中文題目：有機磷酸酯阻燃劑暴露與慢性腎臟病惡化的關聯性：一個一年期縱貫性分析

英文題目：The association between exposure to organophosphate flame retardants and progression of chronic kidney disease: A one-year longitudinal analysis

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Background:

Organophosphate flame retardants (OPFRs) are widely utilized flame retardants and serve as additives in several commercial products, including furniture, building materials, clothing, electronics, coatings, and cosmetics. Despite being considered less bio-accumulative than conventional flame retardants such as polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs), OPFRs have been detected in various environmental matrices, such as bodies of water, sediments, soil, air and indoor dust, as well as biological samples. As emerging pollutants, the hazardous effects of OPFRs on human health might include neurotoxicity, developmental toxicity, reproductive toxicity, carcinogenicity, and nephrotoxicity. In previous studies, potential renal tubular toxicity of OPFRs has been identified in proximal tubule cell cultures. Additionally, the associations between renal disease and urinary OPFR concentrations have been demonstrated in the U.S. general population, according to the analysis of the U.S. National Health and Nutrition Examination Survey (NHANES) 2013–2014. However, the nephrotoxic potential of OPFRs has less been investigated in patients with chronic kidney disease (CKD). In this prospective longitudinal study, we assessed the urinary OPFR concentrations to evaluate the exposure pattern of OPFRs and the associations between renal deterioration and OPFR exposure in the CKD population.

Method:

Adult patients (≥ 20 years of age) with non-dialysis-dependent CKD stage 3–5 were recruited from a multidisciplinary renal care program in the Kaohsiung Chang Gung Memorial Hospital between December 2020 and March 2021. The concentrations of 10 OPFR compounds in first-void urine samples in the morning were measured at enrollment using an ultra-performance liquid chromatography-tandem mass spectrometry (Waters, Milford, MA, USA). Serial estimated glomerular filtration rate (eGFR) levels were collected (i.e., baseline, 6-month and 12-month eGFR levels corresponding to the levels at enrollment, 6 months after enrollment, and 12 months after enrollment, respectively). Baseline patient characteristics and comorbidities were also recorded. Categorical variables are presented as numbers (*n*) with percentages, and continuous variables are presented as medians with interquartile ranges (IQRs). To evaluate the associations between OPFR exposure and eGFR deterioration, univariate and multivariate linear generalized estimating equation (GEE) analyses were performed. For the analyses, OPFR compounds with a detection rate of ≥ 50% were included, and the limit of quantitation (LOQ)/√2 was assigned to the non-detected samples for analysis. Logarithmic transformation of urinary OPFR concentrations was performed prior to GEE analyses because of their right-skewed distributions, and the multivariate analysis was adjusted for age, sex, body mass index, CKD staging, diabetes, hypertension, severity of proteinuria, and all covariates with a p-value of < 0.05 in univariate analyses using the enter method. The effects of OPFR compounds independently associated with eGFR deterioration in the multivariate analysis were also examined in specific subgroups, stratified by sex, diabetes, CKD staging, and age.

Results:

In this investigation, 160 CKD patients were enrolled for analysis (stages 3, n = 78 (48.75%); stage 4, n = 48 (30.00%); stage 5, n = 34 (21.25%)). The median age of the cohort was 68 years (IQR, 59－76), and women accounted for 32.50% of all patients. The overall detection rate of urinary OPFRs in the study cohort was 98.75%, with a median urinary ΣOPFRs of 2.003 μg/g creatinine (Cr; IQR, 0.796－4.072), which indicated a universal exposure to OPFRs in this population. In the GEE analyses, both 6-month and 12-month eGFR levels decreased significantly compared with baseline eGFR levels, with declines in eGFR of 1.657 mL/min/1.73m^2 (95% confidence interval (CI), -2.406－-0.908, $p < 0.001$) and 2.321 mL/min/1.73m^2 (95% CI, -3.118－-1.524, $p < 0.001$), respectively. With the univariate and multivariate GEE analyses, urinary bis-2-chloroethyl phosphate (BCEP) concentration was identified as an independent predictor negatively associated with eGFR levels within one year, with a decline in eGFR of 2.645 mL/min/1.73m^2 per log μg/g Cr of BCEP (95% CI, -5.081－-0.209, p = 0.033). In the subgroup analyses, the urinary BCEP concentration remained an independent predictor of lower eGFR levels in the populations with non-diabetic status, CKD stage 4－5, and age < 65 years (β (95% CI), mL/min/1.73m^2 per log μg/g Cr of BCEP, -3.808 (-7.168－-0.448), p = 0.026; -2.780 (-4.541－-1.020), p = 0.002; -4.295 (-6.913－-1.677), p = 0.001). Furthermore, urinary BCEP concentrations were independently associated with lower eGFR levels in both female and male subgroups (β (95% CI), mL/min/1.73m^2 per log μg/g Cr of BCEP, -5.312 (-8.552－-2.072), p = 0.001; -4.547 (-7.636－-1.459), p = 0.004).

Conclusion:

In conclusion, our study indicated an extensive exposure to OPFRs in the CKD population. Among OPFRs, urinary BCEP concentration was associated with eGFR deterioration within one year, and the effects might be particularly important in CKD patients with non-diabetic status, late-stage CKD, and age < 65 years. Our findings highlight the nephrotoxic potential of OPFRs in the CKD population, and further large-scale investigation is warranted.