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Review

Association of persistent organic pollutants and non-persistent pesticides with diabetes and diabetes-related health outcomes in Asia: A systematic review

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ABSTRACT

Background: Over half of the people with diabetes in the world live in Asia. Emerging scientific evidence suggests that diabetes is associated with environmental pollutants, exposures that are also abundant in Asia.
Objective: To systematically review the literature concerning the association of persistent organic pollutants (POPs) and non-persistent pesticides with diabetes and diabetes-related health outcomes in Asia.
Methods: PubMed and Embase were searched to identify studies published up to November 2014. A secondary reference review of all extracted articles and the National Toxicology Program Workshop on the association of POPs with diabetes was also conducted. A total of 19 articles met the inclusion criteria and were evaluated in this review.
Results: To date, the evidence relating POPs and non-persistent pesticides with diabetes in Asian populations is equivocal. Positive associations were reported between serum concentrations of polychlorinated dibenzodioxins and dibenzofurans (PCDD/Fs), polychlorinated biphenyls (PCBs), and several organochlorine pesticides (DDT, DDE, oxychlordane, *trans*-nonachlor, hexachlorobenzene, hexachlorocyclohexane) with diabetes. PCDD/Fs were also associated with blood glucose and insulin resistance, but not beta-cell function. There were substantial limitations of the literature including: most studies were cross-sectional, few studies addressed selection bias and confounding, and most effect estimates had exceptionally wide confidence intervals. Few studies evaluated the effects of organophosphates.
Conclusions: Well-conducted research is urgently needed on these pervasive exposures to inform policies to mitigate the diabetes epidemic in Asia.

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Abbreviations: BMI, body mass index; CHLs, chlordanes; CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; EOI, exposure opportunity index; FBG, fasting blood glucose; GIS, geographic information system; GC, gas chromatography; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; HOMA-IR, homeostasis model assessment-estimated insulin resistance; HRGC, high-resolution gas chromatography; HRMS, high-resolution mass spectrometry; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; MESH, medical subject heading; NA, not applicable; OC, organochlorine; OCDD, octa-chlorodibenzo-p-dioxin; OGTT, oral glucose tolerance test; OR, odds ratio; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzodioxins; PCDFs, polychlorinated dibenzofurans; PCP, pentachlorophenol; PCQs, polychlorinated quarterphenyls; POPs, persistent organic pollutants; PPAR, peroxisome proliferator-activated receptor; QUICKI, quantitative insulin sensitivity check index; SAT, subcutaneous adipose tissue; T2D, type 2 diabetes; TCDD, 2,3,7,8-tetrachlorodibenzodioxin; TEQ, toxic equivalent concentration; VAT, visceral adipose tissue.

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1. Introduction

Rapid agricultural and industrial development over the past 50 years in Asia has led to high exposure levels of potentially toxic chemicals including persistent organic pollutants (POPs) and non-persistent pesticides (pyrethroids and organophosphates). Over half of regional pesticides (including herbicides, insecticides, and fungicides) are used in China, but per hectare of agricultural land, Korea takes the lead at over 50 kg formulated product per hectare agricultural land compared to just over 25 kg formulated product per hectare agricultural land in Malaysia, the second highest consumer per hectare in the region (Food and Agriculture Organization of the United Nations, 2005). Reported pesticide use in India is much lower at less than 5 kg formulated product per hectare agricultural land (Food and Agriculture Organization of the United Nations, 2005). However, in regard to insecticide use for vector control (largely malaria prevention), India accounted for 82% of global use of dichlorodiphenyltrichloroethane (DDT) between 2000 and 2009: over the 10-year period of observation, 3623 metric tons of DDT were used for indoor residual spraying in India compared to only 805 metric tons in all of Africa (Berg et al., 2012).

Concurrent with these increases in chemical exposure, the prevalence of diabetes has increased rapidly in Asia. In 2000, the prevalence of diabetes in China was just 2.7% and in India 5.8% (International Diabetes Federation, 2000). By 2013, these numbers had jumped to 9.6% and 8.6%, respectively (International Diabetes Federation, 2013). Today, 43% of the 382 million adults with diabetes in the world live in just two Asian countries: 98.4 million people in China and 65.1 million people in India (International Diabetes Federation, 2013). While scientific evidence has pointed to changes in dietary intake and physical activity as key culprits in this epidemic (Popkin et al., 2001), the role of non-traditional risk factors such as environmental pollutants remains an emerging area of diabetes research.

The state of the evidence linking POP exposure to diabetes was summarized during a U.S. National Toxicology Program Workshop conducted in January 2011 (Thayer et al., 2012; Taylor et al., 2013). The primary conclusion of the Workshop was that evidence is sufficient to support an association of some organochlorine POPs, particularly *trans*-nonachlor, dichlorodiphenyldichloroethylene (DDE), polychlorinated biphenyl (PCB) congener 153, and dioxins, with type 2 diabetes (Taylor et al., 2013). While not sufficient to establish causality, the Workshop findings were further supported by a recent meta-analysis and systematic review on the same topic: the first concluded that hexachlorobenzene (HCB) and total PCBs, but not DDE or DDT, are significantly associated with type 2 diabetes (Wu et al., 2013), and the second concluded that dioxins, PCBs, and HCB were associated with the disease (Magliano et al., 2014). More recently, researchers in Belgium confirmed that PCB congener 153, total PCBs, and DDE are significantly associated with abnormal glucose tolerance by oral glucose tolerance test (OGTT) among obese individuals (Dirinck et al., 2014).

Experimental studies in mice and rats tend to support that chronic exposure to low doses of POPs fed as part of fish oil or salmon filets impairs insulin-mediated glucose uptake in muscle and adipose tissue (Ruzzin et al., 2010; Ibrahim et al., 2011). More specifically, for example, dioxins are known to exert their effects through binding with and activating the aryl hydrocarbon receptor, which in turn antagonizes peroxisome proliferator-activated receptor (PPAR)-γ and reduces glucose transport activity (Remillard and Bunce, 2002). However, high doses of POPs tend to have the opposite effect in animal studies (Fried et al., 2010; Ibrahim et al., 2012), highlighting the need for further dose–response characterization. Mechanisms linking the non-persistent pesticides, organophosphates, to hyperglycemia are reviewed elsewhere (Rahimi and Abdollahi, 2007) and likely involve several pathways: oxidative and nitrosative stress, pancreatitis, stimulation of the adrenal gland, and disruption of liver tryptophan metabolism.

Recent reviews presented comprehensive summaries of environmental and human POP exposures in India (Sharma et al., 2014) and POP levels in water in China (Bao et al., 2012), but to our knowledge, no review has summarized the health effects of these exposures in Asian populations. The objective of this study was to systematically review the literature concerning the association of POPs and non-persistent pesticides (pyrethroids and organophosphates) with diabetes and diabetes-related health outcomes in Asia.

2. Methods

2.1. Search strategy and study selection

PubMed and Embase were searched to identify human studies published in English up to November 2014 (material). The exposure search terms “pesticides,” “polychlorinated biphenyls,” “persistent organic pollutants,” “hydrocarbons, chlorinated,” and “organophosphates” were combined using the operator “OR” and then nested. The outcome search terms “diabetes mellitus,” “hyperinsulinism,” “hyperglycemia,” “insulin resistance,” “glucose intolerance,” “beta-cell function,” and “blood glucose” were combined using the operator “OR” and then nested. Medical subject heading (MeSH) terms were expanded to include all narrower terms in the hierarchical list. The nested exposure terms and nested outcome terms were then combined using the operator “AND.” We excluded citations with the following, non-relevant terms using the operator “NOT”: “warfarin,” “mitotane,” “diphosphoglycerate,” “dichloroacetate,”