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Blood Mercury Can Be a Factor of Elevated Serum Ferritin: Analysis of Korea National Health and Nutrition Examination Survey (KNHANES 2008–2012)

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Abstract Serum ferritin as well as blood mercury are reported to be associated with chronic inflammation. However, the relation between serum ferritin and blood mercury has not yet been established. We utilized the Korea National Health and Nutrition Examination Survey (KNHANES, 2008–2012) 10,977 subjects (5433 males and 5544 females). To evaluate the association of serum ferritin and blood mercury cross-sectionally, complex sample analysis was conducted after adjustment for the relevant variables. Serum concentrations of ferritin and blood mercury were higher in males than in females (115.7±1.7 vs. 40.9±0.7 ng/mL and 5.0±0.1 vs. 3.6±0.1 μg/L, respectively). Serum ferritin and blood mercury concentrations had significant correlations in both genders after adjustment (r=0.062, P<0.001 in males; r=0.055, P<0.001 in females). The analysis of covariance (ANCOVA) test showed significantly higher serum ferritin according to the tertile of blood mercury (P=0.007) in males. The adjusted odds ratio of having the highest tertile of serum ferritin in the top tertile of blood mercury in males was 1.52 (95 % confidence interval (CI), 1.05–2.21). Thus, the current study indicates that blood mercury concentration can be a factor for the elevated serum ferritin concentration.

Keywords Ferritin · Mercury · Inflammation · Korean

Introduction

Ferritin, an iron storage protein, can be a biomarker for iron status and low-grade inflammation [1]. Elevated serum ferritin concentration can relate to a variety of systemic conditions including infection, neoplasm, and chronic or acute inflammation. Without iron overload, elevated serum ferritin levels can cause the increase in ferritin synthesis from acquired or genetic disorders or increased release of ferritin from damaged cells [2]. Therefore, patients with a history of chronic alcohol ingestion, features of metabolic syndrome (obesity, insulin resistance or diabetes, dyslipidemia, and hypertension), chronic inflammatory conditions, renal insufficiency, malignancy, or marrow failure often present with hyperferritinemia [3]. The exact pathophysiology of many chronic diseases, such as hypertension, diabetes, and metabolic syndrome, is unclear. Recent studies have shown that a low-grade chronic inflammation is considered to be one possible cause of such chronic disease [4]. Interestingly, it has been reported that serum ferritin concentration is correlated with cardiovascular disease, diabetes, metabolic syndrome, nonalcoholic fatty liver, and autoimmune diseases [5–8]. A similar correlation between serum ferritin concentration and such diseases has also been found in the Korean population [9–12].

Mercury, a heavy metal which can be harmful to health, can be exposed by various environmental sources. Experimental studies strongly suggest an association between chronic exposure to methylmercury and an alteration of nitric oxide (NO) synthesis [13]. Consequently, chronic exposure to methylmercury is associated with an increased risk of cardiovascular diseases in some populations [14]. In addition, mercury exposure can lead to chronic inflammatory diseases, such as diabetes, obesity, hepatitis, autoimmune disease [15]. Furthermore, we have previously reported a synergistic relationship between serum ferritin and blood mercury and their association with the prevalence of hypertension [16].

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There has been no study on the relationship between serum ferritin and blood mercury concentration. Therefore, this cross-sectional study determines the association between serum ferritin concentration and blood mercury concentration in a large population-based set of Korean data.

Materials and Methods

Study Data

The Korea National Health and Nutrition Examination Survey (KNHANES) has been conducted periodically by the Korea Centers for Disease Control and Prevention and provides comprehensive information on health status, health behavior, nutritional status, and socio-demographics in 600 national districts in Korea. For this cross-sectional study, data were used from the fourth and fifth (2008–2012) KNHANES containing blood mercury and ferritin concentrations. Data on demographic characteristics, diet, and health-related variables were collected through personal interviews and self-administered questionnaires. Physical examinations, blood sampling, and urine sampling were carried out at a mobile examination center. From an initial total of 45,811 men and women, 34,652 people were excluded due to missing data (which included serum mercury, 24,641 subjects, and ferritin data, 10,011 subjects). One hundred and sixty-three subjects who had medical illnesses (current cancer, chronic renal failure, and azotemia; serum creatinine >1.4 mg/dL) were also excluded. After that, 19 subjects who had blood mercury levels above 50 μg/L and ferritin levels above 1000 ng/mL were further excluded. Ultimately, the analysis of this study was conducted with the data of 10,977 subjects (5433 males and 5544 females), as shown in Fig. 1. Even though a large number of subjects were excluded according to our exclusion criteria, the qualified data were still representative of the Korean population considering their relatively even distribution (17.9 % in 2008, 17.8 % in 2009, 21.1 % in 2010, 21.5 % in 2011, and 21.7 % in 2012). All participants provided written informed consent before participating in the examination.

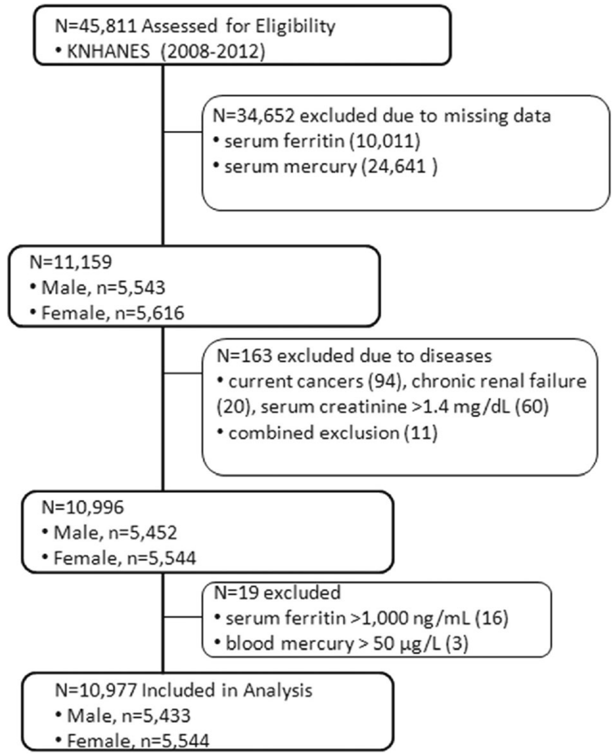

Fig. 1 Selection of study data

Measurements

Blood samples were taken after an eight-hour fast year-round. The total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDLC), and creatinine concentrations were measured using a Hitachi 7600-110 chemistry analyzer (Hitachi, Tokyo, Japan). Fasting blood sugar (FBS) was measured using an automated analyzer with an enzymatic assay (Pureauto S GLU; Daiichi, Tokyo, Japan). Serum ferritin was measured with a chemiluminescent immunoassay (ADVIA Centaur, Siemens), and the inter-assay coefficients of variation (CV) were between 0.4 and 6.9 %. Blood mercury in the whole blood was measured with the gold-amalgam method (DMA-80, Milestone, Italy), and the inter-assay coefficients of variation (CV) were 0.47–6.08 %. Body mass index (BMI) was calculated as the ratio of weight/height^2 (kg/m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the right arm using a standard mercury sphygmomanometer (Baumanometer; Baum, Copiague, NY). We used a self-administered questionnaire to collect information about hypertension, type 2 diabetes, smoking status, alcohol intake, job, moderate physical activity, and total energy intake. In women, the questionnaire further included information about menopausal status, hormone replacement therapy, and oral contraceptive use, which we used to make proper adjustments. Current smokers were defined as those who had smoked more than five packs of cigarettes during their life and were currently smoking, past smokers were smokers who had smoked in the past but had quit, and nonsmokers had no history of smoking. Regular alcohol drinkers were defined as those who are current drinkers or drinking at least equal to or more than once a month, and others were all deemed nondrinkers.

Statistical Analysis

The complex sample analysis was used for the KNHANES data to weight all values following the guidance of statistics from the Korea Centers for Disease Control and Prevention.

Due to the skewed data of blood mercury concentration, we ran the blood concentration into a log transformation and compared the results. Partial correlation analysis is a brief method to evaluate the relation of serum ferritin concentration and blood mercury concentration. Firstly, the partial correlation analysis was run in both genders after adjusting for age, BMI, job, alcohol intake, smoking, moderate physical activity, and total calorie intake. In women, menopause, hormone replacement therapy, and oral contraceptive use were also included as adjustment factors. To compare the concentration of serum ferritin and blood mercury, blood mercury concentration was stratified into tertiles. After this process, we evaluated serum ferritin concentrations (as a dependent variable) and blood mercury tertiles (as fixed factors) by the analysis of covariance (ANCOVA) test after adjustment for age, BMI, job, alcohol intake, smoking status, moderate physical activity, daily total energy intake, and serum iron concentration. Females were further adjusted for menopause, hormone replacement therapy, and oral contraceptive intake. Finally, serum ferritin concentrations were further stratified into tertiles to determine the association of serum ferritin with blood mercury. The odds ratios of having the highest tertile of ferritin by serum mercury tertile were calculated in males using logistic regression analysis after adjustments for age, body mass index, job, moderate physical activity, smoking status, alcohol intake, total calorie intake, and serum iron concentration. All *P* values were used to assess the significance of all analysis, and *P* values <0.05 were considered significant. Data were analyzed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA).

Results

General characteristics of all study subjects are presented in Table 1. A total of 10,977 subjects, including 5433 males and 5544 females, were analyzed in this cross-sectional study. The mean ages of the males and females were 37.9 and 38.5 years old, respectively. Compared with females, the serum concentrations of ferritin and blood mercury were significantly higher in males (115.7±1.7 vs. 40.9±0.7 ng/mL and 5.0±0.1 vs. 3.6±0.1 μg/L, respectively).

By partial correlation analysis, serum ferritin and blood mercury concentrations showed a significant correlation in both genders after adjustment (r=0.062, P<0.001 in males; r=0.055, P<0.001 in females) (Table 2).

Table 3 showed the relation between serum ferritin concentration and blood mercury tertile. With the increasing tertile of mercury, serum ferritin concentrations were significantly higher in the third tertile than those in the first tertile in males. When comparing the odds ratio of having the highest tertile of ferritin by the tertile of blood mercury, the adjusted odds ratio (OR) in the top tertile of blood mercury in males was 1.52 (95 % confidence interval (CI), 1.05–2.21) (Table 4).

Table 1 General characteristics of the study subjects (n=10,977)

Variable	Males (n=5433)	Females (n=5544)
Age (year)	37.9 (0.2)	38.5 (0.2)
BMI (kg/m^2)	23.9 (0.1)	22.7 (0.1)
Total cholesterol (mg/dL)	183.5 (0.7)	183.6 (0.6)
HDL cholesterol (mg/dL)	49.8 (0.3)	56.2 (0.3)
Triglycerides (mg/dL)	145.4 (2.1)	107.0 (1.5)
FBS (mg/dL)	96.3 (0.4)	92.9 (0.3)
Hb (mg/dL)	15.3 (0.1)	13.0 (0.1)
Fe (μg/dL)	129.3 (1.2)	100.3 (0.9)
Ferritin (ng/mL)	115.7 (1.7)	40.9 (0.7)
Mercury (μg/L)	5.0 (0.1)	3.6 (0.1)
Smoking, *n* (%)		
Yes	2149 (44.9)	289 (5.9)
No	2634 (55.1)	4646 (94.1)
Alcohol		
Yes	3659 (74.4)	2072 (41.0)
No	1262 (25.6)	2983 (59.0)

Data are expressed as mean (standard error) after data weighting

BMI body mass index, *HDL* high-density lipoprotein, *FBS* fasting blood glucose, *Hb* hemoglobin, *Fe* serum iron concentration

Discussion and Conclusion

This cross-sectional study indicated that there was a significant correlation between serum ferritin and blood mercury concentration in both genders after adjusting for the relevant variables. Specifically, the serum ferritin concentration and the odds ratio of having the highest tertile of serum ferritin concentration according to blood mercury tertile were significantly higher in the third tertile than in the first tertile of mercury in males.

In previous studies, the serum ferritin level was positively associated with the prevalence of metabolic syndrome, high TG, glucose level [1], and diabetes mellitus [9]. Kim et al.

Table 2 Partial correlations between serum ferritin and blood mercury

	Males	Females
r	0.062	0.055
P	<0.001	<0.001

All values represent the Pearson partial correlation coefficient (r) after adjustment for age, body mass index, job, alcohol intake, smoking, moderate physical activity, and total calorie intake. In women, we further adjusted for menopause, hormone replacement therapy, and oral contraceptive use. Blood mercury concentration was log transformed due to the skewed data

Table 3 Serum ferritin concentrations by blood mercury tertile

	Males (n=5433)				Females (n=5544)			
	T1 (0.36–3.24)	T2 (3.25–5.66)	T3 (5.67–43.24)	P	T1 (0.37–2.42)	T2 (2.43–3.91)	T3 (3.92–38.50)	P
Ferritin (ng/mL)	116.0±3.3	126.2±4.1	134.8±5.1[a]	0.007	39.6±1.6	42.0±1.2	44.4±1.6	0.145

Data represent mean±standard error. P values are P for trend from ANCOVA test after adjustment with age, BMI, job, alcohol intake, smoking status, moderate physical activity, daily total energy intake, and serum iron concentration; in females, we further adjusted for menopause, hormone replacement therapy, and oral contraceptive intake. Blood mercury tertile was log-transformed blood mercury concentration

[a] Represents $P<0.05$ in the comparison between T1 and T3

reported that elevated serum ferritin levels were associated with insulin resistance, type 2 DM, impaired fasting glucose (IFG), and metabolic syndrome in Korean men, but only associated with IFG in Korean women [10]. In addition, elevated serum ferritin concentration was found to be a predictive factor for obesity during a 5-year follow-up in Korean men [12] and an independent marker of early coronary artery atherosclerosis in Koreans [5].

Chronic exposure to mercury can induce various health outcomes, such as chronic inflammation, and cardiovascular diseases. The association between the urinary and blood mercury concentration and cardiovascular mortality in workers of mercury mines and mills [17] and the risk of sudden cardiac death has been reported [18]. In addition, such association between blood mercury and chronic inflammation was also found to be relevant in children, in which elevated blood mercury was significantly associated with blunted diurnal cortisol level and elevated acute phase proteins, suggesting systemic inflammation [19]. Interestingly, the relationship between blood mercury concentration and obesity has been reported in elderly Koreans. You et al. determined that blood mercury concentration is related to the waist-to-hip ratio, which is a central obesity index, in Korean men [20]. On the other hand, several studies have shown that there was no significant association between the level of mercury and chronic diseases, such as cardiovascular diseases [21] and hypertension [22, 23]. It is interesting to note that the authors of these studies concluded that their results were due to the confounding factors such as lifestyle, diet, and exercise that could influence the clinically adverse effect of mercury on human health.

Table 4 Odds ratio of having the highest tertile of serum ferritin (123.7–993.3 ng/mL) by blood mercury tertile in males

Tertile of blood mercury	OR (95 % CI)
T1	1 (reference)
T2	1.33 (0.97–1.82)
T3	1.52 (1.05–2.21)

Data are represents odds ratio with 95 % confidence interval by logistic regression analysis after adjustment for age, body mass index, job, moderate physical activity, smoking status, alcohol intake, total calorie intake, and serum iron concentration. Blood mercury tertile was log-transformed blood mercury concentration

OR odds ratio, *CI* confidence interval

Until now, there has been little research regarding the elevated serum ferritin concentration in human. Although the evidence is not sufficient, the current study indicates that elevated blood mercury concentration from chronic exposure can be related with the higher serum ferritin concentration. Previous studies showed that serum ferritin was a biomarker of chronic inflammation and might be a pathophysiologic factor for many chronic diseases such as hypertension, diabetes, and metabolic syndrome. In addition, chronic exposure to mercury has been suggested as a cause of chronic inflammation in human health. The current study is in agreement with such previous studies. The association seems to be due to the direct effect of chronic mercury intoxication or indirect effect of the accumulation of mercury, which induces inflammation in the human body. We only had the positive correlation between serum ferritin level and blood mercury tertile in men in our study. It is probably due to the lower and narrowest concentrations of serum ferritin and blood mercury in females than in males in our study. Rushton et al. explained that the reference range of serum ferritin for females of reproductive ages was lower than that for equivalently aged males [24]. There are potential limitations in this study. First, due to the nature of cross-sectional study, the causality between elevated serum ferritin and blood mercury concentrations cannot be explained in this study design. Second, the skewed pattern of serum ferritin and blood mercury may not be adequate to show a dose-dependent relationship, even though we compared the results after log transformation, which may not show a dose-dependent relationship. Third, this study's results originate from a single ethnicity. Fourth, quantitative adjustment for mercury exposure such as fish consumption, environmental exposure, dental amalgam, or occupation was not possible. Despite of these unavoidable limitations, we believe this study is meaningful in that it was the first study evaluating the relationship of serum ferritin and the blood mercury level, which are important factors in chronic inflammations in human.

In conclusion, elevated blood mercury concentration is associated with the higher serum ferritin in Korean men and women and that such association was found to be more prominent in men. Further study is needed to clarify the cause of such exact relation of blood mercury with serum ferritin.

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