• Investigation •

The J-shape association of serum total IgE levels with age-related cataract

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Abstract

• AIM: To address the association between serum total IgE levels and age-related cataract in adults.

• METHODS: The study participants consisted of 1052 adults aged 40y or older in the Korean National Health and Nutrition Examination Survey 2010. We performed multivariable logistic regression analyses using the quartile cut-points of total IgE levels.

• RESULTS: The odds ratios (ORs) for nuclear and any cataract with ≥267 kU/L of serum IgE levels were 1.75 [95% confidence intervals (CI), 1.04-2.96] and 2.00 (95%CI, 1.22-3.27), respectively, comparing to 35-87 kU/L. Interestingly, participants with ≤35 kU/L of IgE levels (OR, 1.67; 95%CI, 1.02-2.72) also had higher risk for any cataract than those with 35-87 kU/L. The risk for any cataract (OR, 1.48; 95%CI, 1.03-2.13) was higher in participants with high total IgE levels (>150 kU/L), comparing to normal participants.

• CONCLUSION: Our findings indicate a J-shaped relationship between serum IgE levels and age-related cataract.

• KEYWORDS: IgE; allergy; cataract; eye

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INTRODUCTION

Age-related cataract is an ocular disease, which is induced by damaging the capsule, epithelium, and constituent fibres of the lens of the eye, is the most frequent cause of blindness. Due to the rapidly aging population in the world, age-related cataract continues to be a major worldwide public health problem.

IgE responses have been described as being beneficial in mammals' protection against parasitic infections, particularly helminth infections, and as being pathological in allergic diseases. Among IgE-related allergic diseases, atopic eczema, allergic rhinitis, and allergic asthma are among the most common causes of chronic diseases[1]. IgE levels in serum can be useful diagnostic tools for those diseases[2]. IgE-related allergic diseases are associated with hypertension, depression, coronary disease, heart failure, conjunctivitis, and age-related cataract[3]. Recent studies reported that very low serum IgE levels had an unexpected association with the incidences of cardiovascular[4] and autoimmune diseases[5].

Based on the relationship of allergic diseases to other chronic diseases, their associations with cataract formation are expected. However, only a little evidence directly suggests the association of age-related cataract with serum IgE levels which is a key factor for allergic diseases. Therefore, this study examined whether serum total IgE levels were associated with age-related cataract using nationally representative population data.

SUBJECTS AND METHODS

This study analyzed data acquired from the Korean National Health and Nutrition Examination Survey (KNHANES) 2010. KNHANES, which investigates health and nutritional status of the representative population of Republic of Korea. KNHANES followed the Ethical Principles for Medical Research Involving Human Subjects, defined by the Declaration of Helsinki. This survey obtained a written informed consent form from each survey participants. Since KNHANES used de-identified public data, the approval of the institutional review board was not required. Serum total IgE levels and cataract information was available for 1171 participants aged ≥40y. We excluded 119 participants who experienced cataract or surgery for cataract, because we assumed that previous eye status of these participants was likely to be affected by their previous systemic health status, including serum total IgE levels, not by current status. In the end, the study population consisted of 1052 individuals (535 men and 517 women).

Serum total IgE levels were measured through the fluorescence enzyme immunoassay using ImmunoCAP 100 (Phadia,

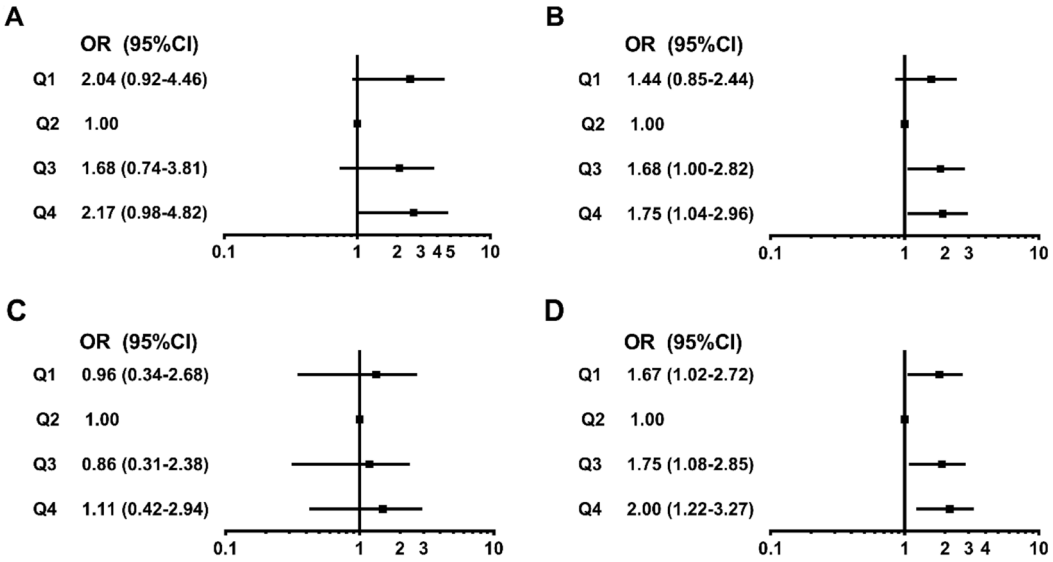

Figure 1 Odds ratios and 95%CIs from multivariable logistic regression analyses for cortical (A), nuclear (B), mixed (C), and any cataract formation (D) according to quartiles of serum IgE levels Each analysis was adjusted for age, sex, obesity status, diabetes mellitus status, education level, income, marital status, metabolic equivalence task, smoking amount, alcohol consumption, vitamin C intake, serum 25-hydroxyvitamin D levels, sun exposure, and family history of eye disease.

Sweden). Range of test was 2.0-5000.0 kU/L. High total serum IgE was defined as a level above 150 kU/L. Participants were diagnosed as having cataract when, in either eye, they had any subtype of cataract [cortical, nuclear, anterior subcapsular (AS), posterior subcapsular (PS), or mixed] discernable through a slit-lamp microscope (Haag-Streit BQ-900; Haag-Streit AG, Koeniz, Switzerland), as previously described[6]. "Any" cataract was defined when any subtype of cataract was found in either eye.

To ascertain the relationship of serum IgE levels with cataract, we performed multivariable logistic regression analyses using the quartile cut-points (35, 87, and 267 kU/L) of total IgE levels. Here we chose the second lowest quintile as the reference group (total IgE levels 35-87 kU/L), because we assumed that very low levels of total IgE levels may be attributed to cataract formation[4-5]. We additionally performed logistic regression analysis to estimate the risk of cataract in participants with high serum total IgE levels (>150 kU/L). Because we observed the rare frequency of AS (n=7) and PS (n=1) cataract, we did not perform statistical analyses for those. We used the firth method with a penalized likelihood function in dealing with cortical and mixed cataract due to the low prevalence of both (cortical, 7%; mixed, 3.5%). We then adjusted the following confounders in each analysis: age (5-year age groups), sex, obesity status (≥25 *vs* <25 kg/m^2), diabetes mellitus status (yes *vs* no), education level (≤elementary, middle *vs* ≥high school), income (≥3000 *vs* <3000 $/mo), marital status (married and living together *vs* not), metabolic equivalence task (Ln-transformed MET-h/wk), smoking amount (Ln-transformed pack-years), alcohol consumption (Ln-transformed g/d), vitamin C intake (Ln-transformed mg/d), serum 25-hydroxyvitamin D levels (Ln-transformed ng/mL), sun exposure (≥5 *vs* <5 h/d), and family history of eye disease (any cataract, glaucoma, retinopathy, strabismus, blepharoptosis, or other eye diseases of the participant's family members *vs* not). We analyzed the data using SAS 9.4 software (SAS institute, Cary, NC, USA). A P value <0.05 was considered to be statistically significant.

RESULTS

Of 1052 participants, the mean age and total IgE levels were 53.8y and 95.4 kU/L, respectively. The prevalence of high total IgE levels and any cataract were 36.0% and 30.4%, respectively. Prevalence of nuclear and any cataract increased across the quartiles of serum total IgE levels (Table 1).

Odds ratios (ORs) for nuclear cataract in participants with ≥267 kU/L and 87-267 kU/L of total IgE levels were 1.75 [95% confidence interval (CI), 1.04-2.96] and 1.68 (95%CI, 1.00-2.82), respectively, as compared to 35-87 kU/L (Q2; Figure 1), whereas, ORs for any cataract were 2.00 (95%CI, 1.22-3.27) and 1.75 (95%CI, 1.08-2.85), respectively. Interestingly, participants with ≤35 kU/L of serum IgE levels (OR, 1.67; 95%CI, 1.02-2.72) also had significantly higher risk for any cataract than those with 35-87 kU/L (Q2). The risk for any cataract formation was significantly associated with high total IgE levels (OR, 1.48; 95%CI, 1.03-2.13; data not shown).

DISCUSSION

The results of the current study indicated that serum total IgE levels were significantly associated with cataract formation. Our findings are consistent with other lines of evidence indicating that cataract can be induced by atopic dermatitis, using corticosteroid, and increased total IgE levels[7-8].

Table 1 Basic characteristics of study participants according to quartiles of serum IgE levels[a]

Variable	Quartiles of serum IgE level (range, kU/L)				P^d
	Q1 (2-35)	Q2 (35-87)	Q3 (87-267)	Q4 (267-5000)	
n	260	262	261	263	
Age (y)	52.6±8.6	53.1±9.1	54.2±9	55.2±8.4	0.003
Women, %	70.4	57.6	44.4	24.0	<0.001
Obesity (≥25 kg/m^2; %)	35.4	32.8	34.5	39.6	0.414
Diabetes mellitus (%)	7.7	9.5	12.6	15.2	0.034
Socio-economic status variable					
Education level (%)					0.282
≤ Elementary school	23.6	26.3	25.8	31.4	
Middle school	18.6	16.2	14.1	18.0	
≥ High school	57.8	57.5	60.2	50.6	
Income (≥3000 $/mo; %)	54.2	52.3	52.1	44.8	0.145
Marital status (married & living together; %)	82.6	84.5	84.4	87.5	0.487
Lifestyle variable[b]					
Metabolic equivalence task, MET-h/wk	613±14	799±12	816±14	1233±11	0.018
Smoking amount, pack-years	1.9±3.5	2.9±4.2	3.9±5.0	8.2±5.0	<0.001
Alcohol consumption (g/d)	1.9±2.8	2.5±3.5	3.3±3.8	5.5±4.6	<0.001
Nutrition variable[b]					
Vitamin C intake (mg/d)	90±2.0	97±2.1	95±2.2	90±2.2	0.595
Serum 25-hydroxyvitamin D levels (ng/mL)	16.3±1.4	17.8±1.5	17.5±1.4	18.9±1.5	<0.001
Eye-related variable					
Sun exposure (≥5 h/d; %)	14.6	14.5	14.2	24.0	0.005
Family history of eye disease (%)[c]	21.9	18.7	14.9	19.0	0.238
Cataract (%)					
Cortical	8.1	4.6	6.1	9.5	0.133
Nuclear	17.7	14.9	23.8	23.2	0.027
Mixed	2.7	4.6	2.7	3.4	0.585
Any	28.9	24.1	32.6	35.7	0.024

[a]Data are presented as % and arithmetic mean±SD unless indicated otherwise; [b]Geometric mean±SD; [c]Family history of eye disease was determined if the participant's family members in a direct line had any cataract, glaucoma, retinopathy, strabismus, blepharoptosis, or other eye diseases; [d]Continuous and categorical variables were analyzed by using analysis of variance and the Chi-square test, respectively.

Several studies supported the biological plausibility that high total IgE levels can increase the risk of cataract formation. A combination of IgE-induced increased serum histamine levels and eye rubbing may break the blood-aqueous barrier[9], which facilitate the passage of antibodies to lens epithelium-derived growth factor (LEDGF), and decreased LEDGF levels by antibodies may lead to the degeneration of lens epithelial cells with resultant cataract formation[10]. Alternatively, oxidative stress, caused by total IgE levels[11], can be another initiating factor for the development of cataract. Regarding to the corticosteroid-induced cataract, Jobling and Augusteyn[12] proposed that steroids may damage the lens by oxidative stress, osmotic imbalance, and disrupted lens growth factors.

Unexpectedly, participants with the lowest levels of total IgE (≤35 kU/L) had a 67% increased risk of any cataract formation, comparing to those with 35-87 kU/L. The mechanism relating to this result is unclear, but several mechanisms can be proposed. A smaller normal number of IgE-secreting plasma cells in mucosal tissues might produce low levels of total IgE[13], which might in turn increase vulnerability to intraocular inflammation and increase the risk of cataract development. Use of statins in some participants might be a cause of the reduced IgE levels[14], which may lead to developing cataract. Magen *et al*[4-5] proposed that IgE deficiency is related to immune dysregulation, chronic inflammation, and autoimmunity. Cataract formation is indeed more prevalent in individuals with celiac disease[15].

Our findings indicate that very high or low levels of total IgE levels may be an important risk factor for cataract formation. Of note, comparing to the other study on total IgE levels[8], our study has some strengths. We excluded participants who previously experienced cataract or surgery for cataract in the study. Moderate total IgE levels (35-87 kU/L) were chosen for reference group on the basis of the systemic effects

of total IgE levels, which was the proper approach to the J-shaped relationship. However, since KNHANES is a cross-sectional survey, causality for our findings was not confirmed. Another limitation of this study is that we did not adjust for some confounders (*e.g.* season). Our study suggests that an individual with IgE-related allergic diseases should be suspected to have cataract, in particular nuclear cataract. Risk of cataract formation should be cautious when treating allergic diseases.

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