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Review

Persistent organic pollutants and diabetes: A review of the epidemiological evidence

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Abstract

The prevalence of diabetes and obesity has increased rapidly over the last few decades in both developed and developing countries. While it is intuitively appealing to suggest that lifestyle risk factors such as decreased physical activity and adoption of poor diets can explain much of the increase, the evidence to support this is poor. Given this, there has been an impetus to look more widely than traditional lifestyle and biomedical risk factors, especially those risk factors, which arise from the environment. Since the industrial revolution, there has been an introduction of many chemicals into our environment, which have now become environmental pollutants. There has been growing interest in one key class of environmental pollutants known as persistent organic pollutants (POPs) and their potential role in the development of diabetes. This review will summarise and appraise the current epidemiological evidence relating POPs to diabetes and highlight gaps and flaws in this evidence.
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1. Introduction

The last few decades have seen epidemics of diabetes and obesity, which are not fully explained by changes in the prevalence of established risk factors, such as physical inactivity and poor diet [1]. In fact, the reasons for the extremely rapid increase in diabetes and obesity over the past few decades remain unclear. Given this, there has been a thrust to look more widely than traditional lifestyle and biomedical risk factors. One key avenue of novel risk factors are those arising from the external environment. Since the industrial revolution, we have introduced many chemicals, (intentionally and unintentionally) into our environment and while these are many and varied, there has been growing interest in the potential health effects of particular environmental toxicants such as persistent organic pollutants (POPs).

Persistent organic pollutants are a class of compounds, which are characterised by their ability to persist in the environment, their low water and high lipid solubility and their bio-magnification in the food chain [2]. POPs include many of the first generation organochlorines (OC), pesticides such as dieldrin, dichlorodiphenyltrichloroethane (DDT), toxaphene and chlordane, and several industrial chemical products or by-products including polychlorinated biphenyls (PCBs), 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), polychlorinated dibenzo-p-dioxin (PCDD), dibenzo-p-furans (PCDFs) and polychlorinated biphenyls (PCBs), hexachlorobenzene (HCB), polybrominated biphenyls (PBB) and perfluorinated compounds (PFCs) such as perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and perfluorononanoic acid (PFNA). Given the large number of POPs which have been identified, a nomenclature has been derived based on the number of halogenated atoms that each compound has. Each individual POP is referred to as a congener and the name of a congener specifies the total number of halogenated substituents and their position. It is believed that POPs with fewer chlorine atoms persist in the environment for less time and are less toxic [3]. Many of these congeners have been and continue to be used in large quantities in chemical and related industries and now represent a global health problem [4].

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POPs are either used as pesticides or generated as by-products of industrial or combustion processes. Dioxin, a key class of POPs, is produced as a by-product in the bleaching of paper products and during certain types of chemical synthesis [5]. POPs can travel great distances and become widely distributed by wind and can end up in countries other than those in which they were produced [6]. Once in the environment, POPs accumulate in the fatty tissue of living organisms, reaching the greatest concentrations at the top of the food chain in fish, mammals and predatory birds [7]. Although humans can be exposed to POPs through direct exposure, occupational accidents and the environment, most of the human exposure nowadays is from the ingestion of contaminated food as a result of bioaccumulation in the food chain. The main source (around 95%) of POPs intake is through dietary intake of animal fats [2].

The mechanisms linking POPs exposure to diabetes have not been fully elucidated, but several pathways have been proposed. *In vitro* and *in vivo* experiments show that TCDD affects glucose homeostasis by reducing glucose uptake by adipose tissue, liver and the pancreas, which is accompanied by decreases in insulin production and secretion by beta cells. The primary mechanism by which these effects are proposed to occur is via the binding of TCDD to the aryl hydrocarbon receptor (AhR) [8]. This binding causes changes in translational and transcriptional mechanisms resulting in decreased glucose transporter (GLUT) expression [9–11]. TCDD has also been suggested to affect pancreatic nitric oxide synthase, the function of which is not yet understood [12], and it has also been shown to increase expression of tumour necrosis factor (TNF) α [13], which linked to insulin resistance. The effects of other POPs such as PCBs are less studied although Baker et al. [14] showed using mice studies that coplanar PCBs cause rapid and sustained impairment of glucose and insulin tolerance through an AhR-dependent mechanism associated with an adipose-specific increase in TNF-α expression.

Further, some of the POPs act as endocrine disrupting chemicals (EDC). EDCs bind to nuclear receptors such as androgen receptors, peroxisome proliferator-activated receptor (PPAR) α and estrogen receptor (ER) α and β. This binding, often at high affinity, can interfere with the synthesis, secretion, transport, binding, action, or elimination of a range of hormones in the body that are responsible for normal cell metabolism. For example, the E_2 receptor is involved with the maintenance of insulin sensitivity. Abnormal binding to this receptor by the EDC may promote insulin resistance [15]. Further PPAR α, which has a role in fatty acid synthesis, is activated *in vivo* by PFOA but the *in vivo* consequences of this appear to be species specific and thus remain controversial. Similarly, dioxins and pesticides can modulate PPAR activity, although little is known about the molecular mechanisms and physiological output from this binding [15].

Most of the current epidemiological data linking POPs to disease is related to dioxins, which have been suggested to be the most toxic pollutant [3]. In a range of animal experiments, TCDD, the most toxic of all dioxins, has been linked to many severe adverse effects including cancer, liver disease and diabetes. Since the 1990s, evidence has accumulated associating POPs with diabetes, high blood glucose levels, insulin resistance and obesity [5]. Such evidence has arisen from occupational cohorts exposed during work or chemical accidents, cohorts who are at high-risk of exposure due to consumption of contaminated fish, and general-population studies. While the data are accumulating in this area, there are conflicting reports and thus a review of the diverse information sources is needed. This review will summarise and appraise the current evidence relating POPs to diabetes and highlight gaps and flaws in the evidence.

2. Methods

PubMed, OVID (Medline) and Web of Science databases were searched to identify potential studies published from 1950 to March 2013. The Medical Subject Heading (MeSH) terms 'diabetes', 'insulin resistance', and 'glucose intolerance' were combined with the operator 'OR'. The MeSH term 'persistent organic pollutant', 'polychlorinated biphenyls', 'organofluorine', 'organobromine' and 'organo pesticides' were entered and combined with the former using the operator 'AND' and the search was limited to human studies published in English. We also reviewed bibliographies and references lists. Our inclusion criteria comprised any cross-sectional, cohort or case-control studies, which explored the relationship between POPs or pesticides and diabetes, insulin resistance, glucose intolerance or HOMA-IR in adults. We excluded studies which used death from diabetes, gestational diabetes or metabolic syndrome as the outcome.

Studies were broadly categorized into high-risk occupational cohorts, non-occupational high-risk cohorts, and general population studies. This was based on the study design employed and whether the paper focused on participants expected to be at high risk of higher POPs exposure for occupational or other reasons.

3. Results

After removal of duplicate studies and reviews, our search identified a total of 388 publications. Review of reference lists identified an additional 8 articles. Among these, a total of 74 articles were identified as potentially eligible and were reviewed in full text (DJM, VHYL) and 41 articles met our inclusion criteria and were included in the systematic review.

The characteristics and results of the studies reviewed for this work are summarised in Table 1 and Table S1 (Table S1; see supplementary material associated with this article online). Given the large heterogeneity in the way the data on POPs were reported and analysed, it was not possible to undertake any formal meta-analyses. Studies are grouped according to the population type.

4. High-risk occupational cohorts

Some of the earliest data linking POPs with diabetes come from occupational cohorts studies, where exposure to pollutants occurred in relation to employment. The most well known of these is the study of US veterans of Operation Ranch Hands from

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