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Is mercury exposure causing diabetes, metabolic syndrome and insulin resistance? A systematic review of the literature

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ABSTRACT

Introduction: Several populations are exposed to mercury (Hg) via their environment, occupation or diet. It is hypothesized that Hg exposure can lead to the development of diabetes mellitus (DM). Metabolic syndrome (MS) is also a possible outcome as its symptoms are closely linked to those of DM.

Method: We conducted a systematic review of the literature by screening Web of Science, MEDLINE, SciFinder and Embase and we included original studies pertaining to the relationship of total Hg exposure (elemental, inorganic or organic) to DM, MS or insulin resistance. The studies were selected based on the PICOS (patients, intervention, comparator, outcomes and study design) criteria and their quality assessed using a nine-point scale. Study characteristics and results were extracted and presented in structured tables. We also extracted covariates entered as confounding factors to evaluate possible biases in selected studies. Finally, a weight of evidence approach was used to assess the causality of the relationship.

Results: A total of 34 studies were included in the present review. Epidemiological data assessment suggests a possible association between total Hg concentrations in different biological matrices and incidence of DM or MS, but the relationship is not consistent. In vivo and in vitro studies support the biological plausibility of the relation between Hg exposure and DM or MS. Five out of nine of Bradford Hill's criteria were fulfilled: strength, temporality, plausibility, coherence and analogy.

Conclusion: Increased total Hg exposure may augment the risk of DM and MS, but the lack of consistency of the epidemiological evidence prevents inference of a causal relationship. Additional prospective cohort studies and careful consideration of confounding variables and interactions are required to conclude on the causal relationship of total Hg exposure on the development of DM or MS.

1. Introduction

Diabetes mellitus (DM) is characterized by either the pancreas not producing enough insulin or organs/tissues not responding adequately to insulin secretion. In both cases, the resulting effect is hyperglycemia that, if left untreated, can lead to DM and damage to susceptible organs. According to the World Health Organization, in 2014, 9% of adults had DM and in 2012, the disease had caused 1.5 million deaths worldwide (Organization WH, 2014a, 2014b). The metabolic syndrome (MS) comprises several cardiometabolic risk factors and symptoms; generally included are high waist circumference, high blood pressure, low high-density lipoprotein cholesterol, elevated plasma triglycerides and hyperglycemia. Individuals with MS exhibit an increased risk of developing DM (Wilson et al., 2005). Both conditions present serious potential health risks and several risk factors are currently being scrutinized in an attempt to limit cardiometabolic morbidity and mortality in populations worldwide.

Exposure to environmental toxicants may play a role in the development of DM and MS (Song et al., 2016; Taylor et al., 2013; Thiering et al., 2016). Mercury (Hg) is a ubiquitous pollutant that is targeted by the Minamata Convention on Mercury, which was adopted and opened for signature on October 10th, 2013 and will likely enter into force in 2017 (Minamata convention on mercury). This international convention aims at reducing Hg emissions worldwide (Kessler, 2013). Hg is released in the environment through burning of fossil fuel, volcano eruptions, industrial processes as well as artisanal and small-scale gold mining (Kessler, 2013).

There are three forms under which Hg can be found: metallic,

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inorganic and organic Hg. Metallic Hg is the elemental form of Hg and is found mainly in the environment as Hg vapor. With the exception of occupational exposure, humans are rarely significantly exposed to this form of Hg and therefore it will not be discussed further in this review. Inorganic Hg (iHg) is commonly found in contaminated soils as either Hg^{+} or Hg^{2+} salts (Park and Zheng, 2012). Populations can be exposed to iHg through various routes such as dental amalgams, skin products and dust present in contaminated areas (Park and Zheng, 2012). Once in water or soils, iHg is transformed by microorganisms to methylmercury (MeHg), the most toxic form of Hg that bioaccumulates and is biomagnified in aquatic food chains. Populations are then exposed to MeHg through the consumption of highly-contaminated predatory fish species (Pirrone et al., 2010).

The relationship between any form of Hg exposure and DM is unclear. However, it is known that Hg can impair the antioxidant defense system, thereby increasing lipid peroxidation and related oxidative stress (Kobal et al., 2004; Salonen et al., 2000; Sener et al., 2003; Wiggers et al., 2008). Elevated MeHg or iHg exposure induces damage in various cell types, including pancreatic islet β-cells. Oxidative stress may be involved in triggering β-cell apoptosis (Chen et al., 2006a). Furthermore, Chen et al. (2006b) reported β-cell damage in rats treated orally with doses of MeHg of 20 μg/kg during 2 weeks, resulting in hyperglycemia (Chen et al., 2006b).

A number of epidemiological studies have investigated the association between biomarkers of Hg exposure and DM or MS development, yielding inconsistent results (Eom et al., 2014; He et al., 2013; Jeppesen et al., 2015; Moon, 2013; Mozaffarian et al., 2013; Park et al., 2009; Virtanen et al., 2014). The lack of systematic literature review precludes any conclusion regarding a possible causal relationship. We used the weight of evidence (WoE) approach described by Adami et al. (2011) to assess whether there is a causal relationship between biomarkers of Hg exposure and cardiometabolic (DM or MS) outcomes (Adami et al., 2011).

2. Methods

2.1. Search strategy

We systematically searched the Web of Science (http://webofknowledge.com), MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed), SciFinder (http://scifinder.cas.org) and Embase (http://www.embase.com/) using combinations of two keywords, each combination comprising one keyword selected from each of the following lists (list 1: diabetes, metabolic syndrome, insulin resistance; list 2: mercury, methylmercury). Therefore, six searches were performed in each database. There were no time period restrictions and no filters were applied. The articles had to be in English or in French and included reports of human studies (subjects of any age), as well as in vivo and in vitro experiments. Finally, a search of the reference lists of the articles retrieved was performed to identify additional studies. The latest search was done on November 11th, 2016.

2.2. Study selection

Two persons, using the same protocol defined *a priori,* screened the search output independently. The articles were first screened by their title to exclude studies not concerning environmental contaminants and a biological outcome. Then, the articles that did not fit the first criteria or did not mentioned Hg exposure based on the abstract reading (either iHg, MeHg or total Hg) were excluded.

2.3. Eligibility criteria

For the remaining papers, the entire article was accessed and a review of the patients, intervention, comparator, outcomes and study design (PICOS) criteria was performed to ensure eligibility of all articles as defined in Liberati et al. (2009). *Participants:* all ages were eligible as well as in vivo and in vitro studies for mechanistic support. *Intervention:* all populations exposed to any forms of Hg were included. Exposure was assessed either as iHg, MeHg or total Hg concentration in matrix in biological samples from populations (i.e. whole blood, serum, toenails or hair), as a dose administered for laboratory animal experiments or exposure concentration in cell culture medium for in vitro studies. Human studies estimating exposure based on geographical location or occupational exposure without providing biological sample concentrations as supporting data were excluded. *Comparators:* groups could be compared either by categorical or continuous concentrations of Hg. *Outcomes:* we considered outcomes as either categorical (i.e. presence of DM or MS, blood glucose or insulin level above or below stated thresholds) or continuous (i.e. continuous blood glucose or insulin concentrations). For MS, the outcomes could either be continuous variables or categorical variables defined according to the MS diagnostic criteria used in the study. For in vivo studies, the outcomes could be either biological measurements of IR characteristics (insulin or glucose levels) or adverse effects related to DM (lipid peroxidation, pancreatic damage). For in vitro studies, we considered either cell death or relevant biomarkers of effect (glucose or insulin uptake, reactive oxygen species (ROS) production or integrity of the cellular components). The cell lines had to be relevant with regard to the mechanism of IR: adipocytes, pancreatic cells or myocytes. *Study design:* original human cohort, cross sectional (case-control) or prospective, in vivo and in vitro studies were considered. Editorials, book chapters, comments, review articles, letter to the editor, meta-analyses and poster abstracts were excluded.

2.4. Data extraction

We assessed the quality of the epidemiological studies using a nine-point criteria checklist as presented by Bonzini et al. (2007)). The criteria evaluated were the study design, sampling procedure, inclusion and exclusion criteria, distribution of participant characteristics, number of participants and response rates, assessment of exposure, ascertainment of outcomes, statistical analysis and quantitative risk estimate with 95% confidence intervals. Each criterion was given equal weight and, if fulfilled, contributed a value of +1. Studies with a score of seven or more were included as they were deemed to provide enough quality information for proper interpretation of the data.

Table 1 lists the information extracted from the articles: author and year, location or setting of the study, design and cohort name if any, number and age of participants, study period, outcome (DM or MS) and how the outcomes were ascertained. Table 2 contains the information related to in vivo and in vitro studies: species/strain, number of animals in the study, method of exposure, outcomes studied and the main conclusions. Table 3 provides information extracted from human studies: quality score, biological matrix, exposure scale, mean, median or geometric mean for the whole population or tertiles/quartiles/quintiles used if the mean or median concentrations were not available, total Hg concentration range and finally the odds ratio (OR) as presented in the article, or any measures used for comparison between groups. Confounding factors that were accounted for in multiple regression analyses performed in the various studies are listed in Table 4.

2.5. Weight of evidence summary of findings

Hill's criteria were used as they are traditionally considered a critical and fundamental step in the assessment of a causal relation in epidemiological studies (Hill, 2015). We examined the evidence presented in the selected scientific articles to determine whether each criterion was fulfilled. The criteria for our WoE approach are: *Strength* - while a small association does not means there is no causal relationship, a strong association is more likely to result from causality; *Consistency* –