International Journal of Hygiene and Environmental Health 217 (2014) 465–472

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Mercury exposure and omega-3 fatty acid intake in relation to renal function in the US population

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ARTICLE INFO

Article history:
Received 10 May 2013
Received in revised form
13 September 2013
Accepted 16 September 2013

Keywords:
Mercury
Renal function
Omega-3 fatty acids

ABSTRACT

It remains unclear whether exposure to low-level mercury (Hg) is associated with impaired renal function, and whether omega-3 fatty acid (FA) intake could affect the association of interest. The current study examined the association of blood Hg and omega-3 FAs with renal function using data from 1046 subjects aged 40 or above from the 2003–2004 National Health and Nutrition Examination Survey. Kidney function was assessed by estimated glomerular filtration rate (eGFR) and occurrence of albuminuria. Logistic regression analyses were applied to assess the association of interest with confounding variable adjustment. The analyses indicated that blood Hg was associated with reduced eGFR (<60 mL/min/1.73 m^2) in a dose-response fashion ($p < 0.05$). The association was particularly apparent with adjustment for blood omega-3 FA levels. The adjusted odds ratio for having reduced eGFR was 2.94 (95% confidence interval = 1.04–8.33) in the highest tertile of blood Hg as compared with the lowest tertile. There was no significant association between Hg exposure and albuminuria. In summary, this study demonstrates that Hg exposure is associated with increased odds of having lower GFR in the US population aged 40 or above. A statistical association with albuminuria was not apparent. We also observed that omega-3 FA intake may play a preventive role in Hg-induced nephrotoxicity. Additional studies are warranted to determine the sources, exposure routes, and forms of Hg most responsible for observed associations.

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Introduction

Mercury (Hg) is a ubiquitous toxic metal that enters the environment as a result of natural and anthropogenic activities such as fossil fuel combustion and mining (U.S. EPA, 1999). Humans are exposed to various forms of Hg (elemental, inorganic, organic or methyl Hg) through different pathways (U.S. ATSDR, 1999). Examples include inhalation of Hg vapor from atmospheric sources or from dental amalgam fillings, and, most importantly, ingestion of fish and shellfish contaminated with Hg, primarily methyl Hg (U.S. ATSDR, 1999; Mahaffey et al., 2009). The health effects of dietary Hg have been studied most extensively with respect to neurodevelopment and cardiovascular endpoints (Grandjean et al., 1999; Guallar et al., 2002; Hallgren et al., 2001; Mozaffarian et al., 2011; Myers et al., 2009; Oken et al., 2008). The epidemiologic evidence is mixed in these cases, in part because of differences in relative Hg and omega-3 fatty acids (FAs) in the available dietary fish. The anti-inflammatory activity of the polyunsaturated omega-3 FAs, eicosapentaenoic acid (EPA, C20:5*n*-3) and docosahexaenoic acid (DHA, C22:6*n*-3), may functionally neutralize the Hg-induced pro-inflammatory activity. These specific fish oils promote cardiovascular health and brain development, and thus potentially could ameliorate Hg toxicity (Fassett et al., 2010; Li et al., 2005; Simopoulos, 2002). As a result, the dietary intake of omega-3 FAs and other anti-inflammatory and protective agents relative to the amount of methyl Hg ingestion may determine the net risk or benefit from the diet (Ginsberg and Toal, 2009; Mozaffarian and Rimm, 2006).

Of note, methyl Hg is distributed to various organs via blood circulation, and then is mainly excreted from feces (conjugated forms of methyl Hg) and urine (inorganic Hg) (U.S. ATSDR, 1999; Clarkson et al., 2003; Nordberg, 2007). The kidney may be an important target for Hg toxicity due to the concentration of Hg in the kidney as part of its distribution and excretion. In fact, experimental animal and human occupational studies support an effect of Hg on the kidney (Hazelhoff et al., 2012; Jin et al., 2009; Langworth et al., 1992; Stacchiotti et al., 2009; Yasutake et al., 1997). For example, chlorakali plant workers exposed to inorganic Hg exhibited higher urinary excretion of N-acetyl-beta-glucosaminidase suggestive of renal tubular damage (Langworth et al., 1992), with various case reports linking occupational Hg exposure with both tubular and glomerular damage (Miller et al., 2013). Rat dietary studies have

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1438-4639/$ – see front matter. Published by Elsevier GmbH.
http://dx.doi.org/10.1016/j.ijheh.2013.09.004

found that methyl Hg can produce tubular damage from short-term exposure (Jin et al., 2009) or both tubular and glomerular damage from chronic exposure (Yasutake et al., 1997). In vitro studies of a proximal tubule cell line incubated with inorganic Hg found oxidative stress, the induction of heat shock proteins and metallothionein, as well as the development of a pathological response involving mitochondrial damage, apoptosis, and necrosis (Stacchiotti et al., 2009). While in vitro, animal and limited human evidence support an effect of Hg on the kidney, it remains unclear whether environmental exposure to low-level Hg is associated with impaired renal function, as well as whether omega-3 intake could affect this association.

Thus, the objective of the current analysis was to test the hypothesis that both Hg exposure and omega-3 FAs, as measured by their levels in blood, are correlated with the occurrence of impaired renal function in the U.S. population. The current study used the data from a cohort of U.S. adults available in a national database, the National Health and Nutrition Examination Survey (NHANES), 2003–2004. This is the only NHANES cycle in which both Hg and omega-3 biomarkers are available in blood. By analyzing the relationship of Hg exposure and omega-3 FA intake with kidney function, this study explores the possibility that at levels commonly found in the US population, Hg may be associated with impaired kidney function, and that omega-3 FAs may have a preventive role in such effect.

Materials and methods

Study design and population

NHANES was conducted by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention to collect data on the health and nutritional status of a representative sample of the non-institutionalized civilian US population by using a multistage, stratified sampling design (U.S. CDC, 2005a). The protocol was approved by the National Center for Health Statistics Institutional Review Board, and all subjects provided written informed consent. The subject selection criteria in the current analysis were: (1) subject was a male or female aged 40 years or older; (2) subject had valid measurement of blood Hg and omega-3 FAs; (3) subject had a body mass index (BMI) $\geq 18.5\,kg/m^2$ at the time of the survey examination. Of 1161 subjects who met inclusion criteria, 115 subjects were excluded because of missing information for any covariate used in the analyses (e.g., age or race). This resulted in a final sample of 1046 subjects.

Measurement of blood Hg and omega-3 FAs

Detailed sample collection and laboratory analysis was reported in the NHANES Laboratory/Medical Technologists Procedures Manual (U.S. CDC, 2005b). In brief, sample collection in the 1046 subjects was in the form of a fasting plasma glucose sample (fasting ≥ 8 h), stored at $-70\,^{\circ}C$ until analyzed. Total Hg in whole blood was measured by inductively coupled plasma mass spectrometry (PerkinElmer ELAN 6100 ICP-DRC-MS) in NHANES 2003–2004 (U.S. CDC, 2005b). The limits of detection (LOD) were 0.14–0.2 and 0.43 μg/L for total and inorganic Hg, respectively. Approximately 11% of total Hg and 72% of inorganic Hg detectable measurements are below LOD and thus were assigned with a fill value, which were calculated as LOD divided by the square root of 2. Electron capture negative-ion mass spectrometry was used to assess the plasma level of omega-3 FAs, as the sum of eicosapentaenoic acid and docosahexaenoic acid levels based on previously published methods (U.S. CDC, 2011; Lagerstedt et al., 2001). The LOD was 0.1 μmol/L for both eicosapentaenoic and docosahexaenoic acid levels in plasma (approximately 99% of measurements > LOD for both).

Assessment of renal function

Metal-induced damage to the kidney as well as aging or disease-related loss in kidney function are tracked by a variety of functional indices including protein leakage into urine (e.g., albuminuria) and decreased glomerular filtration rate (GFR) (Levey et al., 2009). For instance, a persistently reduced GFR ($<60\,mL/min/1.73\,m^2$) signifies chronic kidney disease (CKD) (National Kidney Foundation, 2002). As a result, the reduced GFR was defined as GFR $<60\,mL/min/1.73\,m^2$ in the current study. Detailed sample collection and laboratory analysis was reported elsewhere (U.S. CDC, 2005c; Chavers et al., 1984). GFR for each subject in NHANES was estimated from their serum creatinine, age and gender as described below. Urinary albumin is an indicator of protein leakage from the kidney and thus renal damage. In brief, urine creatinine was analyzed with a CX3 analyzer using the Jaffé reaction and urinary albumin level was assessed by a solid-phase fluorescent immunoassay. The fluorescent immunoassay is a non-competitive, double-antibody method for the quantitative determination of human albumin in urine (Chavers et al., 1984). The CKD Epidemiology Collaboration (CKD-EPI) formula was then used to estimating GFR (Levey et al., 2009): CKD-EPI GFR = 141 min $(Scr/\kappa,1)^{\alpha} \times \max\ (Scr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if African American], where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. The urinary albumin–creatinine ratio (UACR in mg/mmol) was measured in single spot urine sample for each subject. The presence of albuminuria was defined as UACR >2.5 mg/mmol in men and >3.5 mg/mmol in women (Coresh et al., 2007).

Collection of demographic and clinical data

Self-reported demographic characteristics including age, gender, BMI, race/ethnicity, and cigarette smoking status were obtained during the survey interview. BMI was calculated from measured height and weight, and categorized as three categories: 18.5–24.9, 25.0–29.9, and $\geq 30\,kg/m^2$. Blood cotinine was measured by an isotope dilution-high performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry with a LOD of 0.015 ng/mL. Diabetes mellitus was accessed by self-reported diagnosis of diabetes, the use of diabetic medications (insulin or oral agents), a nonfasting plasma glucose ≥ 200 mg/dL, or a fasting plasma glucose ≥ 126 mg/dL. Hypertension was defined as an average systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, a physician's diagnosis or the use of anti-hypertensive medication (Mancia and Grassi, 2005).

Statistical analyses

Total blood Hg was analyzed both as a categorical variable based on its weighted distribution (<33th percentile, 33–66th percentile, >66th percentile) and as a continuous variable. We assessed group differences with the analysis of variance (ANOVA) for continuous variables and the Cochran-Mantel-Haenszel chi-square test for categorical variables across total blood Hg categories. Logarithmic transformations were performed to normalize the continuous data whenever necessary. We used simple and multiple logistic regression models to investigate crude and adjusted relationships between blood Hg and renal functions. Growing evidence suggests diabetes and hypertension are two leading causes of kidney disease