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Persistent organic pollutants and biomarkers of diabetes risk in a cohort of Great Lakes sport caught fish consumers

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ABSTRACT

Background: Exposure to persistent organic pollutants (POPs) is associated with increased diabetes risk, although the mechanism of action is not well delineated.
Methods: We investigated established diabetes biomarkers that could implicate potential mechanistic pathways, including C-reactive protein (CRP), a marker of systemic inflammation; gamma glutamyl transferase (GGT), a liver enzyme associated with oxidative stress; and adiponectin, an adipokine modulating glucose regulation and fatty acid oxidation. These biomarkers as well as hemoglobin A1c (HA1c), and POPs [polychlorinated biphenyls (PCBs), *p,p*-dichlorodiphenyldichloroethylene (DDE) and polybrominated diphenyl ethers (PBDEs)] were measured in a cohort of Great Lakes sport caught fish (GLSCF) consumers. We examined associations of POPs and fish consumption with HA1c and incident diabetes, and evaluated mediation and moderation by the diabetes biomarkers.
Results: Odds of incident diabetes were elevated with exposure to DDE and PCBs. DDE and PCB 118 were positively, and fish meals were inversely, associated with HA1c. CRP was inversely associated with saltwater and total fish meals, particularly in persons with higher adiposity, but did not mediate the associations of fish meals with HA1c. There were few associations of POPs with adiponectin, CRP and GGT, with the exception of positive associations of PCB 118 with GGT, PBDEs with GGT in older persons, and PBDEs with adiponectin. Adiponectin, CRP and GGT did not mediate associations of DDE and PCBs with HA1c or incident diabetes. However, the association of DDE with HA1c was stronger in persons with higher CRP, GGT and BMI, and lower adiponectin, while the association of PCB 118 with HA1c was stronger in persons with higher GGT.
Conclusions: These findings suggest that adiponectin, CRP and GGT did not mediate effects of POPs on diabetes or HA1c. However, POPs may have stronger effects on blood glucose in persons at higher risk for diabetes.

1. Introduction

There is accumulating evidence that environmental contaminants are associated with increased diabetes risk. Many studies have investigated the risk of diabetes with exposure to one or more persistent organic pollutants (POPs), including polychlorinated biphenyls (PCBs), dibenzo-p-dioxins and chemicals with related toxicological properties, and persistent pesticides such as DDT and its metabolite *p,p*-dichlorodiphenyldichloroethylene (DDE) (reviewed by Kuo et al. (2013) and Taylor et al. (2013)). While associations have been noted in many studies, chemicals with multiple modes of action have been implicated.

Possible biologic pathways through which POPs could affect diabetes incidence have been hypothesized, including insulin

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resistance (Kern et al., 2004), pancreatic beta cell destruction (De Tata, 2014), mitochondrial dysfunction (Lee, 2011), alterations in steroid metabolism (Persky et al., 2011; Persky et al., 2012), antagonism of PPARγ expression (Remillard and Bunce, 2002), and induction of low grade chronic inflammation (Fujiyoshi et al., 2006), oxidative stress (Lee et al., 2008), and autoimmunity (Langer et al., 2002). This study explored some of these potential pathways using biomarkers of diabetes risk. Selected biomarkers were C-reactive protein (CRP), adiponectin, and gamma glutamyl transferase (GGT). C-reactive protein is a general marker of systemic inflammation, which is increased in obese persons and associated with increased risk of type 2 diabetes, independent of obesity (Dehghan et al., 2007; Duncan and Schmidt, 2006). Adiponectin, an adipokine, is positively associated with insulin sensitivity, is decreased in obesity and in persons with type 2 diabetes, and has been related to decreased risk of incident diabetes independent of adiposity (Li et al., 2009). Adiponectin has anti-inflammatory properties, including inhibition of tumor necrosis factor α and IL-6 production and induction of anti-inflammatory cytokines (Fantuzzi, 2005). GGT is a liver enzyme associated with oxidative stress that is related to increased type 2 diabetes risk, with stronger effects in persons with higher BMI (Nakanishi et al., 2003).

A significant route of exposure to POPs is through ingestion of contaminated food, in general, and fish in particular. Sport caught fish from the Great Lakes have elevated levels of PCBs and other POPs and frequent consumers of these fish have higher exposures than the general population (Turyk et al., 2012). Increased risk of diabetes with elevated POP levels has been noted in Great Lakes fish consuming populations (Codru et al., 2007;Turyk et al., 2009a), but investigations of the effects of fish consumption on diabetes risk have been inconsistent (reviewed by Wu et al. (2012) and Zhang et al. (2013)). We previously reported a relationship of DDE with incident diabetes (Turyk et al., 2009a) and of DDE and PCB 118 with prevalent diabetes (Turyk et al., 2009b) in participants in the Great Lakes Fish Consumption Study.

Hemoglobin A1c (HA1c), or glycated hemoglobin, is useful as a measure of glucose control over the lifespan of the red blood cell (3–4 months). It therefore represents more long-term glucose regulation than acute fluctuations and recently has been adopted as a test for diabetes ($\geq$6.5%) and prediabetes (5.7–6.4%) (American Diabetes Association, 2010). Because diabetes risk increases for persons with fasting plasma glucose values at the higher end of the normal range, it has been suggested that diabetes risk prediction may be more accurate if glycemic measures are treated as continuous rather than categorical variables (Tabak et al., 2012). Continuous glycemic measurements (i.e. fasting plasma glucose and HA1c) have been analyzed in relation to POP exposures in several investigations (Calvert et al., 1999; Grandjean et al., 2011; Henriksen et al., 1997; Jorgensen et al., 2008; Langer et al., 2014; Michalek et al., 1999; Suarez-Lopez et al., 2015), but the effects of POP exposures on continuous HA1c levels have not yet been evaluated in the Great Lakes Fish Consumption Study.

The current study measured diabetes biomarkers in participants in the Great Lakes Fish Consumption Study. Our purpose was to determine 1) if POPs or fish consumption were related to levels of adiponectin, CRP, and GGT; 2) if adiponectin, CRP, and GGT were related to incident diabetes or to continuous levels of HA1c; and 3) if the associations of POPs or fish consumption with incident diabetes and continuous HA1c were mediated or modified by adiponectin, CRP, and GGT.

2. Methods

2.1. Participants

The Great Lakes Consortium for the Health Assessment of Great Lakes Sport Fish Consumption was organized in 1992 (Anderson et al., 1996), and study design of the Great Lakes Fish Consumption Study through 2004–2005 has been previously described (Turyk et al., 2009b). Briefly, approximately 4,200 participants with frequent and infrequent Great Lakes sport fish consumption were recruited, including Great Lakes fishing charter boat captains, anglers who fished from inland Wisconsin lakes, and infrequent consumers (reporting consumption of fewer than six meals of Great Lakes sport fish in any year of the previous 20 years). Between 1994 and 2005, biological samples were collected at least once from 948 participants and tested for persistent pollutants (Anderson et al., 2008; Hanrahan et al., 1999; Persky et al., 2001). The current analysis incorporates data collected at follow up in 2004–2005 and in 2010.

2.2. Data collection

Self-reported diagnosis of diabetes, date of diagnosis, demographics, height, weight, smoking, alcohol use, medication use, and fish consumption were assessed by survey. In 2004–2005, 515 participants were surveyed (Turyk et al., 2009b) and data on fish meals consumed in the past year was assessed, and summarized as commercial (fresh water and saltwater) fish meals and sport caught fish meals (Great Lake or other body of water). Health data assessed in 2010 was available from 598 participants, of whom 402 also participated in the 2004–2005 data collection.

In 2004–2005, non-fasting blood was collected in red-top vacutainer tubes, allowed to clot for 20 min at room temperature, centrifuged for 15 min, transferred to solvent-rinsed glass vials, and stored at −20 °C until analysis. All laboratory tests were performed by technicians blinded to participant characteristics. Sera samples were analyzed for DDE, and for PCB and PBDE congeners as previously described (Anderson et al., 2008). Briefly, sera were extracted with hexane/ethyl ether, with clean-up and fractionation using Florisil, silica-gel and concentrated sulfuric acid. PBDEs were analyzed by gas chromatography–mass spectrometry and PCBs and DDE by gas chromatography.

Total cholesterol and triglycerides were measured by Quest Diagnostics (Auburn Hills, MI and Wood Dale, IL). Total serum lipids were calculated by the formula:

Total lipid=(total cholesterol mg/dL+2:27*triglycerides mg/dL)+62:3.

HA1c was measured in whole blood by Quest Diagnostics through affinity chromatography, which measured total glycosylated hemoglobin, from which HA1c is calculated.

Stored sera samples were assayed in 2010 for adiponectin, CRP, and GGT. Because sera samples had been through prior freeze-thaw cycles during testing for hormones in 2004–2005, we evaluated the stability of test results for these biomarkers after a series of freeze-thaw cycles in serum obtained from four donors. These tests did not indicate systematic decline in biomarker measurements with increasing freeze-thaw cycles.

Quality control was monitored using internal positive and negative controls. Inter-assay coefficients of variation (CVs) were calculated from repeated assays on 4–5% of the participant samples. For adiponectin and CRP, each participant sample was assayed in duplicate and CVs were calculated for each duplicate pair. The average CV was then calculated for each assay plate and the intra-assay CV was the average of all the plate averages. For GGT, a single measurement was obtained for each participant sample precluding calculation of an intra-assay CV.