AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

Five Heavy Metallic Elements and Age-Related Macular Degeneration

Korean National Health and Nutrition Examination Survey, 2008–2011

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Objective: To investigate the association between age-related macular degeneration (AMD) and 5 heavy metallic elements (lead, mercury, cadmium, manganese, and zinc).

Design: A cross-sectional study using a complex, stratified, multistage, probability cluster survey.

Participants: Participants of the Korean National Health and Nutrition Examination Survey from 2008 to 2011.

Methods: Using a standardized protocol, AMD was determined by fundus photograph grading. Blood concentrations of lead, mercury, cadmium, manganese, and zinc were measured. Associations between AMD and these 5 elements were estimated using logistic regression analyses (LRAs). The distributions of the 5 metallic elements in blood were analyzed, and the same set of LRAs estimating the association between AMD and logarithmic-transformed blood concentrations of the 5 elements were also conducted.

Main Outcome Measures: Association between AMD and 5 heavy metals.

Results: Lead was positively associated with both early AMD and late AMD in all LRAs. Mercury and cadmium also had a positive association with late AMD in all LRAs, but not with early AMD. In contrast, manganese and zinc had an inverse association with late AMD in all LRAs. Manganese and zinc were not associated with early AMD. Using logarithmic-transformed blood concentrations for each metallic element, the LRAs showed similar results compared with those of the LRAs using nontransformed blood concentrations, despite the skewed distribution of these metallic elements in the blood.

Conclusions: This study suggests that the toxic heavy metals (lead, mercury, and cadmium) may negatively influence late AMD, whereas essential heavy metals (manganese and zinc) may favorably influence late AMD. Lead may widely affect the pathogenesis of both early and late AMD. *Ophthalmology 2014;■:1–9 © 2014 by the American Academy of Ophthalmology.*

*Supplementary material available online at www.aaojournal.org.

Age-related macular degeneration (AMD) is the leading cause of blindness in industrialized countries and has blinded >3 million people worldwide.[1] The socioeconomic costs for AMD have sharply increased in countries with an increasingly aging population.[2] Numerous studies have sought to determine risk factors for AMD, and there is some evidence that heavy metallic elements might play a role in the development and progression of AMD. In early 2000, the Age-Related Eye Disease Study (AREDS) raised the issue of an association between AMD and heavy metallic elements, finding that consumption of a high level of zinc (and antioxidants) can reduce the risk of developing advanced AMD.[3] Zinc is an essential metallic element, not only in antioxidant and anti-inflammatory pathways, but also in the immune system and for enzyme function,[4–6] and many studies have investigated the association and protective mechanisms of zinc on AMD. Cadmium has also drawn considerable attention; some studies have shown that cadmium might play a role in AMD pathogenesis, especially in a smoking population.[7–9] Recent evidence suggests that the association between cadmium and AMD exists because cadmium increases oxidative stress and produces inflammatory cytokines.[10,11] In addition, zinc and cadmium, both bivalent cation metallic elements, share numerous binding sites for biomolecules (e.g., metallothionein) and several intracellular metabolic pathways (e.g., mitogen-activated protein kinase pathways).[12–14] Alteration of these mechanisms and pathways may play a role in the pathogenesis of AMD. Other metallic elements (e.g., manganese, lead, and mercury) are also known to be associated with these biomolecules and intracellular pathways, suggesting an association with AMD similar to zinc and cadmium. In addition,

http://dx.doi.org/10.1016/j.ophtha.2014.07.039
ISSN 0161-6420/12

several studies have implied that lead and mercury, well-known toxic metallic elements that can cause devastating health-related morbidities, might be causally involved in AMD pathogenesis, as well as in other ocular pathologies.[7,15–22]

However, to date there has been no population-based study investigating the association between AMD and blood concentrations of heavy metallic elements. Such a study could provide insights into the causal relationship between AMD and heavy metallic elements and help to verify the assumptions derived from the experimental research. A number of researchers have reported an association between heavy metallic elements and other diseases of aging, including hypertension, peripheral artery disease, cognitive decline, and cataracts, which are prevalent in the general population.[16,23–25] On the contrary, AMD has a relatively low prevalence in the general population: 6.0% for early AMD and 0.6% for late AMD in a Korean population aged ≥40 years.[26] A large-scale epidemiologic study with reliable ophthalmologic examination is required to determine the association between AMD and heavy metallic elements. Recently, we reported the prevalence and risk factors of AMD in Korea using the Korea National Health and Nutrition Examination Survey (KNHANES) for 2008–2011.[26] The KNHANES is a large, population-based, government-led survey that can produce nationally representative estimates. The 2008–2011 KNHANES measured blood concentrations of heavy metallic elements as well as conducted detailed ophthalmic examinations, including fundus photography and its grading. As a follow-up study, we evaluated the association between AMD and heavy metallic elements using the same data set as our previous study.[26]

Methods

The KNHANES is an ongoing, population-based, cross-sectional survey in South Korea conducted by the Korea Centers for Disease Control and Prevention and the Korean Ministry of Health and Welfare. We recently reported the nationally representative estimates for prevalence and risk factors of AMD using the 2008–2011 KNHANES databases analyzing >16 000 participants aged ≥40 years[26]; the present study also used the same database set for analysis. Briefly, the 2008–2011 KNHANES selected 3840 to 4600 households in 192 to 200 enumeration districts representing the civilian, noninstitutionalized South Korean population; it used a rolling sampling design involving a complex, stratified, multistage, probability cluster survey. A total of 37 753 subjects participated in the 2008–2011 KNHANES, and blood concentration of heavy metals was measured only in a selected subpopulation, a total of 8800 participants who can provide nationally representative estimates. The subpopulation for heavy metal measurements consisted of 10 randomly sampled participants in each district with stratification of age and sex from the annual KNHANES databases. Lead, cadmium, and mercury were measured each year (2008–2011); manganese was measured only in 2 years (2008 and 2009), and zinc was measured only in 1 year (2011). Each of the 5 data sets regarding the heavy metallic elements can produce nationally representative estimates as well. Measuring methods for heavy metal elements were as follows: Lead, cadmium, and manganese were measured by graphite furnace atomic absorption spectrometry (AAnalyst 600; Perkin-Elmer, Turku, Finland); mercury was measured by the gold amalgamation method (DMA-80; Milestone, Sorisole, Italy); and zinc was measured by an inductively coupled plasma/mass spectrometer (ICP-MS, PerkinElmer, Waltham, MA).

AMD was graded in subjects aged ≥40 years. Fundus photographs were taken with a nonmydriatic fundus camera (TRC-NW6S; Topcon, Tokyo, Japan). Patients were defined as having early AMD if the fundus photograph met 1 of 2 criteria: (1) the presence of soft, indistinct drusen or reticular drusen, or (2) the presence of hard or soft distinct drusen with pigmentary abnormalities (increased pigmentation or hypopigmentation of the retinal pigment epithelium [RPE]) in the absence of signs of late AMD. Late AMD included the presence of signs of wet AMD or geographic atrophy. Wet AMD was defined as retinal pigment epithelial detachment or serous detachment of the sensory retina, subretinal or sub-RPE hemorrhages, or subretinal fibrous scars. Geographic atrophy was defined as a circular discrete area (175 microns in diameter) of retinal depigmentation with visible choroidal vessels in the absence of signs of wet AMD. Each fundus photograph was graded at least twice using the grading protocol of the International Age-Related Maculopathy Epidemiological Study Group,[27] and all AMD grading was verified by the Epidemiologic Survey Committee of the Korean Ophthalmologic Society.[28] The details of the AMD grading, including the method of resolving discrepancies and interrater reliability, have been described previously.[26] Participants having both a gradable fundus photograph of ≥1 eye and data for blood concentrations of heavy metals were included in the present study.

Covariates analyzed in this study were defined and categorized as follows. The participants were divided into 4 age groups: 40 to 49, 50 to 59, 60 to 69, and ≥70 years. Smoking status was defined as never smoker (someone who has never smoked a cigarette), ex-smoker (someone who smoked in the past but does not smoke cigarettes currently), and current smoker (someone who smokes cigarettes currently). Occupation was categorized as white collar (managers, professionals, clerks, and service/sales workers), blue collar (agriculture, forestry, fishery workers, craft and related trade workers, plant and machine operators and assemblers, and simple labor), and inoccupation (unemployed, retired, students, and homemakers). Residence was categorized into urban and rural areas on the basis of the address of the participants. Household income status was divided into 2 groups: subjects with >50% household income and those with ≤50% household income according to the equalized gross annual household income. Hemoglobin was measured by an XE-2100D (Sysmex, Kobe, Japan), and participants with a hemoglobin concentration of <13 g/dl (in men) and <12 g/dl (in women) were designated as anemic. Body mass index (BMI) was estimated as the ratio of weight (in kilograms) to height (in square meters). Participants were categorized into 2 groups: those with BMI <25 kg/m^2 and those with BMI ≥25 kg/m^2.

Descriptive data were estimated for each of the 5 metallic elements, including weighted mean and standard error according to AMD grades and covariates, as stated. The KNHANES sample weight was then used for heavy metal surveys adjusted for oversampling, nonresponse, and the Korean population. The standard errors of estimates were calculated to account for the design of the