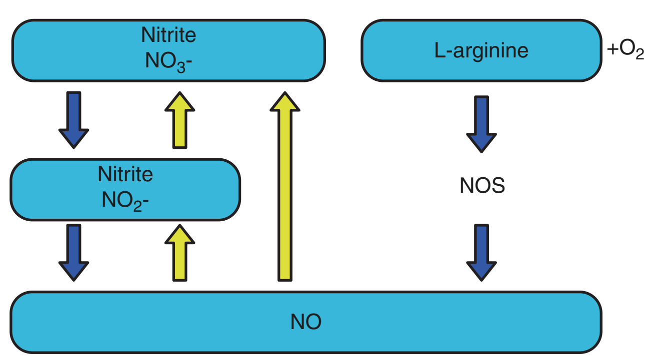

Fig. 40.1 The nitrate-nitrite-NO pathway

J. H. Kang (✉)
Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA
e-mail: nhjhk@channing.harvard.edu

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Fig. 40.2 The classification of vegetables according to nitrate content [11]

Nitrate content(mg /100g fresh weight)	Vegetable varieties
Very low, <20	Artichoke, asparagus, broad bean, eggplant, garlic, onion, green Bean, mushroom, pea, pepper, potato, summer squash, sweet potato, tomato, watermelon
Low, 20 to <50	Broccoli, carrot, cauliflower, cucumber, pumpkin, chicory
Middle, 50 to <100	Cabbage, dill, turnip, savoy cabbage
High, 100 to <250	Celeriac, Chinese cabbage, endive, fennel, kohlrabi, leek, parsley
Very high, >250	Celery, cress, chervil, lettuce, red beetroot, spinach, rocket (rucola)

Fig. 40.3 Results—main findings

		Q1	Q2	Q3	Q4	Q5	
Women	Median (mg/day)	80	114	142	175	238	
	Cases	210	173	207	199	211	
	Person-time	227,054	227,827	226,545	227,053	226,982	
Men	Median (mg/day)	81	117	148	185	254	
	Cases	98	89	101	111	84	
	Person-time	108,530	109,243	108,596	108,704	108,180	
Pooled	MV RR (95% CI)	1.00 (ref)	0.78 (0.65, 0.94)	0.82 (0.67, 0.99)	0.81 (0.53, 1.24)	0.67 (0.52, 0.85)	0.01

40.4 Statistical Analysis

The relation between dietary nitrate intake and incident POAG was evaluated with Cox proportional hazard models with time-varying covariates. Analyses were stratified by age in months and period at risk and adjusted for the following variables, ancestry; family history of glaucoma; self-reported history of hypertension; diabetes; body mass index; cumulatively averaged intakes of total energy, alcohol, and caffeine; pack-years of smoking; physical activity; number of eye exams reported during follow-up; and multivitamin use, and in NHS only additionally adjusted for age at menopause and postmenopausal hormone status. We calculated pooled multivariable relative risks (RRs) and their 95% confidence intervals (CIs).

40.5 Results

Main findings (RR in women and men and pooled) are shown in (Fig. 40.3). Compared with those consuming 80 mg/day of dietary nitrate intake (lowest 20%, Q1), the RR for consuming 240 mg/day (highest 20%, Q5) was 0.79 (95%CI: 0.66–0.93). There was a linear dose-response (linear $p = 0.02$).

Figure 40.4 shows the results about the POAG subtype analyses (Fig. 40.4): paracentral (Pc) versus peripheral (Pr) and IOP ≥ 22 mmHg (HTG) versus IOP < 22 mmHg (NTG). The association was more evident ($p = 0.01$) for Pc loss (Q5 RR = 0.56; 95%CI: 0.40–0.79; linear $p = 0.0003$) than for Pr loss only (Q5 RR = 0.85; 95%CI: 0.68–1.06; linear $p = 0.50$). The association did not differ ($p = 0.75$) by IOP (HTG: Q5 RR = 0.82; 95%CI: 0.67–1.01; linear p = 0.11; NTG: Q5 RR = 0.71; 95%CI: 0.53–0.96; linear $p = 0.12$).

Other results are as follows. Green leafy vegetables were the largest contributor of nitrate intake (statistically accounted for 56.7% of nitrate intake differences). Compared to the reference group of 0.31 servings/day, the RR for the group with 1.45+ servings/day was 0.82 (95%CI: 0.69–0.97; linear $p = 0.02$) and RR = 0.52 for paracentral loss (RR = 0.52; 95%CI: 0.29–0.96; linear $p = 0.0002$). Compared to the reference group of 0.11 servings/day of iceberg lettuce, the RR for 0.86 servings/day was 0.89 (95%CI: 0.75–1.06; linear $p = 0.06$) and RR = 0.69 for paracentral loss (95%CI: 0.49–0.97; linear $p = 0.001$).

40.6 Discussions

40.6.1 Consistency of Findings with Prior Literature

Our results are similar to those found by Coleman et al. [13] and Giaconi et al. [14]. In both studies, kale/collard greens were associated with 55–70% lower POAG relative risk.

40.6.2 Biological Mechanism

Alterations of the nitric oxide system may lead to dysregulation of ocular blood flow and elevated IOP, which may be etiologic factors for POAG. Although nitric oxide is mainly generated endogenously via the L-arginine/nitric oxide pathway, when there is hypoxia [15] or when this pathway is compromised as in POAG, the nitrate-nitrite-nitric oxide pathway can be an alternate source of nitric

		Q1	Q2	Q3	Q4	Q5	P-trend	P-het
Pooled§ - POAG with IOP ≥22 mm Hg (n=998 cases)	MV RR (95% CI)	1.00 (ref)	0.85 (0.69, 1.04)	0.93 (0.76, 1.13)	0.90 (0.61, 1.32)	0.82 (0.67, 1.01)	0.11	0.75
Pooled§ - POAG with IOP <22 mm Hg (n=487 cases)	MV RR (95% CI)	1.00 (ref)	0.73 (0.55, 0.98)	0.79 (0.59, 1.05)	0.86 (0.65, 1.13)	0.71 (0.53, 0.96)	0.12	
Pooled§ - POAG with peripheral VF loss only (n=836 cases)	MV RR (95% CI)	1.00 (ref)	0.82 (0.58, 1.15)	0.98 (0.72, 1.34)	1.00 (0.65, 1.54)	0.85 (0.68, 1.06)	.50	0.01
Pooled§ - POAG with early paracentral VF loss (n=433 cases)	MV RR (95% CI)	1.00 (ref)	0.89 (0.67, 1.20)	0.77 (0.57, 1.04)	0.77 (0.57, 1.04)	0.56 (0.40, 0.79)	<.001	

Fig. 40.4 Results—POAG subtype analyses

oxide. The role of nitric oxide in alterations in regulating vascular function was supported by the association with early paracentral loss.

40.7 Limitations

1. Underascertainment of cases due to lack of standardized eye exams for all participants.
2. Misclassification of dietary nitrate intake due to lack of detailed info on soil conditions, storage, etc.
3. Confounding by other dietary factors.
4. Lack of generalizability as most participants were Caucasian.
5. This is the first study to evaluate dietary nitrates and glaucoma, indicating that more confirmation is needed in other studies.

40.8 Summary

Higher intake of nitrate and green leafy vegetables was associated with modestly lower risk of primary open-angle glaucoma; this further supports the role of nitric oxide in glaucoma pathogenesis.

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