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The role of oxidative stress in cardiometabolic risk related to phthalate exposure in elderly diabetic patients from Shanghai

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ABSTRACT

The effect of human exposure to phthalates and consequent contribution to the development of cardiometabolic health problems is unknown. However, oxidative stress has been established as playing an important role in the pathogenesis of cardiometabolic outcomes. In this study, we aimed to explore whether exposure to phthalate metabolites could induce cardiometabolic risk by increasing oxidative stress in a diabetic population from Shanghai. We collected paired blood and urine samples from a total of 300 volunteers, and measured 10 phthalate metabolites in urine and biomarkers of oxidative stress from serum including glucose and lipid levels, and liver and kidney damage. The insulin resistance (IR) risk was assessed by the surrogate indices including homeostasis model assessment-insulin resistance (HOMA-IR) and triglyceride glucose (TyG). We used multivariable linear regression to assess the association between phthalates and these physiological parameters. Mediation and modification analyses were performed to identify the role that oxidative stress played in the underlying mechanisms. The results showed that most of the determined phthalate metabolites were positively associated with HOMA-IR, 8-hydroxy-2′-deoxyguanosine (8-OHDG), and malondialdehyde (MDA). In the mediation analysis, only γ-glutamiltransferase (GGT) was found to be a significant mediator of the association between phthalates and TyG. In the modification analysis, exposure to phthalates strengthened the association between oxidative stress (MDA and 8-OHDG) and HOMA-IR. Our findings demonstrate that exposure to phthalates might be positively associated with elevated IR and oxidative stress. The direct participation (mediation effect) of GGT might play an important mechanism in promoting IR.

1. Introduction

Cardiovascular disease (CVD) and metabolic disease pose significant personal, societal, and economic burdens. The inter-relationship between CVD and metabolic disease is termed cardiometabolic health (Cassidy et al., 2017). Many research studies have established the role of food, physical activity, lifestyle, and genetic variations in the etiology of cardiometabolic risk. Meanwhile, there is increasing recognition of the metabolic impact of environmental endocrine disruptors (EEDs). A number of phthalates, including butyl benzyl phthalate (BBzP), di-nbutyl phthalate (DBP), diethyl phthalate (DEP), and di-(2-ethylhexyl) phthalate (DEHP) are well recognized as EEDs due to their reproductive and developmental toxicity (Lind and Lind, 2011; Martino-Andrade and Chahoud, 2010). Phthalates are a group of synthetic chemicals predominantly used as plasticizers in industrial applications (Schettler, 2006; Chou and Wright, 2006). They can be detected ubiquitously from human urine due to the wide range use of phthalate-containing products (Koo and Lee, 2004; Silva et al., 2005).

Disturbed production of androgen hormones by phthalates may be associated with a number of cardiometabolic health problems, including type 2 diabetes (T2D), CVD, metabolic syndrome, liver and kidney dysfunction (Swan, 2008; Pan et al., 2006; Main et al., 2006). There is an emerging body of evidence, which suggests that phthalates may obstruct lipid and glucose homeostasis and may induce insulin

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resistance (IR), leading to an increased risk of T2D or CVD (Kim et al., 2013; Lind et al., 2012a; James-Todd et al., 2012; Svensson et al., 2011). However, the link is limited and evidence is inconsistent. With respect to CVD in particular, the majority of previous studies have been limited to pregnant women, children and their mothers in birth cohorts (Trasande and Attina, 2015; Trasande et al., 2013). Even in these specific populations, the link remains inconclusive. The conflicting findings could be due to the different populations and statistical methods used, while the cross-sectional design used in most of the previous studies would not be able to determine if phthalate exposure was associated with relevant outcomes. The associations between short-term exposure assessment biomarkers and long-term outcomes may also lead to a high degree of inconsistency in previous literature. Therefore, it is largely unknown whether or not human exposure to phthalates can contribute to the development of T2D or CVD, even if the risk is likely to be true in theory.

The onset of T2D and metabolic syndrome after exposure to phthalates would suggest that IR is an important underlying mechanism, and some studies have suggested that oxidative stress alterations, induced by phthalates, is a causative factor (Tran et al., 2017). There is strong experimental evidence to support adverse effects of phthalate exposures on pathways of oxidative stress related to metabolic disease development (Meruvu et al., 2016). However, population-based evidence is very limited. Several human studies have shown an association between urinary phthalate metabolites and oxidative stress (Tran et al., 2017; Rocha et al., 2017). Recently, one study reported that phthalates were associated with oxidative stress in patients with diabetes (Duan et al., 2017). However, the generation of reactive oxygen species (ROS) is already enhanced in diabetes patients, therefore it is difficult to determine if elevated oxidative stress is the cause or symptom in diabetes patients. Thus, it is still unclear whether phthalate exposure affects cardiometabolic risk by elevating oxidative stress or whether the interaction between oxidative stress and phthalate exposure affects cardiometabolic risk in diabetes patients.

To investigate the potential influence of phthalates on cardio-metabolic risk and the possible role of oxidative stress, we performed a cross-sectional study of cases. We initially examined the relationship between urinary levels of phthalate metabolites and cardiometabolic risk factors including serum levels of glucose, lipid, biomarkers of hepatic and kidney damage, and the IR risk assessed by surrogate indices. Then, we used the conceptual models of moderation and mediation effects suggested by Bolin et al. (Bolin, 2014) to explore the role of oxidative stress on the relationship between phthalates and cardiometabolic risk factors. In mediation models, a mediator variable explains why a relationship exists between the predictor and outcome variables. In a moderation model, a moderator variable reduces or enhances the relationship between a predictor variable and an outcome variable, or it can even change the direction of this relationship (Bolin, 2014). Guided by these conceptual models, we formulated two hypotheses: (1) oxidative stress serves as a mediator between phthalates and cardiometabolic risk; and (2) phthalates serve as a moderator between oxidative stress and cardiometabolic risk. The evidence of (1) and/or (2) would indicate that there is a relationship between phthalates and oxidative stress, and consequent effects on cardiometabolic risk in patients with diabetes.

2. Methods

2.1. Study population

From March 2017, study participants aged > 50 years were recruited from the outpatient clinic of Huangpu Community Hospital, Shanghai, China. The hospital had their own system of diabetes health management, and required its registered diabetic patients to attend routine examinations annually on the month of March. The system had 2300 living registered individuals at the time of March 2017. Using a simple random sampling method, we invited a total of 300 registered individuals to participate in our study. All participants finished the questionnaire investigation. Characteristics of the study population, including sex, age, nationality, weight, height, smoking and alcohol-consumption status, exercise status, education level, and family history of diabetes were obtained by questionnaire. Participants reported their weekly exercise frequency ("never", "one to three times per week" and "three or more times per week"). BMI was calculated by dividing weight in kilograms by height in meters squared (kg/m^2). Participants produced snapshot urine samples, and fasting blood samples during the routine examination. The study was approved by the ethics committee of Fudan University and all participants gave their written informed consent.

2.2. Biochemical analysis (serum samples)

Fasting glucose, HbA1c, fasting insulin, triglyceride (TG), total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), alanine aminotransferase (ALT), γ-glutamiltransferase (GGT), blood urea nitrogen (BUN), creatinine (CR), and uric acid (UA), were all measured at the hospital laboratory using the fasting serum samples. In this study, 8-hydroxy-2′-deoxyguanosine (8-OHDG), and malondialdehyde (MDA) in fasting serum were determined as oxidative biomarkers. All biochemical indices were quantitatively determined using the sandwich enzyme–linked immunosorbent assays kit (R &D Systems, MN, USA) according to the manufacturer's instructions.

2.3. Derived parameters

The homeostasis model assessment-insulin resistance (HOMA-IR) was used as an index of IR. This was calculated as (fasting insulin × glucose) / 22.5. The triglyceride glucose (TyG) index, recently proposed as a surrogate marker of IR (Unger et al., 2014), was calculated as ln (TG [mg/dL] × glucose [mg/dL] / 2).

2.4. Phthalate analysis (urine samples)

Urine collection and metabolite measurement was previously described using liquid chromatography tandem mass spectrometry (API 4000, LC-MS/MS, Shimadzu, USA). Details pertaining to this methodology have been provided elsewhere. Briefly, 1 mL of urine sample was incubated with β-glucuronidase at 37 °C for 120 min. The sample was subsequently acidified with 1 mL of aqueous 2% (v/v) acetic acid, mixed with 100 μL of internal standard (100 μg/L), and loaded on to a PLS column previously activated with 2 mL methanol and 2 mL of aqueous 0.5% (v/v) acetic acid. After sample loading, the column was washed and eluted with 1 mL of methanol and 2 mL of aqueous 0.5% (v/v) acetic acid, respectively. The eluate was passed through a 0.2-μm filter and analyzed (10 μL) by LC-MS/MS coupled to an AQUASIL C18 column.

For the quality control of laboratory procedures, we processed four matrix-spiked samples at two different spiking concentrations (10 and 25 ng/mL), and two procedural blanks in each batch of 30 samples. The average recoveries and relative standard deviations (RSD) of target metabolites in spiked samples ranged from 71.5% to 109.1% and from 1.2% to 7.4% at 10 ng/mL respectively, and ranged from 58.5% to 139.2% and from 0.8% to 8.1% at 25 ng/mL, respectively. Trace concentrations of MEP, MnBP, MiBP, and MEHP were detected in procedural blanks with average concentrations and RSDs ranging from 0.05 to 0.8 μg/L and from 3.7% to 9.3%, respectively. Sample concentrations of these metabolites were determined after subtraction of the blank values (Dong et al., 2017a). The results of quality assurance are presented in Table S1.

Ten phthalate metabolites were measured in this study, including monomethyl phthalate (MMP), monoethylphthalate (MEP), mono-n-butylphthalate (MnBP), monoisobutylphthalate (MiBP),

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