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Mercury, eicosapentanoic acid and docosahexaenoic acid demonstrate limited effect on plasma paraoxonase-1 activity and blood pressure among avid seafood consumers in the Long Island Study of Seafood Consumption, NY, USA☆,☆☆

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ABSTRACT

Background and aim: Moderate fish consumption is recommended for prevention of coronary heart disease (CHD) as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have known beneficial effects on risk factors such as reducing blood pressure (BP) and increasing paraoxonase-1 (PON-1) activity. However concomitant methylmercury (MeHg) exposure from fish consumption may mitigate these benefits and the net effect on BP and PON-1 activity has not been extensively studied in western populations consuming diverse seafood types. We studied the correlation between EPA, DHA and Hg levels with BP and PON-1 activity in a population of avid seafood consumers.

Methods: Two hundred and eighty-eight avid seafood consumers from Long Island, NY had blood samples drawn for total blood mercury (THg), plasma EPA and DHA levels, and plasma PON-1 activity. Average systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP) were measured.

Results: Subjects' mean EPA + DHA was 4.9% total fatty acids, mean THg was 7.6mcg/L. Mean SBP was 122.5 mmHg, mean DBP 70.3 mmHg, mean PP 52.2 mmHg and mean PON-1 activity 421.2U/L. THg was not associated with any of the BP measures in adjusted linear regression models; EPA + DHA was significantly inversely associated with PP ($p = 0.02$). THg was associated with a significant increase in PON-1 activity ($p = 0.04$), while EPA + DHA was associated with a significant decrease in PON-1 activity ($p = 0.007$); although the size of the effects was small.

Conclusions: Our findings suggest blood THg and serum DHA + EPA levels have limited relationship to BP and PON-1 activity, and may not be important modulators of these known CHD risk factors in this population of avid seafood consumers.

1. Introduction

Moderate fish consumption, especially fish rich in omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), is recommended by the American Heart Association (AHA) (Kris-Etherton et al., 2002) because of benefits for coronary heart disease (CHD), peripheral vascular disease prevention, and positive effects on risk factors such as blood pressure (BP) (Buscemi et al., 2013; Kris-Etherton et al., 2002). Serum paraoxonase-1 (PON-1) is an enzyme associated with the high density lipoprotein (HDL) particle (Aviram, 2004) and low levels of activity are a risk factor for coronaryevents (Mackness et al., 2003). Dietary supplementation

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of omega-3 fatty acids has been shown to increase PON-1 activity (Kouchak et al., 2011; Mohammadi and Rafraf, 2012) suggesting increased fish consumption may also impact this CHD risk factor. At least one study has shown Hg from seafood consumption is associated with decreased PON-1 activity (Ayotte et al., 2011), but other studies showed decreased PON-1 activity only for a specific genetic variant of PON-1 (Drescher et al., 2014).

Increased rates of seafood consumption are not always associated with decreased risk for CHD (Hooper et al., 2004; Kris-Etherton et al., 2002; Virtanen et al., 2004), potentially because of exposure to contaminants such as methylmercury (MeHg) found in fish (Rissanen et al., 2000). Specifically increased BP, an important risk factor for CHD, has been positively correlated with mercury (Hg) exposure attributed to seafood consumption (Valera et al., 2008, 2009). However correlations between blood Hg and BP are inconsistent across studies (Nielsen et al., 2012; Valera et al., 2011a,b, 2013). A large study sampled from the general US population did not find any evidence of clinically relevant adverse effects of Hg in toenail clippings on incidence of stroke, heart disease or overall CVD (Mozaffarian et al., 2011).

Given the conflicting evidence on the importance of EPA, DHA and Hg levels from seafood consumption on overall CHD risk, we aimed to investigate the relationships between these variables and the specific CHD risk factors BP and PON-1 activity. We studied avid seafood consumers from a suburban population in the coastal, northeastern United States known to be at increased risk for Hg exposure from fish (Mahaffey et al., 2009), whose consumption pattern generally followed the AHA fish consumption guidelines of at least two fish meals per week.

2. Methods

2.1. Recruitment

We solicited individuals who self-identified as avid seafood consumers from the Long Island, NY area using advertisements and in-person recruitment activities targeted to high-fish consumers at local fishing piers, community sites, on the university campus and in the local newspaper. We recruited adult, avid seafood consumers predicted to be at risk for elevated Hg exposure due to regular fish consumption (weekly or daily, depending on seafood type) to ensure power to study possible mercury-related effects. Study participants completed an online screening survey and their Hg exposure was assessed using the seafood mercury concentrations from our Seafood Hg Database (Karimi et al., 2012). A total of 996 individuals completed the screening questionnaire, 746 were deemed eligible for the study and of those, 288 participants enrolled in the study and completed a clinical appointment at the Clinical Research Core at Stony Brook University Hospital. Two individuals did not complete the study, and three of the participants did not have records of PON-1 measure, therefore the sample size is 286 in the BP analysis, and 283 in the analysis of PON-1. At the appointment, trained nurses obtained written consent and collected questionnaires, morphometric data, a list of current medicines being taken, and blood specimens. Participants answered questions about demographics, smoking history, medical history, omega-3 supplement use, and seafood intake patterns, among other factors. The study was approved by Stony Brook University's Institutional Review Board for human subjects (IRB#185935-19).

2.2. Measures

Participants had plasma omega-3 polyunsaturated fatty acid measures EPA and DHA, saturated fatty acids, polyunsaturated fatty acids, total cholesterol, triglycerides, and GSSG measured. Fasting blood specimens for fatty acid analysis were collected in 3 mL vacutainer tubes with K_2EDTA (BD Medical). Blood was centrifuged within 45 min of collection, and an aliquot of plasma was removed and stored at −80 °C. Plasma specimens were sent to Lipid Analytical Lab, University of Guelph, Canada for analysis. Fatty acid concentrations in the phospholipid fraction were analyzed and the EPA and DHA percentage of total fatty acids were calculated. Triglycerides and cholesterol were measured by the university hospital's laboratory. Samples for blood total mercury (THg) and Se were collected in BD trace element blood collection tubes. Blood THg was used to estimate exposure to MeHg (e.g., Ayotte et al., 2011; Valera et al., 2008) because nearly all of the mercury is in the methylated form for the fish consuming population (Mahaffey et al., 2009). Metals analyses are described in detail elsewhere (Karimi et al., 2014a, 2014b) but briefly described here. Metal specimens were stored at 4 °C and sent to RTI International's Trace Inorganics Laboratory (Research Triangle Park, NC) for THg and Se analysis. Serum samples were collected to measure the rate at which PON-1 hydrolyzes paraoxon by spectrophotometric method. Significant genotypic variability exists for PON-1, but meta-analysis results suggest measured PON-1 enzyme activity is a more important predictive factor for CHD than PON-1 genotype (Mackness et al., 2001). The three repeated measurements of BP (systolic (SBP), diastolic (DBP) and pulse pressure (PP)) were collected from participants in the seated position. PP was calculated by subtracting DBP from SBP. The average of the three blood pressure measures was calculated and used in analysis. The primary endpoints were SBP, DBP and PP, and PON-1 activity. One individual had an erroneous BP recording (systolic lower than diastolic) and therefore this measure was not considered in the analysis.

2.3. Statistical analysis

Simple and multiple linear regression analyses were carried out investigating associations with SBP, DBP, PP, and PON-1 activity. Because of departures from normality, natural log transformation was applied to SBP, DBP, PP, and PON-1 activity in order to comply with the model assumptions. This study has 80% power to detect at least a small effect size (Cohen's f^2) of 0.06 (corresponding to an $R^2 \sim 0.06$) in a multiple regression analysis with 10 covariates. Covariates included in multiple regression models were those associated with the dependent variable using $p < 0.1$ in simple linear regression. Possible confounding factors that were eligible to be included in multivariable analysis included age, gender, ethnicity, selenium, BMI, household income (<$25,000, $25000–$110000,>$110000), highest level of education (Not a College Graduate and at least a College graduate), saturated fatty acid, unsaturated fatty acid, cholesterol, triglycerides, diabetes, history of hypertension, and GSH and GGSG (analyzed in whole blood using a GSH/GSSG assay kit according to instructions provided (Product # GT40, Oxford Biomedical Research, Inc., Rochester Hills, MI, USA)). Analyses were also stratified by gender. A series of sensitivity analyses were also conducted. We (1) excluded those currently on blood pressure medication (N = 49), (2) excluded those with past history of hypertension, heart attack, angina, or stroke (N = 63), (3) re-ran analyses in different age groups stratified by the median, (4) re-ran analyses only using the last two BP measures instead of all three, (5) re-ran analyses using omega3/omega6 concentrations instead of EPA + DHA as a percentage of fatty acids, (6) re-ran analyses using non-transformed dependent variables, and (7) re-ran the analyses limiting the covariates to those associated with both the predictor variables (Hg or EPA + DHA) and the dependent variables and not considered on the causal pathway (the models no longer included diabetes, saturated or unsaturated fatty acids, or history of hypertension); results did not change materially and are not presented.