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Human adipose tissue levels of persistent organic pollutants and metabolic syndrome components: Combining a cross-sectional with a 10-year longitudinal study using a multi-pollutant approach

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ABSTRACT

We aimed to assess the influence of long-term exposure to POPs on the risk of metabolic syndrome, combining a cross-sectional with a 10-year longitudinal follow-up design. Residues of eight POPs were quantified in adipose tissue samples from 387 participants recruited between 2003 and 2004 in Granada province (Spain). The outcome ("metabolically compromised") was defined as having ≥ 1 diagnosis of type 2 diabetes, hypertension, hypertriglyceridemia, and/or low HDL cholesterol. The cross-sectional analysis was conducted in the initial cohort, while the 10-year longitudinal analysis was conducted in those 154 participants free of any of the so-mentioned metabolic diseases and classified as "metabolically healthy" at recruitment. Statistical analyses were performed using single and multi-pollutant approaches through logistic and Cox regression analyses with elastic net penalty. After adjusting for confounders, β-hexachlorocyclohexane (β-HCH) and hexachlorobenzene (HCB) were independently associated with an increased risk of being metabolically compromised (unpenalized ORs = 1.17, 95% CI = 1.01–1.36 and 1.17, 95% CI = 0.99–1.38, respectively). Very similar results were found in the 10-year longitudinal analysis [HRs = 1.28, 95% CI = 1.01–1.61 (β-HCH); 1.26, 95% CI = 1.00–1.59 (HCB)] and were in line with those obtained using elastic net regression. Finally, when the arithmetic sum of both compounds was used as independent variable, risk estimates increased to OR = 1.25, 95% CI = 1.03–1.52 and HR = 1.32, 95% CI = 1.02–1.70. Our results suggest that historical exposure to HCB and β-HCH is consistently associated with the risk of metabolic disorders, and that these POPs might be partly responsible for the morbidity risk traditionally attributed to age and obesity.

1. Introduction

The emergent obesity epidemic is at the center of worldwide public health concerns, along with its implications for chronic diseases (Guh et al., 2009). Although unhealthy dietary patterns and sedentary lifestyles are recognized as the main triggers of this epidemic, mounting evidence is signaling other environmental stressors, such as exposure to endocrine disrupting chemicals (EDCs), as an additional risk factor for obesity and metabolic disorders (Dhurandhar and Keith, 2014). Thus, increasing data suggest that long-term exposure to a group of EDCs designated persistent organic pollutants (POPs) may have a relevant impact on a cluster of metabolic conditions (obesity, dyslipidemia, high blood pressure and insulin resistance) known as the metabolic syndrome (MetS) (Alberti et al., 2009).

POPs are highly lipophilic compounds that resist metabolism and biodegradation and therefore tend to have a relatively long half-life in

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the environment and to bioaccumulate and biomagnify in the food chain (Mrema et al., 2013). The result is the virtually universal exposure of living organisms, including humans (Jakszyn et al., 2009). These chemicals include organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs), which have been used in a variety of commercial products, e.g., insecticides (dichlorodiphenyltrichloroethane [DDT], dicofol, lindane), fungicides (hexachlorobenzene [HCB]), and coolant and heating exchange fluids (polychlorinated biphenyls [PCBs]). Although legal restrictions in most countries have caused a worldwide decline in the production and handling of many POPs, human exposure remains relevant to public health due to their ubiquity and because current generations might suffer the effects of accumulated exposure throughout their lives, especially during critical windows of development (Tang-Péronard et al., 2015). Moreover, part of the POP body burden is transferred to subsequent generations during gestation and breastfeeding (Shen et al., 2007), and most studies have considered diet, especially fatty food, to be the main current source of exposure in the general population (Gasull et al., 2011; Arrebola et al., 2012). Other sources, such as indoor inhalation or dermal exposure, might also be important for certain POPs and population groups (Bräuner et al., 2016; Luo et al., 2014).

Although adipose tissue was once considered a simple energy storage depot, it is now known to be a complex endocrine organ with autocrine, paracrine, and neuroendocrine actions that influence appetite, energy regulation, lipid oxidation, immune and vascular functions, and hormonal status (Galic et al., 2010). Adipose tissue also appears to have an important toxicological function by sequestering POPs and other lipophilic contaminants in order to protect other more sensitive lipophilic organs (e.g., the brain) from an overload (La Merrill et al., 2013). Therefore, adipose tissue constitutes a reservoir for long-term POP accumulation and can act as a source of chronic exposure to POPs through their slow release into the bloodstream, which might have relevant consequences in several chronic diseases (La Merrill et al., 2013).

Adipose tissue is itself a target of pollutants, and some authors have suggested that POPs are taken up by adipocytes and accumulate within lipid droplets, where they might exert a major local effect by interfering with lipid metabolism, insulin sensitivity, and endocrine function (Bourez et al., 2013; La Merrill et al., 2013). Given the relative frequency of clinical exceptions to the paradigm “more fat means more metabolic disease” (Muñoz-Garach et al., 2016), lipophilic contaminants are therefore increasingly seen as potentially explaining, at least in part, the link with adipose tissue inflammation and dysfunction, the underlying mechanisms thought to determine whether obese individuals remain metabolically healthy or not (Muñoz-Garach et al., 2016).

The action mechanisms proposed for POPs include interaction with nuclear receptors such as peroxisome proliferator-activated receptor gamma (PPAR-γ) and aryl hydrocarbon receptor (AhR) (La Merrill et al., 2013), and with endogenous endocrine-related enzymes and inflammation pathways, causing oxidative stress and epigenetic modulation (Mrema et al., 2013). The diverse action mechanisms of different POP families and the potential interaction of complex mixtures, with additive, synergistic and/or antagonistic effects, complicate elucidation of the effects of POPs on metabolism (Rajapakse et al., 2002; Biemann et al., 2014). Furthermore, direct metabolic disrupting effects may coexist with long-term obesogenic effects that would lead to increased adiposity and therefore higher metabolic risk (Heindel et al., 2015; Lee et al., 2011).

Further complications are introduced by the simultaneous exposure of humans to complex low-level mixtures of EDCs that can potentially interfere with metabolism, including POPs (CDC, 2015; Braun et al., 2014). The short and long-term health risks posed by these mixtures remain unclear and are causes of increasing concern. However, the vast majority of epidemiological studies have considered exposure to chemicals in a one-compound-at-a-time approach that may not address the true effect of chemical mixtures on human health (Braun et al., 2016). Consequently, one of the goals of current environmental epidemiology is the development of alternative and complementary multi-pollutant approaches to disentangle independent associations among several co-exposures and assess their combined effect (Lenters et al., 2016).

Few epidemiological studies have analyzed the association between POP exposure and MetS (Lee et al., 2007b; Lee et al., 2011; Lee et al., 2014a; Park et al., 2010; Tomar et al., 2013). The present study was prompted by previous reports on associations between exposure to individual POPs and the risk of diabetes, hypertension, and elevated serum lipids in this same population (GraMo cohort) (Arrebola et al., 2013, 2014, 2015a). The study objectives were to assess the relationship between long-term exposure to eight POPs and the risk of developing MetS components and to examine whether POP exposure is in part responsible for the metabolic risk traditionally attributed to body mass index (BMI) and age. The causality of these relationships was explored by combining a cross-sectional with a 10-year longitudinal design, using both a single-chemical and a multi-pollutant approach.

2. Methods

2.1. Study cohort

This research is part of a wider hospital-based study that aims to characterize the exposure to POPs of an adult cohort from Southern Spain and to assess its potential health effects (GraMo cohort). The study design, recruitment, and methods are extensively described elsewhere (Arrebola et al., 2009, 2010). In brief, study subjects were recruited in two public hospitals from Granada province: San Cecilio University Hospital in the city of Granada (240.000 inhabitants, urban area) and Santa Ana Hospital in the town of Motril (50.000 inhabitants, semi-rural area). Participants were recruited between July 2003 and June 2004 from patients undergoing non-cancer-related surgery. Following the standard surgery protocols of the hospitals, all participants were under 12-h fasting conditions at sample collection. Inclusion criteria were: age over 16 years, absence of cancer, non-prescription of hormonal therapy, and residence in one of the study areas for at least 10 years. Reasons for surgery included a total of 70 different health issues. Given this heterogeneity, they were grouped into four categories: hernias (41%), gallbladder diseases (21%), varicose veins (12%), and other conditions (26%). All participants signed their informed consent to participate in the study, which was approved by the ethics committees of both hospitals.

Out of the 409 individuals who were contacted, 387 agreed to participate and were included in the initial cohort. All analyzed adipose tissue biopsies were collected at recruitment (n = 387) and were used for the cross-sectional analyses in the present study. Out of this initial cohort, all participants free of any metabolic disease at recruitment (n = 169) were then included in the 10-year follow-up study. Out of these 169 participants, 15 were excluded from the follow-up due to missing information or discrepancies in their clinical records, leaving a final subsample of 154 individuals. All participants were users of the public health system. No statistically significant differences in sex distribution or age were found between participants and non-participants (data not shown in tables). Main characteristics of the study population are summarized in Table 1.

2.2. Exposure assessment

Samples of 5–10 g of adipose tissue were intra-operatively collected and immediately coded and stored at − 80 °C until chemical analysis. Sample analysis and purification procedures were conducted as previously described (Rivas et al., 2001; Moreno Frías et al., 2004). In brief, chemical extraction with *n*-hexane was conducted on 200 mg of adipose tissue, and the solution was then purified through 2 g of alumina in a glass column. All extracts were stored in glass tubes at − 80 °C.

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