HYPERURICEMIA RISK AFTER EXPOSURE TO MODERATE-TO-HIGH LEVELS OF PCDD/FS

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Introduction

Hyperuricemia, the predisposing condition for gout, has been associated with hypertriglyceridemia and diabetes mellitus (Berkowitz 1966), and is also a risk factor for coronary artery disease (Abbott et al. 1988). According to the National Health and Nutrition Examination Survey (NHANES) 1999-2008 survey, about 31.9 million 10.4% of Americans (about 31.9 million people), and perhaps as many as 20.1% of American adults, may have hyperuricemia (Zhu et al. 2010). Hyperuricemia can occur with decreased renal function and in genetic disorders that increase the production or limit the excretion of uric acid (Wortman et al. 1998). It is also probably associated with glucose intolerance via multiple mechanisms, but the central one may be that insulin resistance increases renal urate absorption (Dessein et al. 2000). Serum uric acid levels may also become elevated if renal excretion is impaired. One mechanism may be a decrease in the glomerular filtration rate (GFR), which may account for the hyperuricemia associated with renal failure or insufficiency (Saggiani et al. 1996). Higher adiposity and weight gain are strong risk factors for gout, whereas weight loss is protective (Meigs et al. 2003; Ford et al. 2002; Choi et al. 2005).

Few studies have shed light on the association between hyperuricemia and the ubiquitous and moderate exposure to PCDD/Fs in the general population. We tested the hypothesis that exposure to PCDD/Fs is associated with an increased risk of hyperuricemia and examined whether the risk was different in males and females.

Materials and Methods

This cross-sectional study was done from July 2005 through May 2010 in a district health center near the deserted PCP factory. The only recruitment criterion was that the participant had to reside near the factory. Details of the study's protocol and all testing procedures are available elsewhere (Chang et al. 2010a, 2010b). Exclusion criteria were major systemic diseases, including diabetes mellitus, alcoholism, hypertension, renal disease, cardiovascular disease (myocardial infarction, stroke, peripheral arterial disease), liver disease, and a known history of exposure to PCDD/Fs or other heavy metals. Participants were also considered to have hyperuricemia if their uric acid was ≥ 7 mg/dL. The GFR is usually estimated (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation (Levey et al. 1999). We used isotope dilution high-resolution gas chromatography/high-resolution mass spectrometry (HRGC/HRMS), as previously described (Chang et al. 2010a, 2010b), to measure seventeen 2,3,7,8-substituted PCDD/Fs in serum samples. Blood biochemistry tests for blood urea nitrogen (BUN), creatinine (CREA), albumin (ALB), and uric acid (UA) were analyzed in the pathology laboratory of National Cheng Kung University Hospital.

To assess the association between uric acid and serum PCDD/F levels by gender, a multiple linear regression was first used; other explanatory variables included age (years), drinking (categorical), bodyfat (%), seafood consumption (kg/month), systolic blood pressure (mmHg), and creatine (mg/dL). We used multiple logistic regression to assess the association between serum PCDD/F levels and hyperuricemia risk. The response variable of interest, measured as a dichotomous variable, was having or not having hyperuricemia (≤ and > 7 mg/dL). The main exposure variables of interest, serum PCDD/Fs, was divided into quartiles (cutoff levels of quartiles of PCDD/Fs were 11.4, 19.9, and 36.4 pg WHO_{98}-TEQ_{DF}/g lipid), and adjusted odds ratios were calculated using the lowest quartile as the reference group.

Results and discussion

Of the initial 3138 study participants, we excluded 1481 patients because of diabetes mellitus (n = 484, 15.4%), alcoholism (n = 20, 7.8% of 258 drinking), hypertension (n = 1022, 32.6%), renal disease (n = 93, 3.0%), cardiovascular disease (n = 75, 2.4%), and liver disease (n = 380, 12.1%), which finally left us with 1657 participants (783 men, 874 women; mean age: 40.1 years) (Table 1). The mean serum PCDD/F level was 24.9 pg WHO_{98}-TEQ_{DF}/g lipid (range: 3.5-540.0 pg WHO_{98}-TEQ_{DF}/g lipid). In

general, men have higher ALB (men: 4.6 ± 0.4; women: 4.5 ± 0.4 g/dL, $p < 0.001$), BUN (men: 15.0 ± 4.8; women: 13.1 ± 3.8 mg/dL, $p < 0.001$), CREA (men: 1.0 ± 0.3; women: 0.7 ± 0.1 mg/dL, $p < 0.001$), and UA (men: 6.4 ± 1.5; women: 4.8 ± 1.9 mg/dL, $p < 0.001$) than women. The percentage of hyperuricemia was significantly higher in men than in women ($p < 0.001$).

We compared associations of serum PCDD/F levels and renal function index (CREA and eGFR) in both genders (Table 2). Serum PCDD/F and CREA levels were higher in men than in women and were significantly correlated (men: β = 0.041, $p = 0.036$; women: β = 0.006, $p = 0.408$) (Table 2). In addition, the eGFR fell gradually with serum PCDD/F levels in all groups (men: β = -8.484, $p < 0.001$; women: β = -10.459, $p < 0.001$). Serum PCDD/F and UA levels were higher in men than in women and were significantly correlated (men: β = 0.253, $p = 0.003$; women: β = 0.080, $p = 0.467$; All: β = 0.180, $p = 0.011$) (Table 3). In addition, men with higher serum PCDD/F levels had a higher hyperuricemia risk than did the reference group (serum PCDD/F levels < 11.4 pg WHO_{98}-TEQ_{DF}/g lipid) after adjusting for confounding factors (25th to < 50th percentile, adjusted odds ratio (AOR) = 1.73 [95% confidence interval (CI) = 1.05-2.85]; 50th to < 75th percentile, AOR = 2.50 [1.50-4.15]; ≥ 75th percentile, AOR = 3.25 [1.88-5.62]) (Table 4). These data show that serum PCDD/Fs affected the risk of hyperuricemia risk in healthy men.

In our large and representative study population of people exposed to moderate-to-high levels of PCDD/Fs, we found that higher serum PCDD/F levels were positively associated with three kidney function indices that were higher than normal: BUN, CREA, and UA levels. Kidney disease can cause increased uric acid levels, which may explain the unusually strong cross-sectional association of chronic kidney disease (CKD) and uric acid levels. Most filtered urate is reabsorbed in the early proximal tubule, which then secretes uric acid into the kidneys; this secretory process is responsible for most excreted uric acid. Hyperuricemia is usually secondary to decreased excretion or increased production of uric acid. In patients with kidney dysfunction, the urinary excretion of uric acid decreases, which may cause hyperuricemia, depending on gastrointestinal excretory compensation (Siu et al. 2006; Vaziri et al. 1995).

In our participants, higher serum PCDD/F levels were associated with higher uric acid levels and reduced eGFR, especially in men. The mechanisms underlying hyperuricemia as a result of reduced renal clearance of uric acid may involve a reduced GFR or dysfunctional handling of filtered uric acid by proximal tubules (Perez-Ruiz et al. 2002). We conclude that moderate exposure to environmental PCDD/Fs reduces urate excretion in the general population. Our results support efforts to reduce potential sources of environmental exposure to PCDD/Fs and to offer possibilities for decreasing the risk of hyperuricemia in the general population.

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Table 1 Demographic characteristics of all study participants (N= 1657).

Characteristic	Men (n =783)	Women (n =874)	All	P Value
	Number (%) or	Mean ± SD (Range)	(n=1657)	
Age (years)	40.8 ± 15.1 (17.0- 84.0)	39.5 ± 13.9 (17.0- 85.0)	40.1 ± 14.5 (17.0- 85.0)	0.196
Body mass index (kg/m^2)	23.9 ± 3.7 (13.8-37.4)	22.9 ± 3.8 (11.5-39.2)	23.4 ± 3.8 (11.5-39.2)	< 0.001
Drinking (%)	190 (24.3%)	30 (3.4%)	220 (13.3%)	< 0.001
Serum creatinine (mg/dL)	1.0 ± 0.3 (0.4- 7.8)	0.7 ± 0.1 (0.4- 1.5)	0.8 ± 0.3 (0.4- 7.8)	< 0.001
Blood urine nitrogen (mg/dL)	15.0 ± 4.8 (6.0- 63.0)	13.1 ± 3.8 (5.0- 29.0)	14.0 ±4.4 (5.0- 63.0)	< 0.001
Uric acid (mg/dL)	6.4 ± 1.5 (1.9-12.3)	4.8 ± 1.9 (1.9-49.0)	5.5 ± 1.9 (1.9-49.0)	< 0.001
Systolic BP (mm Hg)	115.0 ± 11.7 (82.0- 138.0)	110.1 ± 12.9 (78.0- 138.0)	112.4 ± 12.6 (78.0- 138.0)	< 0.001
Diastolic BP (mm Hg)	72.1 ± 8.5 (50.0- 88.0)	68.4 ± 8.9 (40.0- 88.0)	70.1 ± 8.9 (40.0- 88.0)	< 0.001
Seafood consumption (kg/month)	10.0 ± 13.6 (0.1- 128.2)	6.6 ± 8.7 (0.1- 74.9)	8.2 ± 11.4 (0.1- 128.2)	< 0.001
Hyperuricemia (%)	233 (30.0%)	115 (13.2%)	348 (21.0%)	< 0.001
PCDD/F (pg WHO_{98}-TEQ_{DF}/g lipid)	22.2 ± 34.0 (3.5-514.0)	27.3 ± 38.9 (4.1- 540.0)	24.9 ± 36.7 (3.5- 540.0)	< 0.001

Abbreviations: BP = blood pressure. P Value: indicates whether demographic characteristics and serum PCDD/Fs differ by gender using the Wilcoxon Rank-Sum test continous variables and Chi-squared test for categorical variables.

Table 2 Multiple linear regression models to evaluate associations of serum dioxin levels with renal function index in all participants

Dependent Variable	CREA				eGFR*			
	Men	(n = 783)	Women	(n = 874)	Men		Women	
Independent Variables	β	*P*	β	*P*	β	*P*	β	*P*
Intercept	0.921	< 0.001	0.638	< 0.001	137.232	< 0.001	167.669	< 0.001
Age (years)	0.001	0.654	0.001	0.001	—	—	—	—
Drinking	-0.046	0.103	0.014	0.548	2.550	0.143	0.139	0.972
Body fat (%)	0.005	0.042	-0.020	0.040	-0.681	< 0.001	-0.202	0.219
Systolic BP (mm Hg)	-0.002	0.125	0.001	0.619	0.014	0.825	-0.182	0.004
Log Dioxin	0.041	0.036	0.006	0.408	-8.484	< 0.001	-10.459	< 0.001

Abbreviations:—, variable not included in method. *eGFR indicates Glomerular filtration rate estimated by using MDRD Study equation
MDRD Equation : GFR (mL/min) = 170 × $[CREA]^{-0.999}$ × $[Age]^{-0.176}$ × $[BUN]^{-0.17}$ × $[Albumin]^{0.318}$ × [0.762 if participant is female]

Table 3 Multiple linear regression models to evaluate associations of serum dioxin levels with uric acid in all participants

	Men			Women			All		
	β	SE	*P*	β	SE	*P*	β	SE	*P*
Intercept	2.842	0.545	< 0.001	-0.284	0.697	0.684	4.848	0.477	< 0.001
Age (years)	-0.013	0.005	0.004	-0.010	0.007	0.173	-0.011	0.004	0.007
Sex (male)	—	—	—	—	—	—	-1.925	0.130	< 0.001
Drinking	0.191	0.123	0.121	0.283	0.338	0.403	0.230	0.128	0.072
Body fat (%)	0.058	0.010	< 0.001	0.104	0.015	< 0.001	0.076	0.009	< 0.001
Systolic BP (mm Hg)	0.012	0.005	0.010	-0.002	0.005	0.763	0.006	0.004	0.097
Creatinine (mg/dL)	0.730	0.158	< 0.001	3.299	0.512	< 0.001	1.043	0.170	< 0.001
Log Dioxin	0.253	0.086	0.003	0.080	0.110	0.467	0.180	0.072	0.011

—, Variable not included in method.

Table 4 Association between serum PCDD/F and the risk of hyperuricemia in male particiants (n=775)

			Hyperuricemia		
Variables		Total	No. (%)	Odds Ratio	95% Confidence Interval
Age (years)	< 40	406	98 (24.1)	1	Reference group
	40-60	287	107 (37.3)	1.16	0.79, 1.69
	> 60	82	28 (34.2)	0.68	0.37, 1.23
Obesity[a,b]	No	348	76 (21.8)	1	Reference group
	Yes	427	157 (36.8)	1.88	1.34, 2.63
Drinking	No	585	160 (27.4)	1	Reference group
	Yes	190	73 (38.4)	1.46	1.02, 2.10
Serum PCDD/F levels	< 25th percentile	194	33 (17.0)	1	Reference group
	25-50th percentile	195	52 (26.7)	1.73	1.05, 2.85
	50-75th percentile	195	67 (34.4)	2.50	1.50, 4.15
	≥ 75th percentile	191	81 (42.4)	3.25	1.88, 5.62

[a] Missing data for 8 participants. [b] Definition of obesity < 30 years old: bodyfat less than 20%; ≥ 30 years old: bodyfat less than 23%
Serum PCDD/F levels categories (pg WHO_{98}-TEQ_{DF}/ g lipid):
(1) < 25th: < 11.4, (2)25th to < 50th: 11.4 to 19.9, (3) 50th to < 75th: 19.9 to 36.4, (4) ≥ 75th: ≥ 36.4