Dietary carbohydrate intake and glycemic index in relation to cortical and nuclear lens opacities in the Age-Related Eye Disease Study¹–⁴

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ABSTRACT

Background: Little is known about the association between dietary carbohydrates and cataract in nondiabetic persons.

Objective: The aim was to test whether recent dietary carbohydrate intakes or glycemic index (GI; a measure of carbohydrate intake quality) was associated with the presence of cortical or nuclear opacities.

Design: A modified Block food-frequency questionnaire was used to obtain dietary information from 3377 participants (aged 60–80 y; 56% were women) in the Age-Related Eye Disease Study (AREDS). Lens status was evaluated by using the AREDS System for Classifying Cataracts. Associations were examined for eyes with only a single, or pure, type of lens opacity by using the generalized estimating equation approach to logistic regression to account for the lack of independence between the eyes of a person.

Results: For participants in the highest quartile, dietary GI was associated with a higher prevalence of all pure nuclear opacities [grade ≥2; odds ratio (OR): 1.29; 95% CI: 1.04, 1.59; P for trend = 0.02] and moderate nuclear opacities (grade ≥4; OR: 1.43; 95% CI: 0.96, 2.14; P for trend = 0.052). The OR in a comparison of the highest with the lowest quartile of intake was 1.27 (95% CI: 0.99, 1.63; P for trend = 0.09) for cortical opacities of any severity (>0% of area opaque), and the OR increased somewhat for moderate cortical opacities (>5% of area opaque; OR: 1.71; 95% CI: 1.00, 2.95; P for trend = 0.056).

Conclusions: Results from the cross-sectional analysis of AREDS baseline data suggest that dietary glycemic quality and dietary carbohydrate quantity may be associated with prevalent nuclear and cortical opacities, respectively. Am J Clin Nutr 2006;83: 1177–84.

KEY WORDS Cataract, lens, nutrition, carbohydrate, glycemic index, glycation, aging, stress, epidemiology, humans, risk factor

INTRODUCTION

Cataract remains the worldwide leading cause of visual impairment (1–3). Americans spend ≈$5 billion annually on cataract surgery, and the costs, as they continue to grow, present a considerable socioeconomic burden (4). In the United States, the prevalence of clinically significant cataract increases dramatically from ≈5% at age 65 y to ≈50% in people aged >75 y (5). An estimated 20.5 million (17.2%) Americans aged >40 y have cataract (6). As life expectancy increases, it is predicted that the numbers of persons with cataract will increase 50% within 2 decades (6). Prevention remains the most cost-effective method to address this public health issue. It is estimated that a delay in cataract formation of ≈10 y would reduce the prevalence of visually disabling cataract by ≈45% (7). Consequently, strategies that prevent lens opacification hold promise not only for enhancing the quality of life for much of the elderly population but also for reducing this enormous public health burden.

Nuclear, cortical, and posterior subcapsular (PSC) cataracts are the 3 major types of age-related cataract, and affect the center, adjacent peripheral, and posterior outer aspect of the lens tissue, respectively. Aggregation and precipitation of the normally well-ordered and soluble lens proteins are involved in all types of cataracts. These changes are observed along with or after the cross-linking of lens proteins, which occurs when amino groups react with open-chain carbohydrates or glycolytic intermediates to form advanced glycation or glycoxidation end-products (1, 8). In addition to the considerable evidence linking aberrant glucose metabolism or diabetes to cataract risk (9–21), in vitro and in vivo animal studies suggest that carbohydrates may play a direct role in cataractogenesis. One study noted a higher rate of cataract formation in nondiabetic mice that consumed higher levels of carbohydrates (22). The few studies that have examined the relation between dietary carbohydrate and various types of cataract or cataract extraction in nondiabetic humans have produced inconsistent results (23–27).

In the present cross-sectional analysis using Age-Related Eye Disease Study (AREDS) baseline data (28), we examined the relation between 2 aspects of carbohydrate nutrition—carbohydrate

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intake and dietary glycemic index (GI)—and the prevalence of cortical and nuclear lens opacities in nondiabetic persons.

SUBJECTS AND METHODS

Age-Related Eye Disease Study population

AREDS is a prospective cohort study designed to assess the cause and prevention of age-related macular degeneration (AMD) and cataract. Details of the study design, presented elsewhere (28), are briefly described here. The ocular eligibility requirements were mainly determined by the AMD component of AREDS. Participants were enrolled in 4 AMD categories, with macular status ranging from essentially no macular lesions in either eye (category 1) to advanced AMD or AMD-related lesions associated with visual acuity >20/32 in only one eye (category 4). All participants were required to have at least one eye with a visual acuity of ≥20/32, and the lens and vitreous had to be sufficiently clear to permit good quality retinal photographs that would permit identification and quantification of small drusen. By requiring that the ocular media be relatively clear, persons with more severe opacities were excluded except for some with advanced AMD. Despite this, the large sample size yielded a cohort with a diverse array of mild to moderately severe age-related lens opacities. A total of 4757 participants, aged 55 to 80 y at recruitment, were enrolled at 11 ophthalmic clinics from 1992 to 1998. The AREDS protocol was approved by each center’s institutional review board before initiation of the study. Informed consent was obtained from participants before enrollment.

Procedures

An eye examination, a limited physical examination, a detailed questionnaire, and a food-frequency questionnaire (FFQ) were administered to the participants at the baseline visits and data on possible risk factors for lens opacities were obtained (29). Data obtained from the general physical and ophthalmic examinations included height, weight, best-corrected visual acuity, intraocular pressure, slit-lamp biomicroscopy, and ophthalmoscopy. The participants provided demographic information, history of smoking, medical history, history of vitamin and mineral use, and daily dietary intake on the questionnaires. A questionnaire that obtained data on sunlight exposure [adult lifetime average annual ocular ultraviolet UV-B exposure: a function of regional ambient UV-B, hours spent outdoors from April through September, outdoor time spent over water, use of_ocular protection–brimmed hat, sunglasses, and prescription spectacles (30)] was implemented in 1996. Specially modified Topcon slit-lamp cameras (Topcon Corporation, Tokyo, Japan) and Neitz retroillumination cameras (Neitz Instruments Company LTD, Tokyo, Japan) were used to take color photographs of the lenses of the participants at baseline (31). The lens photographs were evaluated at a reading center by trained and certified examiners. The AREDS System for Classifying Cataracts (32), which is an extension of the Wisconsin System for Classifying Cataracts from Photographs (31), was used to assess the presence and severity of nuclear, cortical, and PSC lens opacities. The extent of cortical and PSC opacities was graded by estimating the area of lens involvement in sectors of a grid overlay on the retroillumination photographs. For PSC, the individual subfield percentages were combined to estimate an overall percentage of involvement within the central 5 mm of the lens and, for cortical opacities, within the full visible lens. Nuclear opacity grades ranged from 0.9 to 6.1 by using cutoffs set by a series of standard photographs with increasingly severe nuclear sclerosis (32).

Eyes were classified into one of 3 nuclear opacity groups: moderate, mild, or clear if the grade was ≥4, <4 but >2, or ≤2, respectively. For cortical and PSC opacities, eyes were classified into one of 3 opacity groups: moderate, mild, or clear if the grade was >5%, ≤5% but >0%, or 0%, respectively.

Study subjects

The recruitment scheme of the present study from the AREDS is shown in Figure 1. Of the available 4757 subjects, we first excluded 856 persons, including 110 persons aged 55 to 59 y in whom cataract prevalence was low and who were all in AMD categories 3 and 4 (29), 6 persons who did not complete the FFQ, 390 persons with diabetes, 154 persons with missing covariates, 105 persons with missing opacity data for both eyes, and 91 persons with invalid calorie intake (valid intake ranged from 400 to 3000 kcal/d for women and 600 to 3500 kcal/d for men). This left 7656 eyes from 3901 persons, with 146 persons contributing only one eye. The distribution of the 7656 eyes is shown by presence of nuclear, cortical, and PSC opacities in Figure 2. Eyes with mixed opacities (n = 1727) were additionally excluded, including 1048 eyes from persons with bilateral mixed opacities and 679 eyes from persons with unilateral mixed opacities, because the various opacities may have multiple but not necessary mutually exclusive etiologies and the use of mixed opacities may reduce our power to detect associations with specific types of opacities. Thus, 524 persons with mixed opacities in both eyes were excluded. The analysis cohort consisted of 3377 participants with 5929 eyes, including 1300 with pure cortical opacities, 2024 with pure nuclear opacities, 89 with pure PSC opacities, and 2516 with no opacities. A total of 825 participants contributed only one eye.

Assessment of carbohydrate variables

A 90-item modified Block FFQ was administered to AREDS participants at baseline. Information about usual dietary intakes over the previous year was collected from the FFQ and classified into 9 possible response categories, ranging from never or <1 time/mo to ≥2 times/d. The daily carbohydrate intake of each person was calculated from the information obtained with the FFQ by summing the product of the frequency of intake, number of servings, and carbohydrate content per serving for individual food items. The carbohydrate content per serving for individual food items was derived from the nutrition database of the Nutrition Coordinating Center at the University of Minnesota. We assessed carbohydrate quality using GI. Jenkins et al (33) developed the index to facilitate identification of potentially clinically useful foods that result in relatively low glycemic responses. The GI for foods is defined as the glycemic response (ie, the area under the glucose response curve up to 2 h) after consumption of a fixed amount of carbohydrate from a test food relative to the glycemic response of a reference food. The GI values for foods in the FFQ were either derived from published values by using white bread as the reference food or imputed from GI values of comparable foods (34). The dietary GI for each subject was calculated as the weighted average of the GI scores for each food
item, with the amount of carbohydrate consumed from each food item as the weight.

The FFQ was validated in relation to 24-h recall by using a subset of the AREDS volunteers \((n = 192)\) \((35)\). Correlations for energy and carbohydrate intake between the 24-h recall and the FFQ were \(0.51 (P < 0.0001)\) and \(0.56 (P < 0.0001)\), respectively.

Carbohydrate variables were adjusted for total energy intake with the use of the residuals method \((36)\).

**Defining covariates**

For our analyses, age, sex, education level (grade 11 or less, high school, college, bachelor, or postgraduate), race (white, black, Hispanic, Asian, or other), body mass index (BMI; in kg/m\(^2\)), alcohol intake (g/d), smoking status (never, former, or current smoker), sunlight exposure [adult lifetime average annual ocular ultraviolet B exposure, adapted from McCarty et al \((30)\); in h/d], vitamin C intake (in mg/d), and total calorie intake were considered as covariates.

**Statistical methods**

For maximal statistical power, we evaluated associations between indicators of carbohydrate nutrition and opacity using eyes as the unit of analysis. We used eyes with only a pure opacity (ie, those with only one type of opacity and without any other type of opacity) as our cases and eyes without any type of opacity as our controls.

Using means (±SEs), medians (when values were not normally distributed), and proportions, we first used demographic factors and potential confounders of associations between carbohydrate intake and dietary GI and lens opacity to describe the included participants \((1, 37, 38)\). For categorical variables, such as education, race, and smoking status, chi-square tests were also used to examine the difference in the overall distributions.

We estimated odds ratios (ORs) that related carbohydrate intake and dietary GI to lens opacity by logistic regression analysis using SAS PROC GENMOD \((39)\). The procedure uses the generalized estimating equation method to estimate the coefficients and adjust the SEs of the model terms for the correlated data resulting from repeated measurements (both eyes) on the same person \((40)\). The comparison group for the eyes with cortical

**FIGURE 1.** Flow chart of the recruitment of subjects from the Age-Related Eye Disease Study (AREDS). PSC, posterior subcapsular.

**FIGURE 2.** Distribution of eyes by presence of cortical, nuclear, and posterior subcapsular (PSC) opacities.
opacities \((n = 1300)\) and the eyes with nuclear opacities \((n = 2024)\) was the group of eyes with no opacities \((n = 2516)\). Small case numbers prevented us from examining associations for PSC opacities.

The participants were divided into 3 categories (the highest 25%, the middle 50%, and the lowest 25% of the distribution) according to their dietary GI or total carbohydrate intake. For each variable, the participants in the lowest 25% of the distribution comprised the referent category. The cutoffs for total carbohydrate intake were 134.0 g/d and 176.1 g/d for the women and 140.7, 179.3, and 223.7 g/d for the men. The cutoffs for dietary GI were 74.1 and 80.7 for the women and 76.5 and 82.1 for the men.

We estimated ORs from 2 models. Model 1 adjusted for age only. Model 2 additionally adjusted for sex, education level, race, BMI, alcohol intake, smoking status, sunlight exposure, dietary vitamin C intake, calorie intake, energy-adjusted glycemic index, and total carbohydrate intake. The unit of analysis was one eye.

RESULTS

Multivariate-adjusted \(P\) values of characteristics by presence of cortical and nuclear lens opacities are shown in Table 1. Compared with controls \((n = 2516\) eyes), cases with pure cortical opacities \((n = 1300)\) were found in significantly older subjects \((68.7\) compared with 66.2 y) and more likely to be found in...
women (56.9% compared with 52.6%). Cases with pure nuclear opacities (n = 2024) were found in significantly older subjects (69.1% compared with 66.2 y), more likely to be found in women (56.9% compared with 52.6%). Cases with pure nuclear opacities (ie, grade 5%) in a multivariate model. The ORs for moderate cortical opacities for the subjects in the highest 25% and the middle 50% of dietary GI had an OR for any nuclear cataract of 1.29 (P = 0.02). Possibly because of a smaller sample size, similar, but only marginally significant, associations (P for trend = 0.052) were found for moderate nuclear opacities.

Multivariate models noted no significant associations between carbohydrate intake and either any (ie, grade ≥ 2) or moderate nuclear opacities (ie, grade ≥ 4; Table 3). In contrast to the results of cortical opacities, dietary GI was significantly associated with the occurrence of nuclear opacities in both models (Table 3). After multivariate adjustment, the participants in the highest 25% of dietary GI had an OR for any nuclear cataract of 1.29 (P for trend = 0.02). Possibly because of a smaller sample size, other potential confounding variables, higher carbohydrate intake was associated with the presence of any cortical opacity at a borderline level of significance (P for trend = 0.09). Compared with the subjects in the lowest 25% of carbohydrate intake, the ORs for any cortical opacities for the subjects in the highest 25% and the middle 50% of carbohydrate intake were 1.27 (P = 0.06) and 1.24 (P = 0.04), respectively. We also evaluated associations with moderate cortical opacities (ie, >5%) in a multivariate model. The ORs for moderate cortical opacities for the subjects in the highest 25% and the middle 50% of carbohydrate intake were 1.71 (P = 0.05) and 1.33 (P = 0.23), respectively (P for trend = 0.056). Dietary GI did not appear to be related to cortical opacities.

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No significant interactions were noted between the carbohydrate variables with significant main effects (total carbohydrate intake on the occurrence of cortical opacities and dietary GI on the occurrence of nuclear opacities) and sex, education level, vitamin C intake, smoking status, and BMI (data not shown).

**DISCUSSION**

The present study suggests positive relations between dietary GI and nuclear opacities and between total carbohydrate intake and cortical opacities. Two other reports, the Blue Mountains Eye Study and the Nutrition and Vision Project (NVP), which is a sub-study of the Nurses’ Health Study, have suggested possible associations between carbohydrate intake and cortical opacities.
Our findings add to an evolving biochemical- and laboratory animal-based hypothesis that dietary carbohydrate may be associated with cataractogenesis (27). Prior supportive evidence include observations of cataract-related damage to lens proteins including glycation, oxidation, crosslinking, aggregation, formation of advanced glycation or glycoxidation end-products, and precipitation of the modified lens proteins (21), as well as higher rate of cataract formation in mice that consumed higher levels of carbohydrate (22). The glycation mechanism has also been linked to the etiology of other age-related chronic diseases, such as diabetes, coronary heart disease, and cancers (41). However, specific mechanisms and rate-controlling steps underlying the associations between carbohydrate quantity and glycemic quality and cortical and nuclear lens opacities, respectively, remain to be clarified. The GI was devised to measure how fast a carbohydrate food can raise blood glucose. It measures the glycemic quality of carbohydrates and better describes the physiologic effects (ie, the ability to raise blood glucose) of carbohydrates than the quantity of carbohydrate. Thus, metabolic studies show that, after consuming equivalent quantities of high compared with low GI foods, it takes a longer time to return to baseline blood glucose concentrations (42). It is possible that higher GI foods may damage the metabolically limited lens nuclear tissue more than lower GI foods by exposing the tissue to glucose for longer periods (43).

Our study had several unique features. First, by recruiting participants from a well-characterized cohort, we were able to use the standardized collection of risk factor information, including previous dietary exposures, and classification of lens opacity by standardized photographic grading. Second, it is unlikely that participants with high-carbohydrate or GI diets were more likely to be identified as cases, because our opacity classifications were

(23, 27). The Blue Mountains Eye Study and the present study evaluated short-term diet (ie, the past year), whereas the NVP study evaluated long-term diet (previous 14 y) (23, 27). The Blue Mountains Eye Study used cutoffs for cortical and nuclear opacities that were comparable to the cutoffs that were used for moderate opacities in the present study (23). Although the present study used lower cutoffs for lens opacities of any severity, especially for cortical opacities, than did the NVP study, the results for cortical opacities were similar in both studies. The marginally significant finding of a relation between total carbohydrate intake and the prevalence of any cortical opacity in the present study may be due, in part, to our use of a lower cutoff for the definition of cortical opacity. This may have reduced the difference in carbohydrate intake between cases and controls and, hence, reduced our power to detect the association. Associations with dietary GI were not noted for nuclear cataract in the NVP. Differences in the designs of the studies may explain the difference in findings. For example, the AREDS used a much larger sample size and, hence, had higher statistical power than did the NVP study. Neither the Blue Mountains Eye Study nor the Beaver Dam Eye Study reported a significant association between carbohydrate intake and nuclear opacity (23, 24). Only 2 (26, 27) of the 5 studies that related dietary carbohydrate to cataract (23–27) tried to relate dietary GI. Neither the NVP (27), which used early opacities as an endpoint, nor the full Nurses’ Health Study (26), which used cataract extractions as an endpoint, found an association. Two studies that used cataract extraction as the outcome of interest (25, 26), including one based on the full Nurses’ Health Study cohort (26), found no significant relation with dietary carbohydrate intake. Our marginally significant findings for dietary GI and nuclear lens opacity need additional corroboration from other studies.
performed by graders who were blind to our nutrition data. Third, because dietary data were collected before the eye examination, it is unlikely that there could have been any change in dietary behavior elicited by recruitment into the present study, and recall bias should have been minimized. In addition, although the onset of visual symptoms resulting from lens opacities may affect dietary reporting, it is unlikely that the participants would have modified their diets based on such relations, because, at the time of the present study, no prior studies had shown positive associations between dietary carbohydrate and lens opacities. Fourth, we controlled for confounding not only by multivariate adjustment, but also by the exclusion of eyes with more than one type of opacity. Fifth, our current findings additionally support our previous hypothesis that the mechanisms of cataractogenesis do not vary by sex or socioeconomic status (27) because we did not find significant interactions with these variables. Finally, despite the difference in the unit of analysis [by person in the previous AREDS report (29) and by eye in the present study], the characteristics of the subjects were similar in the present study and in the previous AREDS study (29), including the observed increased risk for both cortical and nuclear lens opacities with advancing age, excess risk of nuclear opacity for women and African Americans, inverse association between educational achievement and lens opacities, increased risk of nuclear opacity for smokers, and no significant association between BMI and either cortical or nuclear opacities. However, in contrast with the previous AREDS report, which did not find a significantly excess risk of cortical opacity in women (29), a significantly higher risk of cortical opacity was noted for women in the present study. This may be due to higher power obtained by using both eyes in our analysis.

Limitations of the present study included the marginally significant association between dietary GI and moderate nuclear opacity, which was possibly due to inadequate power. The possibility of misclassification due to the underestimation of the FFQ may have also decreased our power. Residual confounding was another concern. Although we adjusted for known cataract risk factors and those associated with cataract and correlated with carbohydrate variables in the AREDS, some unmeasured factors may have still confounded our results. However, on the basis of our analysis and current knowledge, we could not identify any factor that was a strong risk factor for cataract, was highly correlated with carbohydrate variables, and could totally explain our findings. Although the AREDS eligibility requirements, which required relatively clear ocular mediae to permit good quality retinal photographs, may have excluded persons with more extensive opacities from enrollment (29), we hypothesize that the present results also apply to persons with severe opacities. Lens opacification is an irreversible accelerating process (44). Therefore, moderate opacities are expected to progress more rapidly than are mild opacities. Thus, the relations that we observed between carbohydrate nutrition and earlier opacities should also pertain to persons with more advanced opacities. In addition, our hypothesized mechanism should apply to different severities of cataractogenesis. However, survival bias may be a concern. Carbohydrate nutrition was identified as an independent risk factor for several major systemic diseases (42), and studies have also indicated that cataract patients have increased mortality (45–48). These competing mortalities may diminish our ability to identify the association between carbohydrate nutrition and severe cataract.

In conclusion, the present study is one of a few studies that have reported the association between carbohydrate nutrition in nondiabetic persons and lens opacities, and it is the first study that has indicated a positive relation between dietary GI and the risk of nuclear cataract. Our results showed that higher carbohydrate intake and dietary GI were positively related to cortical and nuclear lens opacities, respectively, independent of established risk factors. These results may shed light on the mechanisms of cataractogenesis. Moreover, this information may add clinically relevant information about risk of cataract and dietary recommendation. Because carbohydrate foods compose the main dietary component for humans, studies that further our understanding of the associations between carbohydrates and lens opacities are worthy of additional evaluation.

All coauthors contributed substantially to this manuscript. C-JC and GG had full access to all data in the study and were responsible for the integrity of the data and the accuracy of the data analysis. C-JC, RCM, and AT conceptualized and designed the study, analyzed and interpreted the data, and critically analyzed the manuscript for important intellectual content. RCM acquired the data. C-JC performed the statistical analysis and drafted the manuscript. GG provided administrative, technical, and material support. RCM and AT were the study supervisors. The authors had no conflicts of interest.

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