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Elevated inflammatory Lp-PLA2 and IL-6 link e-waste Pb toxicity to cardiovascular risk factors in preschool children☆

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ABSTRACT

Cardiovascular toxicity of lead (Pb) manifests primarily as an effect on blood pressure and eventual increased risk of atherosclerosis and cardiovascular events. Therefore, we investigated vascular inflammatory biomarkers and cardiovascular effects of Pb-exposed children. A total of 590 children (3–7 years old) were recruited from Guiyu (n = 337), an electronic waste (e-waste)-exposed group, and Haojiang (n = 253), a reference group, from November to December 2016. We measured child blood Pb levels (BPbs), and systolic and diastolic blood pressure. Pulse pressure was calculated for the latter two. Serum biomarkers including lipid profiles and inflammatory cytokines, and plasma lipoprotein-associated phospholipase A2 (Lp-PLA2) were detected. Unadjusted regression analysis illustrated that higher ln-transformed BPb associated with lower systolic blood pressure and pulse pressure. After adjustment for various confounders, the relational degree of lnBPb and blood pressure measures became slightly attenuated or not significant. Elevated BPb was associated with higher Lp-PLA2, interleukin (IL)-6, triglycerides (TG) and lower high-density lipoprotein (HDL). Lp-PLA2 remained inversely associated with pulse pressure and HDL, but positively with ratios of total cholesterol to HDL (Tc/HDL) and low-density lipoprotein to HDL (LDL/HDL). IL-6 was associated negatively with systolic blood pressure, pulse pressure and HDL, and positively associated with TG, Tc/HDL and LDL/HDL. The mediation effect of biomarkers on the association of BPb with pulse pressure was insignificant except for Lp-PLA2. Available data supports the conclusion that e-waste-exposed children with higher BPbs and concomitant abnormal measures of cardiovascular physiology have an augmented prevalence of vascular inflammation, as well as lipid disorder.

1. Introduction

Environmental lead (Pb) exposure constitutes a major public health problem. Though a concerted effort to reduce Pb exposure has been attempted, e.g. the banning of tetraethyl Pb as a vehicle fuel additive (Li et al., 2014), Pb is still the most prominent and widespread environmental contaminant in Guiyu, a typical electronic waste (e-waste) recycling area in southeast China, with a nearly 30-year history of unregulated e-waste disposal (Chen et al., 2011; Lin et al., 2017; Xu et al., 2015a,b). Many electronic components (e.g. cathode ray tube screens, batteries, and resistors) and printed circuit boards are comprised of nearly 10–20% Pb, which is released into the environment by informal manual dismantling processes involving physical and chemical methods (Kaya, 2016). Although Guiyu is a site of heavy metal and organic pollutant co-exposure, local children are primarily exposed to Pb because Pb is present widely in the air, soil, water, sediment and plants (Song and Li, 2014b). Our previous investigations revealed that Pb levels in soil and dust samples are respectively 2.32-times and 4.10-times higher than nearby reference areas (Yekeen et al., 2016). Pb concentrations

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in plants along Guiyu roadsides reach up to 18.74 mg/kg (Alabi et al., 2012). In our recent study, Pb levels as high as 152.96 ng/m^3 in $PM_{2.5}$ have been observed in Guiyu (Zeng et al., 2016). Furthermore, Pb levels in the riverine surface water and sediment of Guiyu are higher than nearby reference areas (Guo et al., 2009). Our earlier studies on Guiyu residents have shown elevated placental Pb levels (median 301.43 ng/g, range 6.51–3465.16 ng/g), and elevated child blood Pb levels (BPbs) (mean 15.30 μg/dL, range 4.40–32.67 μg/dL), throughout more than a decade of Pb testing (Dai et al., 2017; Guo et al., 2010; Huo et al., 2007). Pb exposure derives from Pb-contained dust and fumes, and Pb-polluted hands, food, water, toys and clothing (Bi et al., 2015). Children are particularly susceptible to Pb, whose toxicity to physical development, hematopoietic system development, immunoregulatory response and neural activity have been shown (Liu et al., 2014; Yang et al., 2013; Zhang et al., 2016). Pb exposure has been identified as an important factor contributing to the development and severity of cardiovascular disease (CVD), such as blood pressure dysregulation, disordered lipid metabolism, and atherogenesis in adults (Cosselman et al., 2015). However, Pb-associated cardiovascular toxicity is insufficiently examined in e-waste-exposed children. Therefore, this study was designed to assess the adverse effects of Pb on cardiovascular risk factors in e-waste-exposed children.

CVD is a major burden on society, and has been developing at younger ages (Danaei et al., 2014). CVD risk factors involve any measurable quality that may be related to an increased probability of developing future CVD (Poreba et al., 2011). Recent epidemiologic evidence identifies Pb hazard in cardiovascular outcomes, such as stroke, coronary heart disease and peripheral arterial disease, where functional mechanisms of oxidative stress play a vital role (Lamas et al., 2016; Navas-Acien et al., 2007; Solenkova et al., 2014). Furthermore, Pb causally promotes CVD in animal studies, and impairs cardiac and vascular function *in vivo* and *in vitro*, where activation of signaling pathways and inflammatory proteins are possible underlying mechanisms (Fioresi et al., 2013; Simoes et al., 2015; Wildemann et al., 2016). Persistent vascular inflammation may initiate the development of atherosclerotic plaques (Widlansky and Gutterman, 2011). The cardiovascular toxicity of Pb manifests primarily as an effect on blood pressure, and eventually as an increased risk of atherosclerosis and cardiovascular events (Prokopowicz et al., 2017). Pb exposure promotes generation of superoxide and hydrogen peroxide in human vascular smooth muscle and endothelial cells (Ni et al., 2004), and endothelial metabolic dysfunction might impede the transport and metabolism of lipids (Eelen et al., 2015). Ratios of total cholesterol to high-density lipoprotein cholesterol (Tc/HDL) and low-density lipoprotein to HDL (LDL/HDL) are better predictors of CVD than LDL or Tc alone. Based on above theories, we examined potential cardiovascular risk factors of Pb-exposed children examining for disordered regulation of blood pressure and lipid profiles.

During the pathophysiological progression of CVD, biomarkers of endothelial inflammation are mechanistically related to endothelial dysfunction and atherosclerotic risk (Peng et al., 2013). Lipoprotein-associated phospholipase A2 (Lp-PLA2), as a vascular-specific inflammatory biomarker, is a pro-inflammatory enzyme that has been implicated in oxidative damage, cytokine release, vascular dysfunction, and lipid metabolism disorders, characteristic of atherosclerotic progression (Ragab et al., 2015). Mainly expressed in monocytes, neutrophils, macrophages and activated platelets, Lp-PLA2 hydrolyzes oxidized phospholipids to yield pro-inflammatory and pro-atherogenic products (e.g. oxidized fatty acids and lyso-phosphatidylcholine) (Chae et al., 2011; Sakka et al., 2015). These products stimulate the expression of endothelial adhesion molecules and cytokines, and recruit monocytes, which are then activated and transformed into macrophages and apoptotic foam cells, ultimately facilitating fatty streak formation and atherosclerosis (Ikonomidis et al., 2014; Li et al., 2017; Oei et al., 2005; Rosenson and Stafforini, 2012). Ambient pollution exerts adverse effects on Lp-PLA2 (Bruske et al., 2011), possibly through oxidative stress-mediated up-regulation of Lp-PLA2 to accelerate atherosclerotic progression (De Keyzer et al., 2009; Wu et al., 2004). Environmental pollutants induce mitochondrial oxidative injury, activate autophagy, and increase the production of inflammatory cytokines [tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-8 and IL-6], especially in susceptible populations (Ruckerl et al., 2014; Zhang et al., 2017). Additionally, the generation of reactive oxygen species (ROS) can stimulate the expression of cytokine cascades through NF-κB-induced transcriptional events (Zhang et al., 2009). IL-1β contributes directly to atherosclerotic plaque development via increased production and decreased clearance of lipid metabolites (McCarty and Frishman, 2014). IL-6 is up-regulated in response to ROS and vascular injury, and highly representative of vascular inflammation, in which the NF-κB-IL-6 signal pathway plays a central role (Brasier, 2010). Previous studies show serum IL-6 is a significant predictor of cardiovascular mortality (Eder et al., 2009; Su et al., 2013). IL-8 acts as a mediator of angiogenesis that could contribute to atherosclerotic plaque formation (Koch et al., 1992). TNF-α up-regulates the expression of arginase in endothelial cells that favors endothelial dysfunction, and increases the transcytosis of lipoproteins across endothelium to accelerate the pathogenesis and progression of atherosclerosis (Zhang et al., 2014). Taken collectively, current evidence highlights the pivotal roles of Lp-PLA2 and cytokines in mediating vascular inflammation, the earliest steps to atherosclerosis.

Available epidemiological research has scarcely explored the pro-inflammatory role of cytokines and Lp-PLA2 in the relationships between BPb and CVD risk factors in susceptible children. The present study aims to investigate preschool children recruited from an e-waste recycling area and the reference area, to evaluate the effects of BPb on CVD risk factors, including blood pressure and lipid profiles. We hypothesize that the capacity of Pb to impair vascular structure will exacerbate endothelial inflammation, perturb blood pressure and reduce the ability to clear lipids, ultimately raising atherosclerotic risk.

2. Materials and methods

2.1. Study population

A total of 590 children (3–7 years old) from Guiyu (n = 337), an e-waste exposed group, and Haojiang (n = 253), a reference group located 31.6 km to the east of Guiyu, were recruited from November to December 2016. The both groups exhibited similar ethnicity, cultural background and population. A questionnaire, on general demographic characteristics, residential environment, child lifestyle and diet habits, and both parent and child medical or disease histories, was administered to children's parents or guardians. All children were screened at entry and enrolled in the study if they were free of any known medical conditions or infectious diseases or CVD. All procedures involving human subjects were approved by the Human Ethics Committee of Shantou University Medical College, China. All participants' guardians provided signed informed consent prior to enrollment. As described previously, fasting venous blood was collected from volunteers (Zhang et al., 2016). Serum was used for lipid profile detection. The rest of the serum supernatant, plasma and whole blood were aliquoted and stored at −80 °C until analysis.