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Association between whole blood mercury and glucose intolerance among adult Inuit in Greenland

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ABSTRACT

Objectives: The Arctic diet is partly constituted by traditional food characterized by top predator animals such as whales, walrus, and seals with high mercury content. Mercury exposure has been associated with glucose intolerance in Western populations. We studied the association between whole blood mercury and glucose intolerance in a highly exposed non-Western population

Methods: Cross-sectional study of 2640 Inuit (18+ years) with information on ancestry, smoking, waist circumference, total energy intake, and physical activity. Mercury, fasting- and 2-h plasma glucose, insulin, and c-peptide were measured in blood. Fasting participants without diabetes were classified into normal glucose tolerance, impaired glucose tolerance, impaired fasting glycemia, or type 2 diabetes. We calculated hepatic insulin resistance with homoeostatic model assessment – insulin resistance index, peripheral insulin sensitivity by $ISI_{0,120}$, and relative beta cell function by c-peptide/insulin ratio. We conducted adjusted linear- and logistic regression analyses.

Results: For an increase in whole blood mercury of 5 μg/L we found a positive association with fasting glucose [% change=0.25 (95% CI: 0.20; 0.30); $p<0.001$], and 2-h glucose [% change=0.23 (95% CI: 0.05; 0.40); $p=0.01$]. Mercury was weakly associated with impaired fasting glycemia [OR=1.03 (95% CI: 1.02; 1.05)], and type 2 diabetes [OR=1.02 (95% CI: 1.01; 1.04)].

Conclusion: While the study found a weak but statistically significant association between whole blood mercury and both impaired fasting glycemia and type 2 diabetes, no associations were found with measures of underlying disturbances in glucose homoeostasis.

1. Introduction

Inuit in Greenland are exposed to high amounts of environmental pollutants including methyl-mercury (MeHg) through the consumption of traditional food. Mercury is released into the atmosphere by burning of fossil fuels, especially coal. Once in the atmosphere, inorganic mercury can enter the aquatic environments through wet or dry disposition and is converted to MeHg by sulphate reducing bacteria. Mercury accumulates especially in the organs and muscle tissue of marine mammals such as seal and whale (Johansen et al., 2000). While these food items are still important in the traditional Inuit diet, they are the main contributors to the intake of mercury, which has been shown to be far above the tolerable daily intakes (TDI) (Johansen et al., 2004). A recent estimate showed that an average Inuit in Greenland (weight 60 kg) would have a mercury intake between 39–54 μg/day (depending on seasonal variation), which exceeds the European Food Safety Authority's TDI of 0.23 μg/kg body weight/day (Johansen et al., 2007). It has been hypothesized that mercury could play a significant role in the development of glucose intolerance. Mouse studies have shown that inorganic mercury can cause pancreatic β-cell dysfunction and apoptosis through oxidative stress (Chen et al., 2010) and methyl-mercury blood levels were also significantly associated with hepatic insulin resistance (HOMA-IR) ($r=0.19$, $p<0.01$) in a cross-sectional study with 1449 participants

Abbreviations: MeHg, methyl mercury; TDI, tolerable daily intake; IFG, impaired fasting glycemia; IGT, impaired glucose tolerance; T2D, type 2 diabetes; HOMA-IR, homoeostatic model assessment for hepatic insulin resistance; OGTT, oral glucose tolerance test; $ISI_{0,120}$, peripheral insulin sensitivity; c-peptide, connecting peptide

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without type 2 diabetes (Chang et al., 2011). The prevalence of type 2 diabetes (T2D) among adult Inuit in Greenland has now increased to approximately 10% and to 21% of pre-diabetic stages (Jørgensen et al., 2002). Interestingly, in previous research we found that a traditional dietary pattern was associated with a higher prevalence of T2D and decreased insulin secretion (Jeppesen et al., 2013) and villages and remote areas had a higher prevalence of diabetes compared to larger towns (Jørgensen et al., 2012). This may suggest a role of dietary environmental contaminants, including mercury, in T2D development (Jørgensen et al., 2008). By contrast, an updated systematic review concludes that the evidence of an association between mercury content in the blood and T2D is insufficient (Kuo et al., 2013). However, the existing evidence is based on studies including individuals with low blood mercury exposure levels. Thus, we aimed to investigate the association between whole blood mercury, T2D and indices of glucose metabolism: hepatic insulin resistance (HOMA-IR), peripheral insulin sensitivity ($ISI_{1,120}$), and beta-cell function as c-peptide/insulin ratio in a population with very high blood mercury concentrations. All three measures have proven to possess good validity and diagnostic capacity between obesity groups and levels of glucose intolerance (Gutt et al., 2000; Katsuki et al., 2001; Pfützner and Forst, 2011).

2. Research design and methods

2.1. Participants

Data for this population-based cross-sectional study were collected from 2005–2010 as part of the Inuit Health in Transition Study (Bjerregaard, 2011). Participants were selected as a stratified random sample of adults (18+) with residence in Greenland. Greenland was divided into strata based on region and size of community, thus each strata contained one or more towns and at least two villages. Towns were defined as having ≥2000 inhabitants; smaller towns with <2000 inhabitants and villages with 10–550 inhabitants. For each town (both large and smaller) a random sample of at least 300 inhabitants was drawn from the Danish Civil Registration System (CPR) were invited to participate, while all inhabitant of villages were invited. For all strata the study contained 9 towns and 13 villages. Ethnicity was determined at enrolment based on the primary language of the participant and self-identification. The total sample selected from the CPR consisted of 5009 Inuit and Danes. The final sample included in the analyses was only of Inuit ethnicity. With a participation rate for Inuit of 68%, the total study sample consisted of 3108 Inuit. Clinical information from blood samples was available for 99% of Inuit participants. Before analyses we excluded participants without valid glucose or insulin measurements ($N=195$) and missing mercury values ($N=44$), non-fasting participants (defined as minimum 8 h of fasting) ($N=107$), and invalid data on physical activity ($N=83$). Furthermore, we excluded three extreme outliers for the glucose and insulin measures ($N=3$). Previously diagnosed cases of diabetes were excluded ($N=37$). The final dataset consisted of 2640 Inuit participants without known diabetes and this study population was used for the descriptive analyses only. For the analyses of association between glucose metabolism and mercury we further excluded observations with missing data for the following confounders: waist circumference ($N=48$), ethnicity ($N=39$), and smoking ($N=5$). Thus the study population for the association analyses was 2548.

2.2. Sample collection

Blood samples were drawn from fasting individuals, defined as having spent a minimum of eight hours without consuming any liquids or food.

2.3. Total blood mercury

A total of 3035 participants had a valid measurement of whole blood mercury. Blood samples were frozen at −20 °C. Mercury was measured by inductively coupled mass spectrometry (ICP-MS) at the Centre de Toxicologie, Institut National de Santé Public, Québec, Canada, as described previously (Nielsen et al., 2012). Before analysis blood samples were diluted 20-fold in a solution containing ammonium hydroxide; the detection limit of mercury was 0.10 μg/L.

2.4. Glucose tolerance measures

From the fasting blood sample we obtained measures on fasting glucose, c-peptide, and fasting insulin. Participants underwent a 2-hour oral glucose tolerance test and the second blood sample was collected. For the oral glucose tolerance test participants received 246.5 ml (333.3 mg/ml) glucose monohydrate, equivalent to 75 g of glucose. Blood was drawn from the cubital vein for both blood samples. Plasma was separated and frozen at −20 °C and transported to one central laboratory at the Steno Diabetes Centre, Gentofte, Denmark for the measurement of plasma glucose, insulin, and c-peptide. Plasma glucose was analysed using Hexokinase/G6P-DH-Determination on a Hitachi 912 System. Insulin measures were analysed by two-site fluoroimmunometric assay for quantification of intact insulin in human serum (Wallac Auto Delfi Perkin Elmer Walthan, MA). C-peptide was analysed by Immunoassay for the in vitro quantitative determination of C-peptide in human plasma using Cobas e411, Roche 2011–04 (Roche Diagnostics, Mannheim, Germany).

Hepatic insulin resistance was calculated using the following equation in the homoeostatic model assessment index (HOMA-IR) (Matthews et al., 1985).

HOMA-IR=fasting insulin (pmol/L)*fasting plasma glucose (mmol/L)/22.5.

To calculate peripheral insulin sensitivity we used the Gutt Index (Gutt et al., 2000), using the following formula:

$$ISI_{0,120} = \frac{\left(75,000 + (\text{glucose}_{t\ 0\ \text{min}} \times 18 - \text{glucose}_{t\ 120\ \text{min}} \times 18) \times 0.19 \times \text{weight}_{kg}/120\right)}{\text{glucose}_{t\ 0\ \text{min}} + \text{glucose}_{t\ 120\ \text{min}}/2} / \log\left(\frac{(\text{insulin}_{t\ 0\ \text{min}}/6.945) + (\text{insulin}_{t\ 120\ \text{min}}/6.945)}{2}\right)$$

We calculated the C-peptide/insulin ratio as a measure of insulin resistance-associated beta-cell function using fasting values for both measures (Pfützner and Forst, 2011). According to the definitions of the World Health Organisation we defined isolated impaired fasting glycemia (IFG) as fasting plasma glucose ≥6.1