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Short Report

Can persistent organic pollutants distinguish between two opposite metabolic phenotypes in lean Koreans?

K.H. Ha [a,b], S.A. Kim [c,d], Y.M. Lee [e], D.J. Kim [a,b,*], D.H. Lee [c,d,e,**]

[a] Department of Endocrinology and Metabolism, Ajou University, School of Medicine, Suwon, Republic of Korea
[b] Cardiovascular and Metabolic Disease Etiology Research Center, Ajou University School of Medicine, Suwon, Republic of Korea
[c] Department of Biomedical Science, Kyungpook National University, Daegu, Republic of Korea
[d] BK21 Plus KNU Biomedical Convergence Program, Department of Biomedical Science, Kyungpook National University, Daegu, Republic of Korea
[e] Department of Preventive Medicine, School of Medicine, Kyungpook National University, 680, Gukchaebosang-ro Jung-gu, Daegu 41944, Republic of Korea

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ABSTRACT

Aims. – This study investigated the association of persistent organic pollutants (POPs), an emerging new risk factor for type 2 diabetes and the metabolic syndrome, with the presence of opposite phenotypes of glucose and lipid metabolism among normal-weight Koreans of similar body composition.
Methods. – Fifty subjects, randomly selected from an ongoing community-based cohort study, from two opposite phenotype groups — metabolically unhealthy normal weight (MUHNW) and metabolically healthy normal weight (MHNW) — were matched for waist circumference, visceral fat mass and demographic variables, then compared for serum concentrations of POPs.
Results. – Most POPs (10 out of 13 compounds) were present in higher serum concentrations in the MUHNW than in the MHNW. In particular, serum concentrations of all compounds of the organochlorine pesticide class were 2.2 to 4.7 times higher in cases than in controls. Compared with the lowest tertile of summary measures of POPs, Odds ratios (95% confidence interval) for the second and third tertiles were 7.4 (1.9–29.4) and 10.4 (2.6–41.2), respectively. Adjusting for possible confounders did not change the results.
Conclusion. – Taken altogether, these findings from the present and previous studies suggest that increased serum POP concentrations may play an important role in the development of unhealthy metabolic phenotypes in lean people.

Introduction

Chronic exposure to low-dose persistent organic pollutants (POPs), strong lipophilic chemical combinations stored mainly in adipose tissues and continuously released into the bloodstream, has recently been linked to type 2 diabetes (T2D) and the metabolic syndrome (MetS) [1,2]. Although obesity is a confirmed risk factor for these common clinical conditions, this viewpoint needs to be re-evaluated because, nowadays, there is no adipose tissue without POP contamination in our modern societies [3].

Also, there are people referred to as "metabolically healthy obese" (MHO) who are obese, yet have normal metabolic profiles [4]. A recent epidemiological study has reported that MHO individuals have distinct profiles of serum concentrations of polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs), compounds typically belonging to POPs, compared with "metabolically unhealthy obese" (MUHO) individuals [5].

On the other hand, there is a unique subset of those who are of normal weight, yet have abnormal metabolic profiles; these people are classified as "metabolically unhealthy normal weight" (MUHNW) [6]. At present, a high percentage of body fat, low fat-free mass and large waist circumference are considered factors differentiating the MUHNW from the "metabolically healthy normal weight" (MHNW) [7].

However, there is also the possibility that POPs may be associated with the metabolic phenotype in normal-weight individuals just as they are in the MHO and MUHO. This hypothesis can best be tested in Asian populations, as a greater risk of metabolic abnormalities among people with low body mass index

* Corresponding author. Department of Endocrinology and Metabolism, Ajou University School of Medicine, 164 World cup-ro, Yeongtong-gu, Suwon 16499, Republic of Korea.
** Co-corresponding author. Department of Preventive Medicine, School of Medicine, Kyungpook National University, 680, Gukchaebosang-ro, Jung-gu, Daegu 41944, Republic of Korea.
E-mail addresses: djkim@ajou.ac.kr (D.J. Kim), lee_dh@knu.ac.kr (D.H. Lee).

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(BMI) scores is more commonly observed in Asian than in Caucasian populations [8].

Thus, the present study aimed to evaluate whether serum concentrations of POPs in the MUHNW are higher than in the MHNW among lean Koreans with BMI scores < 25 kg/m^2. As the study also intended to investigate the role of POPs after excluding factors related to visceral obesity, these two groups were carefully matched for waist circumference and visceral fat mass as well as for age and gender.

Methods

This matched case–control study was conducted with data from the Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) study, a prospective cohort study ongoing since 2013. Detailed information on the CMERC study has been described elsewhere [9]. Our present study was performed with participants recruited in Suwon-si, Yongin-si and Hwaseong-si in 2016. The study protocol was reviewed and approved by the Institutional Review Board of Ajou University (IRB No. AJIRB-BMR-SUR-13-272), and all participants provided written informed consent before participation.

Of the 2640 participants who agreed to the collection of additional sera for the POP measurements, there were 189 MUHNW subjects with BMI scores < 25 kg/m^2 who met MetS criteria, whereas 1449 MHNW with BMI scores < 25 kg/m^2 did not meet these criteria. MetS was defined according to the modified National Cholesterol Education Program (NCEP)/Adult Treatment Panel (ATP)-III definition. Among the components of MetS, POPs were more consistently associated with abnormalities of glucose or lipid metabolism than of blood pressure, according to previous studies [10]. Therefore, 50 MUHUW cases with abnormalities of both glucose and lipid metabolism (fasting glucose ≥ 100 mg/dL, triglycerides ≥ 150 mg/dL, high-density lipoprotein [HDL] cholesterol < 40 mg/dL in men or < 50 mg/dL in women) were selected. Controls were randomly matched to each MUHNW subject for age (± 3 years), gender, waist circumference (± 2 cm) and visceral fat mass (± 0.1 kg) from MHNW subjects who had no metabolic abnormalities of either glucose or lipid metabolism. The sample sizes used for this study were calculated to detect an odds ratio (OR) of 3.15 with a power of 80%.

As details of the measurement of demographic information, medical history and health-related behaviours were presented in a previous article on the CMERC study [9], the present report only briefly describes how the indices related to obesity were measured. Height (cm) and weight (kg) were measured using an automatic height–weight scale (BSM330; InBody Co., Ltd., Seoul, Republic of Korea), and BMI was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured at the midpoint between the lowermost ribs and iliac crest with a measuring tape (seca GmbH & Co. KG, Hamburg, Germany). Whole-body dual-energy X-ray absorptiometry (DXA) scans were performed using a Lunar iDXA densitometer (GE Healthcare, Chicago, IL, USA) and analyzed using its enCORE software platform (GE Healthcare).

All blood samples were collected after 8 h of fasting, and biochemical assays were performed at a centralized laboratory (Seoul Clinical Laboratories, Seoul, Republic of Korea). HDL cholesterol and triglyceride levels were determined using enzymatic methods; fasting glucose and insulin levels were determined using a colorimetric method and radioimmunoassay (SR 300; STRATEC Biomedical Systems AG, Birkenfeld, Germany), respectively. Resting systolic and diastolic blood pressures were measured three times using an automated blood pressure monitor (HEM-7080IC; Omron Healthcare, Lake Forest, IL, USA). Homoeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting glucose (mg/dL) × fasting insulin (μIU/mL)/405 [11].

Serum concentrations of PCBs and OCPs were determined at the laboratory of Hanyang University (Ansan, Republic of Korea) using high-resolution gas chromatography (HRGC) with high-resolution mass spectrometry (HRMS; AutoSpec Premier, Waters Corp., Milford, MA, USA). Although a total of 37 POPs (19 PCBs and 18 OCPs) were measured, seven PCBs and six OCPs were selected that had detection rates ≥ 70%: PCB 105; PCB 118; PCB 138; PCB 153; PCB 170; PCB 180; PCB 187; β-hexachlorocyclohexane; p,p′-dichlorodiphenyldichloroethylene (DDE); p,p′-dichlorodiphenyltrichloroethane (DDT); trans-nonachlor; cis-nonachlor; and heptachlor epoxide. For this study, wet concentrations of POPs were used. As dyslipidemia was used to define cases, lipid-standardized concentrations—obtained by dividing wet-weight concentrations by total serum lipids—were not valid, as previously discussed [1]. POP concentrations below the limit of detection (LOD) were assigned the value of LOD/3. Table S1 (Supplementary data, Table S1see supplementary materials associated with this article online) presents the detection rates and distributions of the selected POP concentrations.

First, serum concentrations of 13 individual compounds from the case and control groups were compared. Second, associations between POPs and the risk of MUHNW were obtained by multiple logistic regressions. In these analyses, results based on summary measurements of POPs were primarily used because people are exposed to various combinations of POPs and the serum concentrations of each compound are strongly correlated (0.45–0.79 for six OCPs and 0.42–0.99 for seven PCBs in the present study subjects). Three summary measures were calculated by summing the rank orders of the individual compounds belonging to the seven PCBs, six OCPs and all POPs (the former two), and the summed measures were then categorized into tertiles. Summary measures based on absolute concentrations of each compound were not used because only a few compounds with high concentrations, such as p,p′-DDE, largely determined the summed values.

Because our study was matched for age-, gender- and obesity-related indices, physical activity, smoking status and a family history of T2D were considered possible confounders. HOMA-IR was also considered a possible confounder because insulin resistance can increase serum concentrations of POPs through uncontrolled lipolysis in adipocytes [12], although this may have been an overadjustment as POPs can also induce insulin resistance [13]. All analyses were conducted using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of our study participants are presented in Table S2 (Supplementary data, Table S2see supplementary materials associated with this article online). Distributions of age, gender, BMI, waist circumference, total fat mass, total lean mass and visceral fat mass levels were similar between the case and control groups. In addition, percentages of physical activity, smoking status and family history of T2D were similar between the groups. However, systolic blood pressure, triglycerides, HDL cholesterol, fasting glucose, fasting insulin and HOMA-IR were significantly higher in MUHNW than in MHNW individuals.

Fig. S1 (Supplementary data, Fig. SIsee supplementary materials associated with this article online) compares the serum concentrations of each compound by metabolic phenotype. Most POPs (10 out of 13 compounds) showed significantly higher serum concentrations in the MUHNW than in the MHNW. In particular,