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Association among total serum isomers of perfluorinated chemicals, glucose homeostasis, lipid profiles, serum protein and metabolic syndrome in adults: NHANES, 2013–2014☆

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ABSTRACT

Perfluorinated chemicals (PFCs) have been used widely in consumer products manufacture. Recent in *vitro* as well as animal studies have found that there are different toxicity and pharmacokinetic profiles between isomers of perfluorooctanoic acid (PFOA) and/or perfluorooctane sulfonate (PFOS). However, the differential effects of linear or branched PFOA/PFOS isomers on human beings have never been reported. Herein, we examined 1871 adult subjects (age older than 18 years) from the National Health and Nutrition Examination Survey (NHANES) 2013–2014 to determine the association between the isomers of PFOA/PFOS and serum biochemistry profiles, including glucose, lipids, protein and components of metabolic syndrome (MS). The results showed that for PFOA, increased linear PFOA was associated with increases in total cholesterol, serum albumin and an enhancement of β cell function as well as a decrease in the serum globulin. Increased branched PFOA was significantly associated with increased fasting glucose. All isomers of PFOA were positively associated with high-density lipoprotein-cholesterol (HDL-C) and negatively associated with glycohemoglobin (HbA1C). The branched PFOS was positively associated with β cell function and inversely associated with serum globulin. Both linear and branched isomers of PFOS were positively associated with the total protein and albumin. The increased branched PFOA was associated with less HDL-C insufficiency defined by the National Cholesterol Education Program Third Adult Treatment Panel (NCEP-ATP III) MS criteria, whereas the increased concentrations of serum total and linear PFOS were associated with less hypertriglyceridemia by the NCEP-ATP III. In conclusion, serum isomers of PFOA and PFOS were associated with glucose homeostasis, serum protein as well as lipid profiles; they were also indicators of MS. This may suggest that there is a distinct difference in the toxicokinetics of the isomers of PFOA and PFOS. Further clinical and animal studies are warranted to clarify the putative causal relationships between isomers and biochemical alterations.

1. Introduction

Perfluorinated chemicals (PFCs) are fluorocarbons with at least one additional atom or functional group (primarily carboxylate, sulfonate, or phosphonate). PFCs are exclusively man-made chemicals that are used to manufacture a variety of consumer and industrial products (Houde et al., 2006). Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), belong to the eight-carbon backbone subgroup, are the two most widely known PFCs. PFOS was added to Annex B of the Stockholm Convention on persistent organochlorine pollutants in 2009 and the use of PFOS has been regulated in Europe since 2008 (2010). In human epidemiological studies, PFOS and/or PFOA exposure have reported associations with clinical outcomes, including cholesterol metabolism, cardiovascular risks (Lin et al., 2013; Min et al., 2012; Shankar et al., 2012), insulin resistance and metabolic syndrome

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(Lin et al., 2009), endocrine dysfunction (Lin et al., 2014) and lower birth weight (Fei et al., 2007). The public health relevance of exposure to PFCs is still being examined because of its widespread persistence and its long-term health implications are still not clear (Lau et al., 2007).

PFCs and their precursors are produced by two major methods, telomerization and electrochemical fluorination (ECF). A linear product of PFOA was manufactured by the telomerization method developed by DuPont since the 1970s. The ECF process is known to yield a mixture of linear (70% for PFOS and 80% for PFOA) and branched isomers (30% for PFOS and 20% for PFOA), as produced by 3M Co. Since the 1940s (Prevedouros et al., 2006). Since 2002, the major manufacturer of ECF PFOS and PFOA, 3M, has been decreasing production, and telomerization has become the main method for producing PFOA since then (Parsons et al., 2008). Thus, the global production of PFOS has declined. However, the production of PFOS has continued in some developing countries (Xie et al., 2013).

In animals, the pharmacokinetics of PFOA and PFOS isomers has been evaluated in animals in various studies (Benskin et al., 2009a; De Silva et al., 2009; O'Brien et al., 2011). These studies have shown a consistent preferential bioaccumulation of linear isomers of PFOA and PFOS in animals. In humans, only one study evaluated the renal clearance of isomer-specific elimination of PFOA or PFOS. It showed a higher urinary excretion of branched isomers (Zhang et al., 2013a), of which might be explained by the higher binding affinities of linear isomers of PFOA and PFOS to serum proteins (Beesoon and Martin, 2015). On the contrary, several previous studies identified branched-PFOS are preferentially retained in human bodies using blood-derived samples (Haug et al., 2009; Karrman et al., 2007; Riddell et al., 2009; Zhang et al., 2013b). These contradicted findings might result from the fundamental differences between animal and human studies, the study population or the methods of study.

In human epidemiological studies, few studies have reported the effects of PFOS and/or PFOA isomers on clinical outcomes. A recent study revealed the profile of PFOS isomer, and the toxicities of individual PFOS isomers by assessing seven PFOS isomers in drinking water in China (Yu et al., 2015). In this report, Yu et al. found that linear PFOS carries the highest risk among all assessed PFOS isomers with respect to thyroid hormone perturbation. Similarly, Jiang et al. evaluated the association between PFOA/PFOS isomers and several clinical parameters in 141 pregnant Chinese women identified that PFOA and PFOS displayed distinct correlations with hematological and biochemical parameters (Jiang et al., 2014). The correlation pattern mostly remains the same within either the PFOA or PFOS group, e.g. the white cell count is negatively associated with levels of linear- and branched PFOA, but positively associated with those of linear- and branched PFOS (Jiang et al., 2014). Furthermore, recent studies demonstrated that PFOA and PFOS can be efficiently transported across the placenta (Chen et al., 2017) with a isomer-dependent concentration difference in umbilical cord serum (Zhang et al., 2017). This suggests that any health effects PFCs may exert are limited not only to the directly exposed individuals but also their offspring.

We previously presented the first report of the correlation between PFCs, glucose homeostasis and metabolic syndrome (Lin et al., 2009). To further explore the role of PFOA/PFOS isomers in clinical outcome, we hypothesized that PFOA/PFOS isomers might have differential effects on clinical outcomes in humans. The goal of this present study is to determine the association between the serum levels of different PFOA/PFOS isomers and biochemical parameters, including glucose homeostasis, serum proteins, lipid profile and metabolic syndrome (MS), by examining data from the NHANES that was collected from year 2013–2014.

2. Materials and methods

2.1. Study design and population

The data were from NHANES 2013–2014. The NHANES is a population-based national survey designed to collect information on the health and nutrition of the U.S. household population and to obtain a representative sample of the non-institutionalized civilian U.S. cohort. Every 2 years, the survey data are released to public. The comprehensive survey operation manuals, consent documents, and brochures of the NHANES 2013–2014 are accessible on the NHANES website (2013-2014). In this study, we limited our analyses to 1871 participants who are at least 18 years of age with blood test results for linear and branched PFOA and PFOS isomers in this study.

2.2. Anthropometric and biochemical data

Based on the statements of the NHANES website, survey data were collected at all study sites by well-trained personnel in accordance with standardized procedures. Sociodemographic information, including age, gender, and race/ethnicity, education level and household income was collected during the household interview. Alcohol intake was determined by the pre-defined questionnaire and was dichotomized. The smoking status was categorized as active smoker, secondhand smoker and non-smoker based on a smoking questionnaire (2016a). Body weight and height were measured using standard methods. Three, and up to 4 blood pressure determinations were collected by a physician using a traditional mercury sphygmomanometer. Blood pressure was measured in the right arm unless otherwise specified. The average systolic and diastolic BP were both obtained. Blood specimens were processed locally and then stored and shipped to central laboratories for analysis. The laboratory measurements were carried out in a mobile examination center. Detailed instructions on specimen collection and processing are discussed in the NHANES Laboratory Procedures Manual (2013). In the present study, laboratory data included insulin, total protein, albumin, globulin, apolipoprotein B, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triglyceride from serum, fasting glucose and two-hour glucose after oral glucose tolerance test from plasma, as well as glycohemoglobin (HbA1C) from whole blood. The insulin resistance status was measured by homeostatic model assessment of insulin resistance (HOMA-IR). The HOMA-IR derived from fasting insulin and glucose (HOMA-IR = [fasting insulin (mIU/L) x fasting glucose (mg/dL)]/405) (Matthews et al., 1985), is widely used in clinical trials and human epidemiological studies to represent insulin resistance. The β-cell function was estimated by the updated HOMA2-IR (Wallace et al., 2004), which is a computerized model to further increase the accuracy of insulin resistance prediction.

2.3. Definition of MS

For subjects above 18 years of age, the diagnosis of MS was based on the National Cholesterol Education Program Third Adult Treatment Panel (NCEP-ATP III) (Clearfield et al., 2014) guidelines of those who present with at least 3 of the following qualifications: waist measurement greater than 35 inches for women and greater than 40 inches for men; serum triglyceride ≧ 150 mg/dl; serum HDL-C < 40 mg/dl in men and <50 mg/dl in women; systolic blood pressure ≧130 mmHg or diastolic blood pressure ≧ 85 mmHg or a self-report of taking anti-hypertensive medications; and fasting glucose ≧ 100 mg/dl or a self-report of taking anti-hyperglycemic medications. The HDL insufficiency was defined here if serum HDL-

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