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Rare earth elements and hypertension risk among housewives: A pilot study in Shanxi Province, China☆

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A B S T R A C T

Studies have shown that residents living near rare earth mining areas have high concentrations of rare earth elements (REEs) in their hair. However, the adverse effects of REEs on human health have rarely been the focus of epidemiological studies. The goal of this study was to evaluate the relationship between REEs in hair and the risk of hypertension in housewives. We recruited 398 housewives in Shanxi Province, China, consisting of 163 women with hypertension (cases) and 235 healthy women without hypertension (controls). We analyzed 15 REEs (lanthanum (La), samarium (Sm), europium (Eu), gadolinium (Gd), terbium (Tb), dysprosium (Dy), holmium (Ho), erbium (Er), thulium (Tm), ytterbium (Yb), lutetium (Lu), Yttrium (Y), cerium (Ce), praseodymium (Pr), and neodymium (Nd)) and calcium (Ca) accumulated in housewives hair over a period of two years. The results revealed that, with the exception of Eu, concentrations of the REEs in hair were higher in the cases than in the controls. The univariate odds ratios (ORs) of the 14 REEs were >1, and four of the REEs (Dy, Tm, Yb, and Y) also had adjusted ORs > 1. The increasing dose-response trends of the four REEs further indicated the potential for increased hypertension risk. Moreover, the REEs were negatively correlated with Ca content in hair. These results might suggest an antagonistic effect of REEs on Ca in the human body. It was concluded that high intake of REEs might increase the risk of hypertension among housewives.

1. Introduction

Hypertension is caused by various factors, including genetics, aging, diet, obesity, and exposure to environmental pollutants (Rahman et al., 1999; Virdis et al., 2010; Zhao et al., 2011). Metals from food and drinking water are reported to be important contributors to regulating blood pressure (Rahman et al., 1999; Sacks et al., 1995; Witteman et al., 1989). Rare earth elements (REEs) include 15 active, mainly trivalent and f-electronic, metals with similar physicochemical properties. They are widely and increasingly used in industrial, medical, agricultural, and zoo-technical areas (Du and Graedel, 2011; USEPA, 2012). The REEs are regarded as emerging trace pollutants (Pagano et al., 2015; USEPA, 2012). He and Rambeck (2000) suggested that REEs are safe and inexpensive alternatives to enhance pig production, without significant effects on meat quality or product safety (He and Rambeck, 2000). Likewise, REE-based fertilizers have been demonstrated to enhance crop yield (Pang et al., 2002; USEPA, 2012).

There is growing evidence that REEs can accumulate in the human body through the food chain (Peng et al., 2003; Tong et al., 2004). Most REEs can easily accumulate in human bones and teeth, and are very difficult to excrete (Brown et al., 2004; Hirano and Suzuki, 1996). Animal studies have revealed that REEs can cause adverse effects by disturbing the balance of oxidative stress in the

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human body (Pagano et al., 2015; Zhao et al., 2013), which play a significant role in hypertension development (de Champlain et al., 2004). Results from these studies have indicated that the relationship between REEs and hypertension risk merits concern and further investigation.

We are unaware of epidemiological studies that have focused on the association between REEs and hypertension risk. However, antagonistic effects of REEs on other minerals have been observed. The biological activities of REEs might be related to the similarities of their ion radii and the coordination numbers with those of other essential elements, such as calcium (Ca), manganese (Mn), magnesium (Mg), iron (Fe), and zinc (Zn) (Pagano et al., 2015). These similarities might result in altered enzymatic activities or the substitution of essential metal ions from their ion-binding proteins. For example, REE ions could competitively replace Ca^{2+}, Fe^{2+}, Zn^{2+}, Mn^{2+}, and Mg^{2+} from their binding sites in proteins (Valcheva-Traykova et al., 2014). Deficiencies of Ca or Mg are associated with an increased prevalence of hypertension (Choi and Bae, 2015; Resnick, 1999; Sacks et al., 1995). Hence, a high intake of REEs might interfere with the ability of these essential nutritional ions to regulate blood pressure.

The factors that influence hypertension should be thoroughly assessed from a long-term perspective, because it is a chronic disease. It was reported that REE concentrations of residents' hair could be used to assess their exposure level (Wei et al., 2013). Likewise, special sections of hair are expected to indicate the exposure levels, assuming a constant hair growth rate. Moreover, hair samples could be noninvasively collected and stored at room temperature at low cost. Therefore, hair sampling has been used to assess long-term intake levels of various metals (Pereira et al., 2004; Wang et al., 2009).

We posed the hypothesis that REEs in human hair are associated with risk of hypertension. Housewives in Shanxi Province, China have very consistent living habits, due to their local culture. We conducted a pilot study with two goals: 1) to investigate the hair concentrations of REEs among housewives in Shanxi Province, China and 2) to determine an association between REEs in hair and the risk of hypertension.

2. Materials and methods

2.1. Study population

This study was conducted in the Pingding County Hospital in Shanxi Province of north China. Details regarding the recruitment of study participants were described elsewhere (Wang et al., 2016). The women were invited to participate in the study if they satisfied the following criteria: (1) they were born in Pingding County, rather than immigrating to the county, (2) they were at least 30 years old, and (3) there were no significant changes in their living conditions over the last 10 years. The questionnaires requested information on age, occupation (farmer or non-farmer), education (primary or lower, junior high, high school or junior college, or above junior college), and active or passive smoking (yes/no). The definition of passive smoking is not smoking, but remaining in a tobacco (*Nicotiana tabacum* L.) smoking environment for more than 30 min.

Hair samples were collected from all the women. The hair was cut from the back of the head, and as close as possible to the scalp, using stainless steel scissors. The samples were then sealed separately in labeled polyethylene zip-lock bags, which were not opened until analysis in the laboratory. A total of 405 housewives were recruited between Aug 2012 and May 2013, and hair samples (>8 cm length) from 398 housewives were included in the study.

Physical examinations, including measurements of height, weight, blood pressure, and heart rate, were performed by county physicians according to standard protocols. Blood pressure was measured three times by experienced physicians, using a cuff with a standard mercury sphygmomanometer on the right arm at 2-min intervals, following a rest period of at least 5 min. Hypertension was defined as a systolic reading of at least 140 mm Hg or a diastolic reading of at least 90 mm Hg, or a previous diagnosis of hypertension requiring treatment with antihypertensive drugs. The study protocol was approved by the institutional review board of Peking University, and signed consent was obtained from all subjects.

2.2. Hair metal analysis

Hair samples close to 24 cm long represented two-year exposure to REEs, assuming a constant hair growth rate of 1 cm per month. Hair was cut into 1-cm segments and 80 mg of hair was weighed and placed in a 5-mL Teflon® tube. The detailed hair wash method was described in our previous study (Li et al., 2016). Briefly, hair samples and blank vials were washed by 1 mL Triton X-100 (Sigma-Aldrich, USA) (vortex for 5 min), 1 time; 1 mL deionized water (vortex for 5 min), 3 times; and 1 mL acetone (J.T. Baker®, USA) (vortex for 5 min), 3 times. Hair samples were digested with 1 mL of HNO_3 in a microwave oven for 50 min. The concentrations of REEs were measured using an inductively coupled plasma-mass spectrometer (ICP-MS; ELAN DRC II, PerkinElmer, USA).

The REEs included in this study were lanthanum (La), samarium (Sm), europium (Eu), gadolinium (Gd), terbium (Tb), dysprosium (Dy), holmium (Ho), erbium (Er), thulium (Tm), ytterbium (Yb), lutetium (Lu), Yttrium (Y), cerium (Ce), praseodymium (Pr), and neodymium (Nd). Hair Ca was measured using an inductively coupled plasma-atomic emission spectrometer (ICP-AES, Thermo iCAP 6000SERIES, Thermo Fisher Scientific, USA). The limits of detection (LODs) were 0.006 ng/mL (La), 0.0004 (Ce), 0.0001 (Pr), 0.003 (Nd), 0.0004 (Sm), 0.001 (Eu), 0.002 (Gd), 0.0004 (Tb), 0.001 (Dy), 0.002 (Ho), 0.012 (Er), 0.007 (Tm), 0.001 (Yb), and 0.0001 (Lu). The measured and referred concentrations of the 15 REEs for the standard hair references (GBW09101a, purchased from the National Standard Material Center in China) were used for quality control as shown in Table S1 in Supporting Information (SI). It was suggested that the measured concentrations were close to the referred measurements. Three procedural blanks and one reagent blank were included with each batch of hair samples. Quantitative analysis was conducted in the Central Laboratory of Biological Elements in the Peking University Health Science Center, and the protocol was qualified by the China Metrology Accreditation (CMA) system.

2.3. Statistical analysis

The REE concentrations of each hair sample were calculated by subtracting the means of corresponding blanks from the measured concentrations. If a concentration was lower than that of the blank, it was considered to be zero. Samples with concentrations below the LOD were also assumed to have a value of zero.

The concentrations of the fifteen REEs in hair were not normally distributed, so medians with interquartile ranges were used to describe these skewed distributions. Differences between the cases and controls, in terms of concentrations of metals, were tested using the Mann-Whitney U test. The cases and controls were compared based on demographic information, using the Pearson's χ^2 test. The quartiles of REE concentrations of all subjects were used as cutoff values. The risks of hypertension associated with hair REE concentrations were estimated using odds ratios (ORs) with 95% confidence internals, based on a logistic regression model. Statistical analyses were performed using SPSS 16.0 software (SPSS Inc.). A two-tailed t-test with a p value (<0.05) was considered to be