EFFECT OF DIOXIN AND DIOXIN-LIKE PCBS ON INSULIN SENSITIVITY IN PREGNANT SUBJECTS AT A CONTAMINATED AREA IN TAIWAN

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Introduction

We have previously ascertained increased body burden of polychlorinated dibenzo-*p*-dioxin, dibenzofurans (PCDD/Fs), and dioxin-like polychlorinated biphenyls (PCBs) in pregnant women living in an contaminated area[1]. There was a factory producing pentachlorophenol (PCP) daily during the period between 1965 and 1979 and closed in 1982 in southwestern Taiwan[2]. Accumulating epidemiological observations reveals that people exposed to high levels of dioxins and dioxin-like compounds have increased risk of developing diabetes mellitus and cardiovascular diseases[3,4]. It was suggested that nondiabetic individuals exposed to TCDD have an increased risk of insulin resistance[5], being precursor of type 2 diabetes mellitus. We aimed to investigate the relationship of PCDD/Fs and dioxin-like PCBs exposure to insulin resistance.

Materials and Methods

The details of geographical locations, study design, and recruited volunteers were illustrated previously[1]. Several well-trained interviewers collected personal data from subjects randomly selected from the name list. Demographic data, residential history, prenatal and postnatal dietary habits, and medical and reproductive histories were recorded. Sixty ml of blood were collected from each pregnant subject living in the study area. Volunteers were asked to fast overnight before the blood samples were drawn. Seventeen 2,3,7,8-substituted PCDD/Fs and twelve dioxin-like PCBs were measured in human serum samples, using isotope dilution high-resolution gas chromatography/high resolution mass spectrometry (HRGC/HRMS)[6]. Serum insulin was measured with the Coat-A-Count radioimmunoassay procedure (Diagnostic Products Corporation, Los Angeles, CA). Fasting glucose was determined with the Paramax Analytical System (Baxter Diagnostics, Irvine, CA), which employed a coupled enzymatic method using hexokinase and glucose 6-phosphate dehydrogenase.

Concentrations of PCDD/Fs and PCBs were expressed as WHO-TEQ values. We calculated the insulin sensitivity (defined as 22.5EXP[-ln(glucose)]/insulin) and QUICKI (quantitative insulin sensitivity check index, defined as 1/[log (fasting glucose)+log (fasting insulin)]) based on fasting glucose and insulin. Dioxins, PCBs, insulin (μU/mL), insulin sensitivity (min^{-1} /μU/mL), and QUICKI values were transformed to natural logarithm and test for normal distribution by Kolmogorov-Smirnov method for parametric analyses. A t-test was used to compare the significances of TEQ values for PCDD/Fs and PCBs and insulin-related parameters. Correlations of individual congeners of PCDD/Fs and PCBs were assessed with Pearson rank correlation coefficients. All statistical analyses were performed using the Statistical Package for Social Science (SPSS) Version 10.0. If the concentrations of the pollutants were below the limit of detection, these concentrations were re-coded to 0 in the data analyses.

Results and Discussion

Forty pregnant women with ages ranging from 21 to 39 years were included in this study. Mean age and standard deviation were 28.2 and 3.9 years, respectively; this group should therefore be considered a relatively young population. The pre-pregnancy and perinatal body mass indices (BMI) were 20.7 ± 3.1 and 25.0 ± 3.3, respectively. The TEQ-based internal levels of dioxins and dioxin-like PCBs, including PCDDs, PCDFs, PCDD/Fs, PCBs and total TEQ and three insulin-related factors, insulin (μU/mL), insulin sensitivity (min^{-1} /μU/mL), and QUICKI as well as the statistically-obtained *p*-values for differences between the groups are

shown in Table 1 and Table 2, respectively. The total TEQ was 14.91 ± 8.32 pg-TEQ/g-lipid and 5.79 ± 4.07 (μU/mL) of insulin. We examined the association between the exposure and the effect including BMI, fasting glucose, HDL, triglyceride (TG), and blood pressure. The statistical *p*-values were adjusted by age, and adjusted by BMI when the test did not include BMI.

Table 1. Levels of dioxins and dioxin-like PCBs and statistical test based on the median of each metabolic syndrome factor.

Characteristics	Level (pg-TEQ/g-lipid)				
(*n*=40)	Total congeners	PCDDs	PCDFs	PCDD/Fs	Dioxin-like PCBs
Overall	14.9±8.3 (3.8, 44.8)[a]	5.8±4.0 (1.8, 20.0)	4.0±2.2 (1.0, 11.0)	9.8±6.0 (2.8, 31.1)	5.2±2.8 (1.0, 13.7)
BMI					
≤ 25.0	13.9±9.6*	5.5±4.8	3.7±2.5	9.2±6.9	5.3±3.4
> 25.0	16.1±6.9*	6.1±3.5	4.3±1.8	10.4±5.1	5.0±2.2
Glucose (mg/dL)					
≤ 84	13.0±6.0^{+}	5.1±2.9	3.8±2.3	9.0±4.8	4.4±2.2^{+}
> 84	16.9±10.0^{+}	6.5±4.9	4.1±2.4	10.6±7.1	5.9±3.2^{+}
HDL (mg/dL)					
≤ 64	13.7±6.1^{+}	5.1±3.0^{+}	3.5±1.5*	8.7±4.4^{+}	4.6±2.3^{+}
> 64	16.0±10.0^{+}	6.4±4.7^{+}	4.4±2.7*	10.8±7.2^{+}	5.7±3.2^{+}
TG (mg/dL)					
≤ 184	13.7±6.2	5.3±3.0	3.7±2.6	9.0±4.6	5.0±2.8
> 184	16.1±10.0	6.2±4.8	4.2±2.6	10.5±7.2	5.3±2.9
Systolic pressure (mmHg)					
≤ 110	15.8±9.7	6.2±4.6	4.0±2.2	10.2±6.8	5.2±3.2
> 110	14.0±6.8	5.4±3.2	3.9±2.2	9.3±5.3	5.1±2.5
Diastolic pressure (mmHg)					
≤ 70	15.1±8.9	5.5±4.3	4.0±2.2	9.5±6.4	5.3±3.0
> 70	14.8±8.0	6.1±3.7	4.0±2.3	10.1±5.8	5.0±2.8

[a]A ± B (C, D) represent mean ± sd (min, max)
$^{+}p<0.1$, $^{*}p<0.05$, $^{**}p<0.01$

To compare the internal concentrations of congeners as a function of age and insulin-related factors, the statistically tested *r*-values for the Pearson correlation between congeners and age, insulin, insulin sensitivity, and QUICKI were determined and displayed in Table 3. Correlation coefficient values for dioxin-like PCBs and insulin sensitivity ranged between –0.28 and –0.46, with age-adjusted values ranging from –0.28 and -0.49 (data not shown). It is noted that four congeners (PCBs 77, 123, 126, and 169) as well as total TEQ of dioxin-like PCBs showed significance with insulin sensitivity but without age. The TEQ of seventeen PCDD/Fs and twelve dioxin-like PCBs for subjects of the present study are illustrated in Fig. 1, the TEQ value for insulin sensitivity-based upper median and lower median are also provided. The two groups of upper and lower media were separated with insulin sensitivity 1.01 min^{-1} /μU/mL. Fig. 1 displayed the PCDD/Fs and dioxin-like PCBs TEQ. Scatter plot and regression fits for insulin sensitivity versus TEQ are shown in Fig. 2. The left and right panels of Fig. 2 represent the correlation for TEQs of total congeners and dioxin-like PCBs, respectively. The linear regressions after age-/BMI-adjustments are presented. The TEQs of dioxin-like PCBs appeared to be predictable by the insulin sensitivity via a particular regression function; however total TEQ was not. Using this analysis, we attempted to examine the magnitude of the effect of serum PCBs levels on insulin sensitivity. Base on the data in Fig. 2, our regression model predicted a 8% decrease in insulin sensitivity for increasing 1 pg-TEQ/g-lipid in PCBs levels in the study pregnant subjects.

Table 2. Levels of insulin and related indices and statistical test based on the median of each metabolic syndrome factor.

Characteristics (n=40)	Insulin (μU/mL)	Insulin sensitivity (min^{-1}/μU/mL)	QUICKI
Overall	5.8±4.1 (0.4, 17.8)[a]	1.7±2.0 (0.3, 11.9)	0.4±0.1 (0.3, 0.7)
BMI			
≤ 25.0	5.1±3.7	0.3±0.2	0.40±0.05
> 25.0	7.0±4.3	0.2±0.2	0.38±0.05
Glucose (mg/dL)			
≤ 84	4.4±2.6*	0.3±0.3**	0.41±0.05
> 84	7.6±4.7*	0.2±0.1**	0.37±0.04
HDL (mg/dL)			
≤ 64	6.4±4.3	0.2±0.2	0.38±0.05
> 64	5.7±3.9	0.3±0.3	0.39±0.05
TG (mg/dL)			
≤ 184	5.2±3.3*	0.25±0.21	0.39±0.05
> 184	6.7±4.6*	0.25±0.24	0.39±0.06
Systolic pressure (mmHg)			
≤ 110	4.8±2.6*	0.25±0.18	0.40±0.04*
> 110	7.4±4.9*	0.25±0.26	0.38±0.06*
Diastolic pressure (mmHg)			
≤ 70	6.4±3.5	0.19±0.10*	0.38±0.04*
> 70	5.6±4.7	0.32±0.30*	0.40±0.06*

[a]A ± B (C, D) represent mean ± sd (min, max)
^{+}p<0.1, $^{*}p$<0.05, $^{**}p$<0.01

Table 3. Pearson correlation coefficient between dioxin-like PCBs congeners and age, insulin, and insulin-related indices

Congeners	Age		Insulin		Insulin sensitivity		QUICKI	
	r^a	p	r^a	p^b	r^a	p^b	r^a	p^b
Dioxin-like PCBs								
3,4,4',5-TeCB 81	0.14	0.37	0.29	0.078	-0.28	0.094	-0.25	0.129
3,3',4,4'-TeCB 77	0.06	0.69	0.29	0.075	-0.33	0.044*	-0.26	0.110
2',3,4,4',5-PeCB 123	0.28	0.07	0.35	0.031*	-0.46	0.003**	-0.34	0.035*
2,3',4,4',5-PeCB 118	0.40	0.008**	0.25	0.131	-0.40	0.014*	-0.25	0.125
2,3,4,4',5-PeCB 114	0.42	0.006**	0.17	0.305	-0.32	0.065	-0.16	0.323
2,3,3',4,4'-PeCB 105	0.39	0.01**	0.29	0.069	-0.42	0.008**	-0.29	0.069
3,3',4,4',5-PeCB 126	0.16	0.31	0.36	0.025*	-0.37	0.023*	-0.33	0.037*
2,3',4,4',5,5'-HxCB 167	0.41	0.007**	0.18	0.267	-0.35	0.030*	-0.19	0.255
2,3,3',4,4',5-HxCB 156	0.49	0.001**	0.19	0.234	-0.34	0.039*	-0.19	0.254
2,3,3',4,4',5'-HxCB 157	0.50	0.001**	0.20	0.230	-0.34	0.038*	-0.19	0.241
3,3',4,4',5,5'-HxCB 169	0.17	0.29	0.34	0.037*	-0.42	0.012*	-0.32	0.046*
2,3,3',4,4',5,5'-HpCB 189	0.50	0.0009**	0.19	0.246	-0.33	0.042*	-0.19	0.247
PCDDs TEQ	0.53	0.0004**	0.04	0.803	-0.16	0.355	-0.03	0.84
PCDFs TEQ	0.50	0.001**	0.07	0.686	-0.18	0.274	-0.06	0.71
PCDD/Fs TEQ	0.53	0.0004**	0.05	0.760	-0.17	0.314	-0.048	0.78
Dioxin-like PCBs TEQ	0.26	0.10	0.30	0.066	-0.42	0.009**	-0.23	0.07
Total TEQ	0.42	0.007**	0.23	0.161	-0.32	0.052	-0.22	0.18

[a]Pearson correlation coefficient between age/insulin-related factors and congeners
[b]The p-values for the Pearson correlation age- and BMI-adjusted
$^{*}p$<0.05, $^{**}p$<0.01

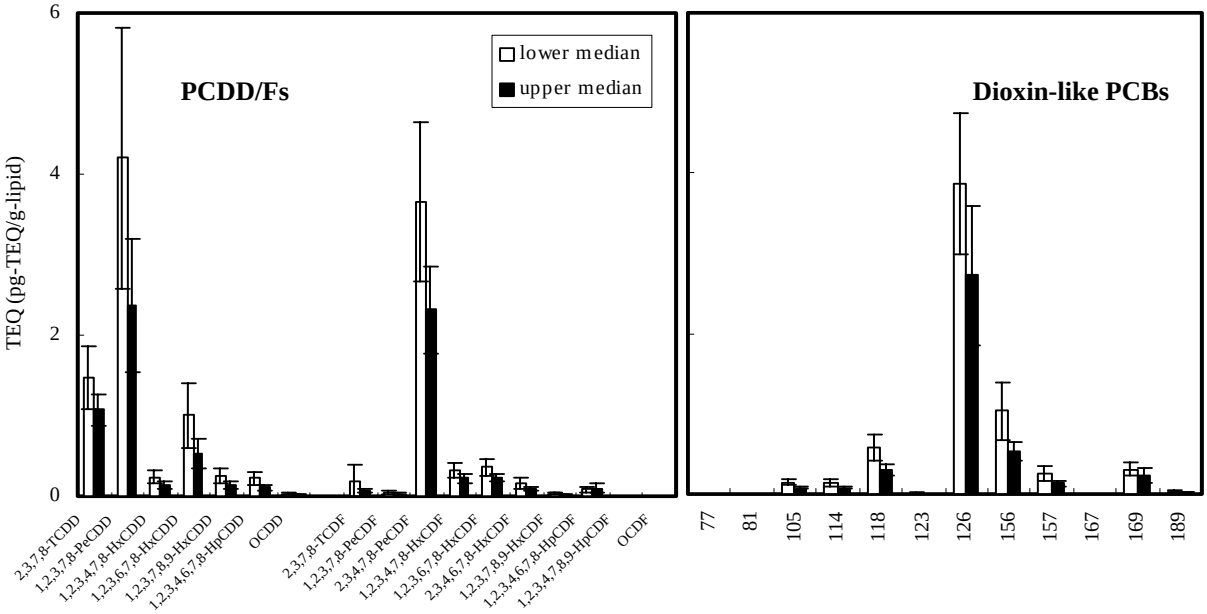

Figure 1. TEQ of PCDD/Fs and dioxin-like PCBs based on upper and lower median of insulin sensitivity. The two groups of upper and lower media were separated with insulin sensitivity 1.01 min^{-1}/μU/mL.

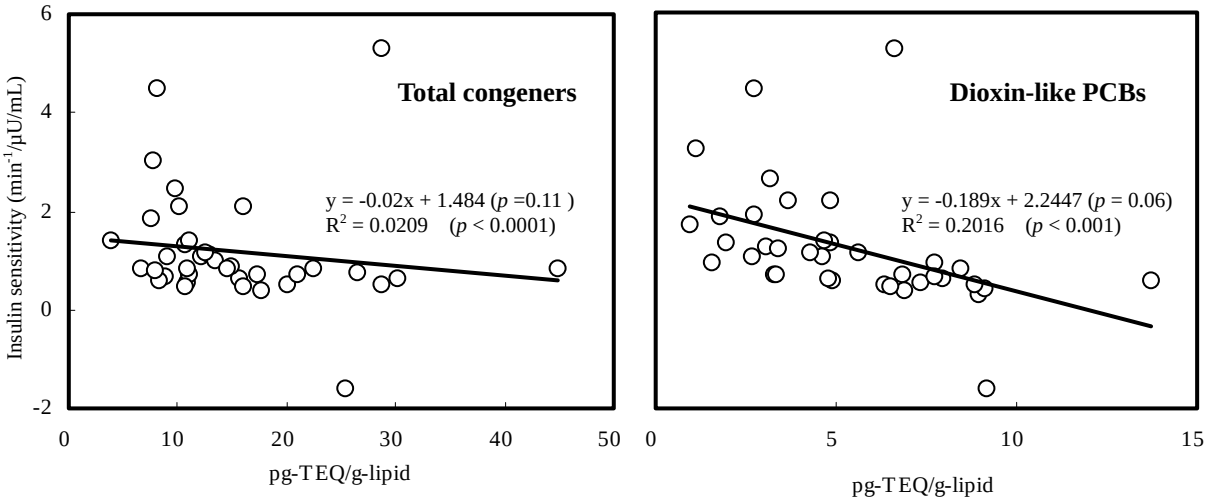

Figure 2. Relationships between the insulin sensitivity and total congeners and dioxin-like PCBs

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