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Serum perfluorinated chemicals, glucose homeostasis and the risk of diabetes in working-aged Taiwanese adults ☆

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ABSTRACT

Background: The link among perfluoroalkyl and polyfluoroalkyl substances (PFASs), abnormal glucose homeostasis and the risk of diabetes has been intensively debated with conflicting evidence.
Objectives: We evaluated the associations among PFASs, oral glucose tolerance testing (OGTT) curves and diabetes prevalence in 571 working-aged Taiwanese participants.
Methods: Exposure measures included serum perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA), and perfluoroundecanoic acid (PFUA). Outcomes were OGTT curves and prevalent diabetes defined by fasting blood glucose (FBG) ≥126 mg/dL, 2-h glucose ≥200 mg/dL, or glycated hemoglobin ≥6.5%. Analyses were performed with multiple logistic regression and functional data analysis.
Results: A total of 39 participants (6.8%) had diabetes in this study. After full adjustment, the increase in the geometric means of FBG, 2-h glucose concentrations, and area under the OGTT curve (AUC_{120}) with a doubling increase in PFOS was 3% (95% CI 1–4), 8% (5–12), and 6% (4–9), respectively. Compared to the lowest-quartile of PFOS concentrations (<2.4 ng/ml), the OGTT trajectories were significantly steeper in participants of the highest-quartile PFOS exposure (>4.8 ng/ml) and the vertical shifting of the mean curve for each PFOS quartile showed a dose–response pattern. The adjusted odds ratio for diabetes comparing the highest to lowest quartile was 3.37 (95% CI 1.18–9.65). For PFOA, PFNA, and PFUA, the opposite pattern of OGTT trajectory and the opposite risk profile for diabetes were observed.
Conclusions: Chronic PFOS exposure was associated with impaired glucose homeostasis and the increased prevalence of diabetes. However, PFOA, PFNA, and PFUA showed a potential protective effect against glucose intolerance and the risk of diabetes. Future research focusing on clarifying possible differential effects of different species of PFASs on glucose homeostasis and establishing the prospective associations between PFASs and diabetes is needed.

1. Introduction

Extensive industrial and commercial applications of perfluoroalkyl and polyfluoroalkyl substances (PFASs) as surfactants, emulsifiers, repellents, paper and textile coatings, non-stick frypan coatings, and food packaging and their persistence in the environment has led to a global PFC exposure (Begley et al., 2005; Buck et al., 2011; Calafat et al., 2007; Lau et al., 2007). The human exposure of PFASs in both occupational and general populations has been recognized (Calafat et al., 2007; Costa et al., 2009; Fei et al., 2007). Although the routes of human exposure remain unclear, potential sources include food (e.g., contaminated marine products and food packaging contamination), drinking polluted water, and indoor dust (Lau et al., 2007).

PFASs are a generic term for a family of perfluoroalkyl and polyfluoroalkyl acids (PFAAs) that are composed of a fluorinated carbon backbone with varying length and a charged carboxylate or sulfonate functional group (Buck et al., 2011; Furl et al., 2010). This structure makes them resistant to biodegradation and dramatically lower surface tension (Conder et al., 2008). The most widely known perfluorinated carboxylates are perfluorooctanoic acid (PFOA) and perfluorononanoic

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acid (PFNA) and for perfluorinated sulfonates, they are perfluorooctyl sulfonic acid (PFOS) and perfluorohexane sulfonic acid (PFHxS) (Lau et al., 2007). PFASs are well absorbed orally and are slowly eliminated in human body without further biotransformation (Lau et al., 2007). The estimated mean serum half-lives are about 5.4 and 3.8 years for PFOS and PFOA, respectively (Olsen et al., 2007).

Increasing evidence has linked PFASs to diverse health effects including carcinogenesis (EPA, 2014), atherosclerosis (Lin et al., 2013), lipid metabolism (Fletcher et al., 2013), glucose homeostasis (Lin et al., 2009), and developmental toxicity (Lau et al., 2007; White et al., 2007). However, the potential mechanisms underlying glucose metabolism disturbance by PFASs remains controversial. Experimental studies has shown the obesity-related metabolic effects of PFASs including endocrine disrupting capacity and differential activation of nuclear receptors especially peroxisome proliferator-activated receptors (PPARs) (White et al., 2011). Recent animal studies also support the potential diabetogenic effect of PFASs (Lv et al., 2013; Wan et al., 2014; Wang et al., 2014). Epidemiologic studies investigating the association between PFASs and diabetes are scarce and the results are not consistent. In a retrospective occupational cohort study, PFOA was associated with a statistically significant increase in diabetes mortality (DuPont, 2006). A Swedish cross-sectional study of the elderly found a significant association between PFASs and diabetes prevalence (Lind et al., 2014). However, this finding was not supported by a community-based case–control study in the C8 Health Project (MacNeil et al., 2009). Among studies using insulin resistance as the endpoint, findings were also inconsistent. In NHANES 1999–2000 and 2002–2003 (Lin et al., 2009) and Danish overweight children (Timmermann et al., 2014), PFASs were associated with higher insulin resistance. However, in NAHNES 2002–2003 and cycle 1 of the Canadian Health Measure Survey (2007–2009), the association between PFASs and insulin resistance was not found (Fisher et al., 2013; Nelson et al., 2010).

The oral glucose tolerance test (OGTT), although costly and cumbersome, is currently the gold standard epidemiological and clinical diagnostic test for diabetes (WHO, 1980). The 2-h post challenge glucose level is also a better predictor of coronary heart disease and cardiovascular mortality than fasting glucose (Qiao et al., 2002). To further clarify the relationship between PFASs and glucose homeostasis, we conducted a cross-sectional study in a community-based sample of adults in Taiwan using OGTT to verify diabetes status and using area under the curve (AUC) to summarize the glucose tolerance curve.

2. Methods

2.1. Study population

Volunteers aged 20–60 years old were recruited from our previous case–control study conducted at outpatient cardiology clinics in the National Taiwan University Hospital, Taipei, Taiwan from 2009 to 2011 (Cheng et al., 2014; Ding et al., 2014). Consecutive patients were invited to participate as the control group investigating work-related factors and cardiovascular disease (Cheng et al., 2014; Ding et al., 2014). A total of 592 participants who consented to the questionnaire, interview, and blood collection and were free of clinically diagnosed diabetes (defined as self-reported physician diagnosis of diabetes and/or use of insulin or hypoglycemic medications) or self-reported coronary heart disease (CHD) or stroke were enrolled and served as subjects in this study. All eligible participants underwent a standard 2-h oral glucose tolerance test (OGTT) and measurement of plasma polyfluoroalkyl chemicals (PFASs). Among 592 participants, we excluded 20 participants who did not complete the oral glucose tolerance test due to non-compliance (missed test at either 30, 60, or 90 min) and 1 participant who was missing glycated hemoglobin level (HbA1c). The final sample size for analyses was 571 participants. This study was approved by the Institutional Review Board (IRB) and Ethics Committee of National Taiwan University Hospital.

2.2. Measurement of PFC concentrations

Plasma samples were obtained at the time of cardiovascular examination and stored frozen at −80 °C before analysis. Plasma PFASs were measured by using a Waters ACQUITY UPLC system (Waters Corporation, Milford, MA) coupled with a Waters Quattro Premier XE triple quadrupole mass spectrometer (Waters Corporation, Milford, MA). Twelve kinds of PFASs were quantified in our study including PFHxS, perfluoroheptanoic acid (PFHpA), PFNA, PFOA, PFOS, perfluorodecanoic acid (PFDeA), perfluoroundecanoic acid (PFUA), perfluorododecanoic acid (PFDoA), 2-(N-methylperfluorooctane sulfonamido) acetic acid (Me–PFOSA–AcOH), 2-(N-ethylperfluorooctane sulfonamido) acetic acid (Et–PFOSA–AcOH), perfluorohexanoic acid (PFHxA), and perfluorooctane sulfonamide (PFOSA). For an unbiased presentation, only PFASs with more than 90% detection rate were included in this analysis. Therefore, only levels of PFOA, PFOS, PFNA, and PFUA were analyzed in this study. The LOD for PFOA, PFOS, PFNA, and PFUA was 1.5, 0.22, 0.75, and 1.5 ng/ml, respectively. PFOS was not observed in any blank samples, but trace amounts of PFOA (up to 1.5 ng/mL), PFNA (up to 0.75 ng/mL), and PFUA (up to 3 ng/mL) were detected. Therefore, the background levels found in the blank samples of each batch were subtracted from the actual measurements to give the reported concentrations of PFOA, PFNA, and PFUA (Lin et al., 2013). The percent of study participants with levels blow the LOD was 4.9% for PFOA, 3.7% for PFNA, 10.1% for PFUA, and none for PFOS. Undetected PFOA, PFOS, PFNA were imputed as the LOD divided by 2 (Lin et al., 2013).

2.3. Oral glucose tolerance testing and diabetes mellitus

After a 10–14 h overnight fast, participants ingested a solution containing 75 g of dextrose while resting in bed. Blood samples were withdrawn from the antecubital vein at 30, 60, 90, and 120 min for determination of plasma glucose. Glucose tolerance was quantified as the area-under-curve integrated from 0 to 120 min (AUC_{120}) after the oral glucose challenge by the trapezoid method (Matthews et al., 1990). The plasma glucose level was determined by a glucose oxidase autoanalyzer (Technician RA 2000 Autoanalyzer, Bayer Diagnostic, Mishawaka, IN). HbA1c was measured by high-peformance liquid chromatography. Diabetes was defined as a fasting blood glucose concentration higher or equal to 126 mg/dL or a 2-h glucose level higher or equal to 200 mg/dl, or a glycated hemoglobin level higher or equal to 6.5% (American Diabetes Association, 2014).

2.4. Other variables

Socio-demographic information such as age, sex, education (categorized as ≤12 years versus >12 years of school), history of medication, physical activity, and household income was recorded during the interview. The extent of alcohol intake was determined by questionnaire and alcohol use was categorized as more than one drink per week. Smoking status was categorized as never and ever-smokers (including current and past smokers). Household income was categorized as either “above 50,000 new Taiwan dollars (NTD) per month” or “below 50,000 NTD.” Regular exercise was defined by self-reported excising more than 30 min at least 3 times of per week, or at least 1.5 h/week. Body mass index (BMI) was calculated as body weight (in kg) divided by the square of body height (in meters). Obesity was defined as a BMI ≥ 27 kg/m^2 for adult Taiwanese (Chu, 2005). Two seated blood pressure and heart rate measurements were made at least 1 min apart after 5 min of rest by using a mercury manometer and the appropriate cuff size. Hypertension was defined as a self-reported physician diagnosis, use of antihypertensive medication or systolic blood pressure > 140 mm Hg or