PostScript

LETTERS

Does dietary lutein and zeaxanthin increase the risk of age related macular degeneration? The Melbourne Visual Impairment Project

Age related macular degeneration (AMD) was one of the five main causes of vision impairment in the combined study of the Melbourne Visual Impairment Project (MVIP) and the Blue Mountains Eye Study (BMES).[1]

A higher dietary intake of lutein/zeaxanthin was significantly associated with lower risk of having exudative age related macular degeneration in the Eye Disease Case-Control Study, but there was no association between lutein/zeaxanthin (LZ) intake and either early or neovascular age related maculopathy in the combined prospective US study.[2 3] Also, a higher fish intake has been associated with a lower risk of progression to advanced AMD among those with low (below median) linoleic acid intake, whereas there was no significant association among those with higher linoleic acid intake.[4]

The aim of this paper is to examine the association of AMD with dietary intake of the carotenoids lutein/zeaxanthin in conjunction with linoleic acid intake in the follow up population based sample of the MVIP.

Methods

Study design

Of 3040 permanent residents recruited in 1992–4, 2594 (85%) of them attended the follow up examinations in 1997–9.[5] At both time points of the study, participants signed an informed consent and underwent a standard procedure including an ophthalmic examination and an interview regarding socioeconomic and demographic characteristics, historic and current symptoms of eye diseases, medical history, and medication use. The follow up survey also included a food frequency questionnaire (FFQ).

AMD detection

AMD was diagnosed by either clinical or photographic examinations.[5] Features of AMD were graded according to the Wisconsin Age-Related Maculopathy Grading System, and AMD was classified according to an international classification system.[5] Neovascular AMD included (i) subretinal fibrous scars or (ii) serous or haemorrhagic detachment of the retinal pigment epithelium (RPE) or sensory retina; intraretinal, or subretinal or sub-RPE haemorrhages. Atrophic AMD included the presence of at least 175 μm in diameter visible choroidal vessels in the central areolar zone of RPE atrophy in the absence of signs of neovascular AMD.[5] Early AMD was defined in the absence of signs of late (neovascular or atrophic) AMD. International classification (IC) early AMD was defined as the presence of soft distinct, soft indistinct, or reticular drusen, or the presence of any pigmentary abnormalities.[5] We also used the Wisconsin definition of early AMD in the BMES or the Beaver Dam Eye Study (BDES), where early AMD was defined as the presence of soft indistinct or reticular drusen in field-2 fundus photograph or the presence of any soft drusen and retinal pigmentary abnormalities in the same field.[5]

Nutritional analysis

We used the FFQ developed and validated by the Cancer Council Victoria that includes 13 different fruit items and 25 vegetable items with 10 frequency options from never to three or more times per day for each item.[6] We used the method of Willett to calculate the energy adjusted LZ intake.[7] Briefly, we first fitted the simple linear regression of the logarithm of the nutrient intake on the logarithm of total energy intake. Next we calculated the difference between the observed and expected values of the logarithm of the nutrient intake and added to this the predicted logarithm of nutrient intake at the population mean of the logarithm of energy intake. Then we exponentiated this quantity to obtain the energy adjusted nutrient score.

Statistical analysis

All statistical analyses were conducted with Statistical Analysis System. The odds ratios were adjusted for age, smoking duration ($\geq$40 years versus $<$40 years), and body mass index. Use of ACE inhibitors and cholesterol lowering medication were not associated with AMD in this sample and were not included in further analyses, although they were significant for predicting AMD in the baseline MVIP.[8] We explored the interaction between LZ intake and an indicator of low (below median) linoleic acid intake. A test with a p value less than 0.05 was considered to be significant.

Results

Of 2594 participants who attended the follow up examination, 2448 (94.3%) had macular assessment, 2322 (89.5%) completed dietary questionnaires, 2345 (90.4%) had smoking data, and 2144 (83%) had body mass index data. Of 2448 participants who had macular assessment, 1760 (71.9%) had photographic macular assessment. We also excluded one participant with a large outlier for daily LZ intake, leaving 1972 participants with a complete record for smoking duration, body mass index, dietary intake, and macular assessment to be included in the analyses (table 1).

Among those with daily linoleic acid intake $\geq$7.17 mg the risk of having late AMD with either grading increased up to fivefold for 1 mg increase in adjusted daily LZ intake, and up to threefold for 1 mg increase in crude daily LZ intake. Also the risk of having early AMD with either grading significantly increased with higher adjusted daily LZ intake. These results are strengthened with the exclusion of participants taking supplements (table 2).

Comment

Our study showed a possible protection of high LZ intake on AMD among those with low level of linoleic acid intake. Thus, our results would not contradict that significant protection of higher LZ intake on AMD in the Eye Disease Case-Control Study if the daily linoleic acid intake median in this US study

Table 1 Participants' characteristics (n = 1972)

Continuous variable	Mean (SD)
Age (years)	61.9 (10.5)
Body mass index (kg/m^2)	26.2 (4.5)
Daily energy intake (kJ)	7441 (2804)
Daily linoleic acid intake (g)	9.4 (5.2)
Daily LZ intake (μg)	803 (414)
Adjusted daily LZ intake (μg)	788 (371)
Daily fat intake (g)	66.1 (30.2)
Adjusted daily fat intake (g)	61.0 (11.4)
Categorical variable	**No (%)**
Female	1038 (53)
Number of years smoked >40	173 (8.8)
Taking an ACE inhibitor (1971*)	299 (15)
Taking blood cholesterol lowering medication (1964*)	52 (2.7)
Taking supplement (s) (1931*)	409 (21)
AMD (International classification)	
Late	36 (1.8%)
Early	421 (21%)
None	1515 (77%)
AMD (Wisconsin)	
Late	36 (1.8%)
Early	147 (7.5%)
None	1789 (91%)
Daily LZ intake (μg/4.18 MJ)	Median
1st quintile	213
2nd quintile	328
3rd quintile	440
4th quintile	562
5th quintile	801

*Number of complete records for the corresponding variable.

Table 2 The odds ratios adjusted for age, smoking, and body mass index and stratified by the daily linoleic acid intake

	Any AMD		Early AMD		Late AMD	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
All participants:						
International classification AMD						
Daily linoleic acid intake ⩾7.17 g	0.70 (0.44 to 1.13)	0.142	0.77 (0.47 to 1.25)	0.296	0.15 (0.03 to 0.69)	0.014
Crude daily LZ intake (mg) (DLAI <7.17 g)	1.02 (0.66 to 1.57)	0.944	1.09 (0.70 to 1.69)	0.713	0.27 (0.04 to 1.70)	0.163
Crude daily LZ intake (mg) (DLAI ⩾7.17 g)	1.42 (1.03 to 1.94)	0.030	1.34 (0.97 to 1.86)	0.075	3.16 (1.28 to 7.79)	0.013
Wisconsin AMD						
Daily linoleic acid intake ⩾7.17 g	0.41 (0.20 to 0.80)	0.010	0.48 (0.23 to 1.02)	0.057	0.15 (0.04 to 0.65)	0.011
Crude daily LZ intake (mg) (DLAI <7.17 g)	0.54 (0.26 to 1.09)	0.087	0.60 (0.28 to 1.28)	0.191	0.26 (0.04 to 1.55)	0.140
Crude daily LZ intake (mg) (DLAI ⩾7.17 g)	1.60 (1.03 to 2.47)	0.037	1.41 (0.86 to 2.31)	0.168	2.83 (1.24 to 6.45)	0.013
International classification AMD						
Daily linoleic acid intake ⩾7.17 g	0.62 (0.38 to 1.04)	0.069	0.70 (0.42 to 1.18)	0.185	0.10 (0.02 to 0.54)	0.007
Adjusted daily LZ intake (mg) (DLAI <7.17 g)	1.04 (0.68 to 1.57)	0.870	1.11 (0.73 to 1.69)	0.636	0.30 (0.06 to 1.66)	0.170
Adjusted daily LZ intake (mg) (DLAI ⩾7.17 g)	1.74 (1.18 to 2.57)	0.005	1.61 (1.08 to 2.40)	0.020	5.50 (1.70 to 17.8)	0.005
Wisconsin AMD						
Daily linoleic acid intake ⩾7.17 g	0.35 (0.17 to 0.73)	0.005	0.44 (0.20 to 0.97)	0.041	0.11 (0.02 to 0.51)	0.005
Adjusted daily LZ intake (mg) (DLAI <7.17 g)	0.71 (0.37 to 1.35)	0.298	0.82 (0.42 to 1.62)	0.571	0.29 (0.06 to 1.51)	0.142
Adjusted daily LZ intake (mg) (DLAI ⩾7.17 g)	2.44 (1.43 to 4.17)	0.001	2.13 (1.19 to 3.83)	0.011	4.72 (1.60 to 13.9)	0.005
Excluding those who took supplements:						
International classification AMD						
Daily linoleic acid intake ⩾7.17 g	0.56 (0.33 to 0.96)	0.037	0.64 (0.37 to 1.12)	0.117	0.12 (0.02 to 0.58)	0.009
Crude daily LZ intake (mg) (DLAI <7.17 g)	0.94 (0.56 to 1.58)	0.817	1.03 (0.61 to 1.75)	0.906	0.27 (0.04 to 1.91)	0.190
Crude daily LZ intake (mg) (DLAI ⩾7.17 g)	1.68 (1.18 to 2.39)	0.004	1.59 (1.10 to 2.28)	0.013	3.65 (1.37 to 9.76)	0.010
Wisconsin AMD						
Daily linoleic acid intake ⩾7.17 g	0.35 (0.16 to 0.78)	0.010	0.46 (0.19 to 1.11)	0.083	0.12 (0.03 to 0.56)	0.007
Crude daily LZ intake (mg) (DLAI <7.17 g)	0.61 (0.27 to 1.40)	0.244	0.75 (0.31 to 1.82)	0.526	0.26 (0.04 to 1.71)	0.160
Crude daily LZ intake (mg) (DLAI ⩾7.17 g)	2.04 (1.26 to 3.30)	0.004	1.85 (1.08 to 3.15)	0.025	3.15 (1.30 to 7.59)	0.011
International classification AMD						
Daily linoleic acid intake ⩾7.17 g	0.50 (0.28 to 0.89)	0.018	0.58 (0.32 to 1.05)	0.070	0.08 (0.01 to 0.49)	0.006
Adjusted daily LZ intake (mg) (DLAI <7.17 g)	1.04 (0.64 to 1.68)	0.870	1.14 (0.70 to 1.86)	0.604	0.32 (0.05 to 1.97)	0.219
Adjusted daily LZ intake (mg) (DLAI ⩾7.17 g)	2.27 (1.46 to 3.53)	<0.001	2.11 (1.35 to 3.32)	0.001	6.39 (1.71 to 23.9)	0.006
Wisconsin AMD						
Daily linoleic acid intake ⩾ 7.17 g	0.32 (0.14 to 0.75)	0.009	0.44 (0.17 to 1.12)	0.085	0.09 (0.02 to 0.47)	0.005
Adjusted daily LZ intake (mg) (DLAI <7.17 g)	0.86 (0.41 to 1.79)	0.684	1.08 (0.5 to 2.36)	0.842	0.30 (0.05 to 1.73)	0.179
Adjusted daily LZ intake (mg) (DLAI ⩾7.17 g)	3.17 (1.74 to 5.77)	<0.001	2.88 (1.5 to 5.54)	0.002	5.18 (1.59 to 16.9)	0.007

DLAI, daily linoleic acid intake.

were similar to that of only 4.9 g in another US study of 261 AMD patients.[2 4]

The main strengths of our study are the relatively large, population based sample, two different definitions of AMD, the use of a comprehensive ophthalmological examination, and the FFQ validated by the Cancer Council Victoria. The daily LZ intake mean was 914 μg in the BMES while it was 803 μg in the MVIP.[9] Furthermore, our quintile medians (μg/4.18 MJ) were from 29% to 36% lower than the population based BDES (table 1).[10] The LZ intakes in other volunteer case-control studies that were from three to five times higher in each quintile than the population based intakes clearly show a ''healthy volunteer bias''.[2 3] Limitations of this study include cross sectional data, a possibility of selection bias because of loss of follow up, and the problem of 24% cumulative missing data.

In our study there was a harmful effect of higher LZ intake on AMD among those with high level of linoleic acid intake. Based on these data LZ supplementation could not be recommended.

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Ethics approval: The protocol of the study was approved by the Human Research and Ethics Committee of the Royal Victorian Eye and Ear Hospital.

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Corneal ectasia associated with Cohen syndrome: a role for COH1 in corneal development and maintenance?

Cohen syndrome[1] is a rare autosomal recessive condition with a pleiotropic phenotype. Ocular findings of high myopia and early