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Short Communication

High serum levels of *p,p'*-DDE are associated with an accelerated decline in GFR during 10 years follow-up

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HIGHLIGHTS

- Organochlorine pesticides are suspected etiological factors of chronic kidney disease.
- *p,p'*-DDE levels were associated with an accelerated reduction in renal function over 10 years.
- The results support nephrotoxicity from DDT/*p,p'*-DDE.

GRAPHIC ABSTRACT

Q1, Q2, Q3 = tertiles of *p,p'*-DDE levels at baseline at 70 years.

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ABSTRACT

Over the past 20 years, the global incidence of chronic kidney disease (CKD) has been increasing and organochlorine pesticides (such as DDT) is a suspected etiological factor. The present study examines the associations between low level background exposure to *p,p'*-DDE (1-dichloro-2,2-bis (*p*-chlorophenyl) ethylene), the main DDT metabolite, and kidney function during a 10-year follow-up. Data was analysed from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study (n = 1016, 50% women, all aged 70 years). Serum levels of *p,p'*-DDE was measured by gas chromatography coupled to high-resolution mass spectrometry (GC/HRMS) at baseline (i.e. age of 70 years). Glomerular filtration rate (GFR) was estimated using serum creatinine and cystatin C at 70, 75 and 80 years of age. A significant decline in GFR was seen during the 10-year follow-up (−24 ml/min/1.73 m2, $p < 0.0001$). A significant negative interaction was seen between baseline *p,p'*-DDE levels and change in GFR over time ($p < 0.0001$) following adjustment for sex, systolic blood pressure, diabetes, BMI, smoking and education level at age 70. Subjects with the lowest levels of *p,p'*-DDE levels at age 70 showed the lowest decline in GFR over 10 years, while subjects with the highest *p,p'*-DDE levels showed the greatest decline.

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Baseline levels of *p,p'*-DDE were related to an accelerated reduction in GFR over 10 years suggesting a nephrotoxic effect of DDT/*p,p'*-DDE. These findings support a potential role for DDT in the epidemic of CKD of unknown etiology (CKDu) in agricultural communities of Sri Lanka and Central America where DDT was previously used.

1. Introduction

The global burden of chronic kidney disease (CKD) is increasing. A large meta-analysis of worldwide data, shows a high prevalence of chronic kidney disease (CKD) ranging from 13.4% in stages 1 through 5, to 10.6% in stages 3 through 5, and the numbers are predicted to increase further (Hill et al., 2016). The reason is mainly due to the increase in the ageing population, and an increase in traditional risk factors such as diabetes and hypertension.

However, countries over a wide span of regions (sugar cane areas of El Salvador, Nicaragua, rice growing area of Egypt, India and Sri Lanka) are experiencing an epidemic of chronic tubulo-interstitial nephritis, affecting predominantly agricultural communities (Weawe et al., 2015; Gifford et al., 2017). The precise etiology is contested, and suspected factors include cadmium, glyphosate, heat stress, arsenic and fluoride, most likely some of these acting in combination. As a result, there are several names given to describe the condition: Chronic Kidney Disease of unknown etiology – CKDu, Chronic Interstitial Nephritis in Agricultural Communities (— CINAC), heat stress nephropathy, and mesoamerican nephropathy (MeN). There is also a possibility that persistent organochlorine (OC) pesticides might play a causative role, thus strengthening the argument to name it a chronic agrochemical nephropathy (Jayasinghe, 2014).

OC pesticides such as 1,1,1-trichloro-2, 2-bis (*p*-chlorophenyl) ethane (DDT) has been, or is still heavily used in some of the areas affected by CKDu. Furthermore, DDT has been shown to induce nephrotoxicity in experimental settings (Marouani et al., 2017). Therefore, we conducted a study to investigate if levels of *p,p'*-DDE (dichloro-diphenyl-dichloroethylene), the more stable break-down metabolite of DDT, were related to deterioration in kidney function.

For that purpose, we used data from the population-based Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study in which *p,p'*-DDE levels were measured at the baseline when all subjects were aged 70 years. Determinations of glomerular filtration rate (GFR) were performed at ages 70, 75 and 80. The age was set at 70 years because the PIVUS sample was initially planned as a cohort to on cardiovascular disease. Since cardiovascular disease is mainly a disease of the elderly, the age chosen was 70 years. The authors later got the opportunity to study environmental contaminants, and subsequently used the data to investigate renal function over time as well. This had an advantage because the elderly have a faster natural rate of decline in GFR than younger cohorts.

The hypothesis tested was whether subjects with higher levels of *p,p'*-DDE at the baseline investigation at age 70, would have a greater decline in GFR over 10 years than subjects with low *p,p'*-DDE levels.

2. Material and methods

2.1. Subjects and basic characteristics

All subjects living in Uppsala Sweden and being 70-year-old, were eligible for this study. The subjects received an invitation by letter within two months of their 70th birthday in randomized order. Of the 2025 invited subjects, 1016 subjects participated (50.1%). Fifty percent of the population were female. The participants were recruited from the City of Uppsala. Thus, there were possibly very few farmers in the study, although we do not have that information.

The baseline investigation was started in April 2001 and completed June 2004 (Lind et al., 2012). The participants were asked to answer a questionnaire about their medical history, smoking and regular medication. All participants were investigated in the morning after an overnight fast. No medication or smoking was allowed after midnight. After five years, all individuals were invited to a re-examination, and 826 individuals attended. At the 10-year follow-up, 602 individuals attended.

The study was approved by the Ethics Committee of Uppsala University and the participants gave written informed consent.

Blood pressure was measured in the supine position after 30 min of rest. Diabetes was defined as a diagnosis of diabetes or fasting plasma glucose ≥7.0 mmol/l. BMI was calculated from height and weight. Education level was defined in three categories: <10 years, 10–12 years and >12 years of schooling. These potential confounders were only evaluated at age 70.

2.2. Analysis of p,p'-DDE

p,p'-DDE was measured in stored plasma samples (—80C) from the 70-year investigation. Analyses of *p,p'*-DDE were performed using gas chromatography coupled to high-resolution mass spectrometry (GC/HRMS) system (Micromass Autospec Ultima, Waters, Mildford, MA, USA). The calculated method detection limit was 2.1 ng/g lipid. All details on the *p,p'*-DDE analyses have been reported elsewhere (Salihovic et al., 2012a; Salihovic et al., 2012b). The *p,p'*-DDE levels were normalized for circulating total lipid levels (Rylander et al., 2006).

2.3. Assessment of kidney function

Glomerular filtration rate (GFR) was determined by the combined use of measurements of serum creatinine and cystatin C (Inker et al., 2012). Serum creatinine was measured by a standard enzymatic method and cystatin C with a particle enhanced turbidimetric assay as previously reported (Carlsson et al., 2010; Ryden et al., 2012; Helmersson-Karlqvist et al., 2016).

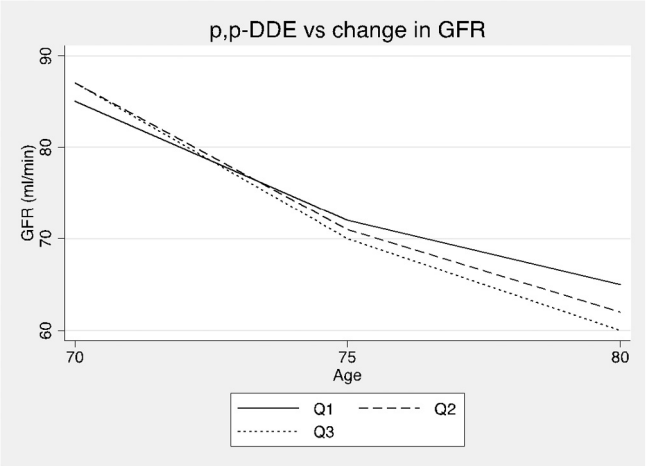

Fig. 1. Mean values in glomerular filtration rate (GFR, ml/min/1.73 m^2) at the 70-, 75- and 80-year investigations divided into tertiles of *p,p'*-DDE levels at baseline at 70 years (Q1-Q3).