The Relationship of Central Foveal Thickness to Urinary Iodine Concentration in Retinitis Pigmentosa With or Without Cystoid Macular Edema

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IMPORTANCE Current treatments for cystoid macular edema (CME) in retinitis pigmentosa (RP) are not always effective, may lead to adverse effects, and may not restore visual acuity. The present research lays the rationale for evaluating whether an iodine supplement could reduce CME in RP.

OBJECTIVE To determine whether central foveal thickness (CFT) in the presence of CME is related to dietary iodine intake inferred from urinary iodine concentration (UIC) in nonsmoking adults with RP.

DESIGN, SETTING, AND PARTICIPANTS We performed a cross-sectional observational study of 212 nonsmoking patients aged 18 to 69 years referred to our institution for RP with visual acuity of no worse than 20/200 in at least 1 eye.

EXPOSURE Retinitis pigmentosa with or without CME.

MAIN OUTCOMES AND MEASURES With the eye as the unit of analysis, the relationship of log CFT measured by optical coherence tomography to UIC measured from multiple spot samples and represented as a 3-level classification variable (<100, 100-199, and ≥200 μg/L), assigning greater weight to patients with more reliable UIC estimates.

RESULTS Analyses were limited to 199 patients after excluding 11 who failed to return urine samples for measuring UIC and 2 outliers for UIC. Of the 199 patients, 36.2% had CME in 1 or both eyes. Although log CFT was inversely related to UIC based on findings from all eyes (P = .02), regression of log CFT on UIC separately for eyes with and without CME showed a strong inverse significant relationship for the former group (P < .001) and no significant relationship for the latter group (P = .66) as tested. For the eyes with CME, CFT ranged from a geometric mean of 267 μm for a median UIC of less than 100 μg/L to a geometric mean of 172 μm for a median UIC of 200 μg/L or greater. In contrast, we found no significant association between CME prevalence and UIC based on the entire sample as tested (odds ratio, 1.01 [95% CI, 0.38-2.67]; P = .99).

CONCLUSIONS AND RELEVANCE A higher UIC in nonsmoking adults with RP was significantly associated with less central foveal swelling in eyes with CME. Additional study is required to determine whether an iodine supplement can limit or reduce the extent of CME in patients with RP.
Based on optical coherence tomography (OCT), cystoid macular edema (CME) occurs as a complication in more than 25% of patients with retinitis pigmentosa (RP) and may be associated with a reduction in visual acuity. Cystoid macular edema in RP ranges from small, rare, off-center cysts within the inner nuclear layer to multiple large cysts spanning the retinal layers and including the foveal center. Accumulation of fluid within the extracellular space could result from a breakdown of retinal pigment epithelial (RPE) tight junctions or diminished retinal capillary endothelial cell adhesion leading to passive leakage of fluid into the retina or from reduced active transport of fluid out of the retina by an impaired pump. The RPE is particularly suspect, because dye leakage through the RPE membrane epithelial (RPE) tight junctions or diminished retinal cellular space could result from a breakdown of retinal pigment epithelium (RPE) tight junctions or diminished retinal capillary endothelial cell adhesion leading to passive leakage of fluid into the retina by an impaired pump. The RPE is particularly suspect, because dye leakage through the RPE membrane epithelial (RPE) tight junctions or diminished retinal cellular space could result from a breakdown of retinal pigment epithelium (RPE) tight junctions or diminished retinal capillary endothelial cell adhesion leading to passive leakage of fluid into the retina by an impaired pump.

Treatment with oral or topical carbonic anhydrase inhibitors can increase subretinal fluid resorption and reduce retinal swelling in RP patients with CME. However, oral carbonic anhydrase inhibitors can lead to systemic adverse effects that may occasionally include kidney stones or anemia, and oral and topical carbonic anhydrase inhibitors can lead to a rebound of edema after termination of therapy or with sustained use. Intravitreal injection of corticosteroids has similarly been found to reduce swelling in these eyes but with a possible rebound of edema. Moreover, patients with advanced CME treated with carbonic anhydrase inhibitors or corticosteroids can show reductions in swelling without commensurate improvements in visual acuity. The latter eyes may have already experienced permanent photoreceptor damage or cell loss as a result of the edema. Therefore, an alternative, safe, well-tolerated treatment for CME for early intervention would be beneficial to avoid the issue of possible irreversible loss of visual acuity.

With a food frequency questionnaire administered to nonsmoking adult patients with RP (n = 316), we identified CME by OCT in 11.9% taking potassium iodide, 150 μg/d (the adult recommended daily allowance), in a multivitamin supplement or less often vs 31.9% not taking the potassium iodide supplement; this difference was statistically significant (M.A.S.; unpublished observation; October 2008 [P = .001]). Moreover, 2 studies reported that iodine improved cell-cell adhesion by increasing the transendothelial resistance of leaky human endothelial cell tight junctions and the transepithelial resistance of leaky human epithelial breast cancer cells. These data raise the possibility that iodine supplementation might impede the development of retinal edema caused by a leaky RPE.

However, taking or not taking an iodine supplement may not represent total dietary intake of iodine. Because (1) dietary iodine is absorbed with 92% bioavailability, (2) 90% of ingested iodine is excreted in the urine within 24 hours, and (3) dietary iodine intake is significantly correlated with urinary excretion of iodine, urinary iodine concentration (UIC) is considered to be a good monitor of recent intake of iodine. We therefore decided to conduct a new observational study to assess whether the degree of CME among nonsmoking adults with RP was related to their UIC.

Methods

Patients

The protocol for this study was approved by the institutional review board of the Massachusetts Eye and Ear Infirmary and conformed to the tenets of the Declaration of Helsinki and to regulations of the Health Insurance Portability and Accountability Act. Written informed consent was obtained from the patients after explanation of the nature and possible consequences of the study.

We excluded patients with a best-corrected Snellen visual acuity of worse than 20/200 in both eyes, because the presence of maculopathy might confound the appearance of CME. Although a previous investigation had reported that CME in RP was not significantly related to aphakia/pseudophakia, as a precaution we excluded patients who had undergone cataract surgery within the past year. We excluded patients who were currently smoking, because the inverse relationship between CME risk and iodine supplementation in the previous analysis was based on nonsmoking patients. We also excluded patients who were taking levothyroxine sodium (for hypothyroidism) or amiodarone hydrochloride (for cardiac arrhythmia) and individuals who had received iodinated radiographic contrast within the previous 6 months—because these patients would markedly skew the distribution of iodine intake—and patients with gastrointestinal malabsorption owing to prior bowel resection, a history of Crohn disease, or a history of inflammatory bowel disease.

We enrolled 212 patients with typical RP and a corrected visual acuity of 20/200 or better in at least 1 eye. Eleven of these patients (5.2%) failed to send in multiple spot urine samples for measuring UIC after their examination, leaving 201 patients (101 men and 100 women aged 18-69 years) with complete data. Our cohort consisted of 41 patients with dominant disease, 151 with autosomal recessive or sporadic disease, 6 with X-linked disease, and 3 with undetermined inheritance.

Dietary Iodine Estimates

Total dietary intake of iodine was estimated from urine samples collected at home. Because UIC from spot samples is the recommended indicator for population assessment and because the day-to-day variation in UIC is considerable, patients were provided with a custom mail-in kit and asked to collect multiple (preferably, 10) spot urine samples during consecutive days for us to derive a better estimate of long-term intake than we could using single spot urine samples or a single 24-hour urine sample. Containers included labels for patients to record the date and time of each sample. The cohort provided a mean of 9.8 (range, 2-10) iodine samples/patient obtained during a mean of 6.1 (median, 4) days.

The urine samples were stored at ~80°C before iodine analysis. The UIC from each spot sample was measured at least twice by a modification of the Benotti method. If the initial 2 measurements were not within 15% of each other, a third or a fourth measurement was obtained and the mean of all measurements reported. The interassay coefficient of variation...
ranges from 2.7% to 7.0%. The cohort was iodine sufficient by World Health Organization standards,27 with an overall median UIC of 143 μg/L. However, we noted that 55 of these patients (27.4%) had a median UIC of less than 100 μg/L, suggesting possible iodine intake of less than the recommended daily allowance of 150 μg/d.

The distribution of median UIC was positively skewed (skewness, 9.22), and UIC values were converted to natural logarithms to better approximate a normal distribution. Two patients with median UIC values of 2272 and 3470 μg/L that reflect dietary intake above the upper tolerable limit for adults of 1100 μg/d28 were found to be outliers by the extreme Studentized deviate test29 and were excluded from further study, leaving 199 patients. The distribution of loge median UIC after removal of the outliers had a skewness of −0.30.

OCT Evaluations

Cystoid macular edema and central foveal thickness (CFT) were coded for eyes with a visual acuity of 20/200 or better and for which the central macula could be visualized adequately by OCT. We used a high-resolution optical coherence tomographer (Stratus model 3000; Carl Zeiss Meditec) to assess retinal structure and measure CFT after pupillary dilation3,30 in 192 of the 199 patients. We recorded twelve 6-mm radial scans spaced in 15° intervals (or, less often, six 6-mm radial scans spaced in 30° intervals). One eye was excluded in each of 23 patients because of a visual acuity of worse than 20/200 (7 cases), a pseudohole (8 cases), or poor imaging (8 cases).

In 33 patients, we recorded tomograms with a high-definition OCT device (Cirrus; Carl Zeiss Meditec); of these, 7 underwent testing on the Cirrus device alone because our Stratus device was unavailable, and 26 underwent testing with both devices to serve as a calibration subset for quantifying CFT (see below). The Cirrus acquisition protocol covered a 6 × 6-mm retinal area with 128 horizontal lines, each consisting of 512 A-scans. The Cirrus files were copied as audio/video interleaved media format movies to a USB drive and ported to a laptop computer (MacBook Pro; Apple) for offline identification of CME and analysis of CFT with publicly available software (ImageJ, version 1.46j; http://image.nih.gov/ij).

Cystoid macular edema was defined as ranging from rare discrete vacuoles 50 μm in height at the level of the inner nuclear layer to multiple vacuoles of more than 400 μm in height that distorted the cytoarchitecture.30 Seventy-two of the 199 patients (36.2%) had CME in 1 or both eyes, including 48 bilaterally, 18 unilaterally, and 6 in whom the second eye was not categorized owing to reduced visual acuity or inadequate imaging.

Central foveal thickness was measured as the distance between the high-reflectance vitreoretinal interface and the RPE-choriocapillaris complex30 based on the vertical and horizontal B-scans of the Stratus device or based on the central B-scan of the Cirrus device. The results obtained from the subset of patients who underwent testing on both instruments led to an algorithm for estimating Stratus CFT from Cirrus CFT ($r^2 = 0.91$); this algorithm was used to infer what the Stratus thickness would have been for those 7 patients who underwent testing only on the Cirrus device, so that the latter patients could be included with the other patients in a group assessment of CFT.

Statistical Analysis

The distributions of CFT by eye were positively skewed (skewness, 2.22 OD and 2.18 OS), so CFT values were converted to natural logarithms to better approximate normal distributions. With the eye as the unit of analysis (to use the data from both eyes of patients with unilateral CME), we used commercially available software (PROC MIXED, SAS, version 9.3; SAS Institute Inc) to perform several analyses with loge CFT as the dependent variable. The software program adjusts for the intrasubject correlation between eyes and permits missing values. In model 1, median UIC was the independent class variable representing 3 ranges (<100, 100-199, or ≥200 μg/L) to minimize the effect of any high-leverage values and to allow for a nonlinear relationship between loge CFT and UIC. Model 2 added CME status as a 2-level classification (0 indicated no CME; 1, CME present) and its cross-product with UIC classification as independent variables; the cross-product term allowed us to determine whether the effect of UIC classification depended on CME status. With the cohort divided by CME status, models 3 and 4 used UIC classification as the only independent variable to estimate the relationships for eyes with and without CME, respectively. For models 1 and 3 we performed linear contrasts to compare CFT differences for specific pairs of UIC ranges, reporting Bonferroni corrections to take into account simultaneous multiple comparisons in identifying significant relationships ($P < .05$).

Patients with RP have been encouraged to consider taking a supplement of vitamin A palmitate and to eat a diet rich in docosahexaenoic acid (DHA) to slow the course of their disease because of results from 3 studies.31-33 Based on a food-frequency questionnaire,34 our patients showed variable amounts of vitamin A and DHA in their diets (including supplements), raising the possibility that 1 or both of these nutrients might confound any significant relationship between CFT and UIC. To test this, we repeated model 3 adjusting for the tertile (0/1/2) of dietary vitamin A or DHA intake as a continuous variable, Last, we used commercially available software (PROC GENMOD, SAS, version 9.3) to perform eye-level logistic regression to test whether the likelihood of CME in the entire cohort depended on UIC classification recoded as a continuous variable to test for trend.

Assessment of the iodine nutrition is more difficult in individuals than in the population, because a substantial amount of diurnal and day-to-day variation exists in an individual’s dietary iodine intake and urinary iodine excretion,23,35 and previous studies have found a high mean within-patient coefficient of variation for UIC.20,25,35,36 Because our distribution of within-patient coefficients of variation had a high mean (59%)37 and substantial variation (Figure 1), we used the weight option in both statistical software programs to weight all analyses presented in the Results section by the normalized inverse-squared within-patient coefficient of variation for UIC to assign greater importance to less variable measurements while controlling for mean level.38 This step proved essential to identifying significant relationships between CFT and UIC.
Results

The \( \log_e \) CFT was inversely related to UIC classification with model 1 \((P = .02)\) (Table). By linear contrasts, the difference in mean \( \log_e \) CFT (geometric mean difference, 24 \( \mu \)m) for UIC of less than 100 vs 100 to 199 \( \mu \)g/L was of borderline significance \((P = .08)\), whereas the corresponding difference (geometric mean difference, 7 \( \mu \)m) for UIC of 100 to 199 vs 200 \( \mu \)g/L or more was not significant \((P = .78)\) after Bonferroni corrections, raising the possibility of an onlineart trend.

However, when we included CME status and its interaction with UIC classification as independent variables (model 2), we found that the relationship between \( \log_e \) CFT and UIC classification depended on CME status \((P < .001)\) (Figure 2), which necessitated reanalyzing the data after separating the cohort into eyes with and without CME. For the subset with CME (model 3), \( \log_e \) CFT was now more strongly related to UIC classification \((P < .001)\), ranging from a geometric mean of 267 \( \mu \)m for a median UIC of less than 100 \( \mu \)g/L to a geometric mean of 172 \( \mu \)m for a median UIC of 200 \( \mu \)g/L or greater (Table). By linear contrasts, the difference in mean \( \log_e \) CFT (geometric mean difference, 79 \( \mu \)m) for UIC of less than 100 vs 100 to 199 \( \mu \)g/L was significant \((P = .008)\), whereas the corresponding difference (geometric mean difference, 16 \( \mu \)m) for UIC of 100 to 199 vs 200 \( \mu \)g/L or greater was not significant \((P = .76)\), after applying Bonferroni corrections, consistent with an onlineart trend. For the subset without CME (model 4), \( \log_e \) CFT was not significantly related to UIC classification \((P = .66)\).

Table. CFT by UIC in Patients With Retinitis Pigmentosa

<table>
<thead>
<tr>
<th>Model No., Median UIC, ( \mu )g/L</th>
<th>No. of Eyes</th>
<th>( \log_e ) CFT (SEM) [Geometric Mean], ( \mu )m</th>
<th>( \text{P Value}^c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>103</td>
<td>5.254 (0.052) [191]</td>
<td>.02</td>
</tr>
<tr>
<td>100-199</td>
<td>157</td>
<td>5.120 (0.039) [167]</td>
<td></td>
</tr>
<tr>
<td>≥200</td>
<td>115</td>
<td>5.076 (0.034) [160]</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>35</td>
<td>5.589 (0.090) [267]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>100-199</td>
<td>50</td>
<td>5.238 (0.077) [188]</td>
<td></td>
</tr>
<tr>
<td>≥200</td>
<td>35</td>
<td>5.149 (0.062) [172]</td>
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</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>68</td>
<td>5.004 (0.048) [149]</td>
<td>.66</td>
</tr>
<tr>
<td>100-199</td>
<td>107</td>
<td>5.055 (0.033) [157]</td>
<td></td>
</tr>
<tr>
<td>≥200</td>
<td>80</td>
<td>5.030 (0.031) [153]</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CFT, central foveal thickness; UIC, urinary iodine concentration.

* The geometric mean value for UIC of less than 100 \( \mu \)g/L was 68 \( \mu \)g/L; for 100 to 199 \( \mu \)g/L, 139 \( \mu \)g/L; and for 200 \( \mu \)g/L or greater, 263 \( \mu \)g/L, based on data for all patients.

* Mean (SEM) reference values for CFT with the same instrumentation are 167 (5) \( \mu \)m based on 22 volunteers aged 25 to 56 years.10

* Calculated using commercially available software (PROC MIXED, SAS, version 9.3; SAS Institute Inc) with the eye as the unit of analysis. See Methods for additional details.

* Median UIC is the independent class variable.

* Includes eyes with cystoid macular edema (CME).

* Includes eyes without CME.

Among patients with retinitis pigmentosa, 120 eyes had cystoid macular edema (CME) (model 3) and 255 eyes had no CME (model 4). Error bars designate SEM. See the Methods section for details of the analyses.
no significant trend between the likelihood of CME based on the entire cohort vs UIC classification (odds ratio, 1.01 [95% CI, 0.38-2.67]; P = .99).

Discussion

This study found that a higher UIC was associated with a smaller CFT among a cohort of 199 patients with RP, more than a third of whom had CME. However, the relationship was different for eyes with and without CME. Eyes with CME showed a strong inverse relationship, whereas eyes without CME showed no significant relationship as tested. Together these 2 findings suggest that higher UIC in this cohort was specifically associated with a reduced swelling due to CME. Including total vitamin A or DHA intake as a covariate in analyses showed that the relationship of CFT to UIC classification in eyes with CME as tested was not confounded by either nutrient.

In contrast, an analysis of the risk for CME by UIC classification based on the entire cohort showed no significant relationship as tested. This finding suggests that UIC classification had no bearing on the initiation of CME regardless of its extent, and we should look in other directions to predict who will develop cysts. For example, the likelihood of cyst formation in RP may, in part, be governed by genetic regulation, because CME has been reported to be rarest in patients with X-linked disease.3,39

Iodine has been shown to promote tight junctions between epithelial cells, which could help to block the passage of fluid across the RPE into the neural retina. Laboratory studies in mammals have demonstrated that sodium iodate and potassium iodate have an affinity for the RPE and in sufficient concentrations will damage it. However, at a low concentration injected intravenously in albino and pigmented rabbits, sodium iodate acutely and reversibly enhanced the c wave, which is a physiological measure of RPE integrity.40 Therefore, perhaps higher physiological levels of iodine could promote RPE integrity in RP patients with intraretinal cysts. Iodine might serve a similar role in patients with CME secondary to uveitis, who are thought to have lost integrity of the outer blood-retina barrier and RPE pump, or in patients with CME secondary to diabetic retinopathy, given that dysfunction of the outer blood-retina barrier has been observed in patients with diabetes mellitus.42-45

One strength of this study was our use of multiple spot urine samples to estimate total dietary iodine intake; the patients contributed a mean of nearly 10 samples each, obtained during a mean of 6.1 days. This method was preferable to attempting to infer total dietary iodine intake from a food frequency questionnaire, which is subject to self-reporting errors. A second strength was our use of the eye as the unit of analysis while taking into account the correlation between fellow eyes, so that patients with unilateral CME—who constituted 25.0% of our patients with CME—could have data from both their eyes included to increase our power in defining the relationships between CFT and UIC.

Conclusions

Although the observed effect of higher levels of dietary iodine intake was clinically significant in our patients with CME, amounting to a 95-μm geometric mean reduction in CFT, this study was observational and, as such, was not designed to prove that higher levels of dietary iodine intake limited the extent of CME. In particular, we do not know that supplementation with potassium iodide, for example, will reduce central foveal swelling once it has already occurred and, therefore, we are not recommending that RP patients with CME augment their dietary intake of iodine at this time. Instead, these data provide a rationale for considering a prospective randomized trial among RP patients to determine whether iodine supplementation, relative to a control condition, can safely limit or reduce the extent of preexisting CME.


