A total of 41 UC cases, 41 CKD controls and 23 healthy controls were recruited. A multi-center prospective prevalent case-control study, carried out at 7 nationwide medical centers covering most of the northern, central, southern and eastern Taiwanese populations. Subjects were Taiwanese healthy adults (healthy controls), patients with UC, patients with CKD but without UC (disease controls) and patients with ongoing UC. UC was confirmed by standard pathology; CKD staging was defined by eGFR classification; healthy controls defined by the clinical examination and urinalysis. Blood and random spot urine specimens were collected at the time of the structured interview for demographic information.

Urine was collected from each patient and frozen immediately after collection. For UC patients, urine samples for analysis were obtained within 14 days of diagnosis, and with patients entering remission within 3 months of collection. For healthy controls, CKD controls and UC patients. Multiple logistic regression analysis was performed to evaluate the associations between risk of UC and log2-transformed urinary concentration of phthalate metabolites, e.g. mono-benzyl phthalate (MBzP), mono-isobutyl phthalate (MiBP), mono-isononyl phthalate(MiNP), monomethyl phthalate (MMP), mono (3-carboxypropyl) phthalate(MCPP). The concentrations of the metabolites were determined using an Ultimate 3000 LC; Dionex, Germany) coupled with a hybrid Q-TOF mass spectrometer (Q-Exactive, Thermo Scientific, USA) using multiple reaction monitoring (MRM) mode. The identity of the phthalate metabolites was confirmed by standard calibration standards.

The demographic and clinical data are shown in Table 1. In UC patients, 16(39%) had upper urinary tract UC (UTUC) and 25 (61%) had bladder UC. In CKD patients, 10(24%) had upper urinary tract UC (UTUC) and 31 (73%) had bladder UC. Among the 7 phthalate metabolites measured, only MEHHP had measurable concentrations in all patients. MIBP and MCPP had roughly measurable concentrations in 50-60% of patients. The rest of the phthalate metabolites were not detected in most patients. The mean concentrations of MEHHP were 46.42±15.54 (µg/g cr) and 48.21±15.71 (µg/g cr) respectively. The UC patients had significantly higher urinary concentration of MEHHP than CKD control patients. The odds ratios were 4.19 (1.36-12.9) and 3.73 (1.15-12.1) for MEHHP tertiles showed a dose-response relationship of odds ratios, when comparing second and third tertile to the lowest tertile. The odds ratios were 1.79 (1.15-2.77) and 1.77 (1.19-2.63) respectively (Table 2).

Conclusions:

In this multi-center, cross-sectional study of Taiwan, higher urinary concentrations of MEHHP showed statistically significant correlation with increasing risk of UC. Our findings would suggest high environmental exposure to phthalates may contribute to the development of UC in CKD patients. Future research with more patients and longitudinal study will be required to provide definitive evidence for a potential association between phthalates and UC development.

References:


Acknowledgement:

Chiu-Ching Huang, Chi Hsi Chang, Ho-Hsin Su, Hung-Chun Chen, Chi-Yun Chang, and Chao Jung Chen. A Preliminary Study from Taiwan.

Introduction:

Increasing epidemiological and experimental evidences support the role of environmental exposures in the development of urothelial cancer (UC). Among the potential environmental factors, tobacco, inorganic arsenic, and aristolochic acid are the well-known and established risk factors for urothelial cancer. Despite the ban for importation of aristolochic acid containing Chinese herbs in 2003, Taiwan still has the highest incidence of UC in the world, particularly in CKD (chronic kidney disease) and dialysis patients. In 2011, the great DEHP plasticizer food contamination in Taiwan was disclosed. It was discovered that illegal addition of industrial grade phthalates as food additives was widely practiced since 1980. In 2011, this issue was disclosed and raised significant concern about its potential health hazard effects. It is well known that patients with CKD are prone to develop UC. Whether exposure to phthalates may contribute to the increased incidence of UC in CKD patients has not been studied before.

Aims:

To investigate if environmental phthalate exposures have a potential impact on UC risk in CKD patients.

Patients:

Present study is a multicenter prospective prevalent case-control study, carried out at 7 nationwide medical centers covering most of the northern, central, southern and eastern Taiwanese populations. Subjects were Taiwanese healthy adults (healthy controls), patients with UC, patients with CKD but without UC (disease controls) and patients with ongoing UC. UC was confirmed by standard pathology; CKD staging was defined by eGFR classification; healthy controls defined by the clinical examination and urinalysis. Blood and random spot urine specimens were collected at the time of the structured interview for demographic information.

Methods:

Urinary phthalates MEHHP in participants of Taiwan UC study. The hazard ratios (95% confidence interval) of UC by the concentrations of urinary phthalate metabolite dimethylphthalate (MeDMP) were not statistically significant. Analysis within healthy controls, CKD controls and UC patients. Multiple logistic regression analysis was performed to evaluate the associations between risk of UC and log2-transformed creatinine-corrected urinary phthalate concentrations.

Results:

A total of 41 UC cases, 41 CKD controls and 23 healthy controls were recruited from July 2012 to December 2013 with written informed consents. CKD control patients were age, sex and CKD-staging best matched with UC patients. The demographic and clinical data are shown in Table 1. In UC patients, 16(39%) had upper urinary tract UC (UTUC) and 25 (61%) had bladder UC. Urinary phthalate metabolites tested were expressed as microgram/gram creatinine (µg/g cr). Among the 7 phthalate metabolites measured, only MEHHP had measurable concentrations in all patients. MIBP and MCPP had roughly measurable concentrations in 50-60% of patients. The rest of the phthalate metabolites were not detected in most patients. The mean concentrations of MEHHP were 46.42±15.54 (µg/g cr) and 48.21±15.71 (µg/g cr) respectively. The UC patients had significantly higher urinary concentration of MEHHP than CKD control patients. The odds ratios were 4.19 (1.36-12.9) and 3.73 (1.15-12.1) for MEHHP tertiles showed a dose-response relationship of odds ratios, when comparing second and third tertile to the lowest tertile. The odds ratios were 1.79 (1.15-2.77) and 1.77 (1.19-2.63) respectively (Table 2). Risk of developing UC per doubling increase of MEHHP was 1.77 after adjusting for age, sex, smoking status and eGFR. No interaction between selected phthalates and smoking status in UC patients has not been studied before.

Table 1. The demographic and clinical data of study subjects in Taiwan UC study

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Fig. 2. Comparison of age-adjusted incidence rate of urothelial cancer (UC) between Taiwan and the United States (Year 1980-2007).

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Discussion:

In past 20 years, the incidence of UC in US declined gradually, while the escalating trend was still observed in Taiwan (Fig.2). In this study, we observed 5 times higher mean urinary levels of phthalate metabolites in Taiwanese healthy controls when compared to US residents (46.42 vs. 8.99 µg/g cr). In US residents, 2015 Fourth National Report on Human Exposure to Environmental Chemicals, p388-393), indicating much higher DEHP exposures in Taiwanese residents (22). In the US, the mean urinary concentrations of MEHHP shrank CKD controls patients (p<0.001, Fig. 1). For MCPP and MIBP measurements, the differences between controls,CKD and UC patients were not statistically significant. Analysis within MEHHP tertiles showed a dose-response relationship of odds ratios, when comparing second and third tertile to the lowest tertile. The odds ratios were 1.46 (0.60-4.46) and 3.73 (1.09-9.75) respectively (Table 2). Risk of developing UC per doubling increase of MEHHP was 1.77 after adjusting for age, sex, smoking status and eGFR. No interaction between selected phthalates and smoking was found. Future research with more patients and longitudinal study will be required to provide definitive evidence for a potential association between phthalates and UC development.