ASSOCIATION BETWEEN DIOXIN EXPOSURE AND METABOLIC SYNDROME IN TAIWANESE LIVING NEAR A DESERTED PCP FACTORY

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Introduction

The metabolic syndrome (MetS) encompasses a cluster of metabolic risk factors such as hypertension, dyslipidemia, insulin resistance, hyperinsulinemia, glucose intolerance, and obesity, particularly central obesity. It has been proposed that this syndrome is a powerful determinant of diabetes and cardiovascular disease[1]. In US general population, even with background exposure to persistent organic pollutants (POPs), the dose–response relationships between serum concentrations of POPs, especially for organochlorine (OC) pesticides and PCBs, and type 2 diabetes still could be found[2]. These findings raise the possibility that some POPs stored in adipose tissues may be a key to the pathogenesis of MetS and type 2 diabetes[3]. The increasing number of patients with metabolic syndrome and resultant lifestyle-related diseases is an urgent issue in Taiwan. Moreover, little is known about the interaction between the PCDD/Fs and insulin resistance in the cause of Mets. A deserted factory in the northwestern section of Tainan City, Taiwan, manufactured pentachlorophenol (PCP) from 1965 to 1979. PCDD/Fs are formed as byproducts of PCP manufacturing. A preliminary investigation[4] showed that marine biota in the nearby sea reservoir were seriously contaminated and that some of the inhabitants living near the deserted PCP factory had been exposed to high PCDD/F levels from eating contaminated seafood from that reservoir. In the current study, we calculated insulin resistance using homoeostasis model assessment (HOMA) based on fasting glucose and insulin levels. Because the insulin resistance heightens the risk of metabolic syndrome sufferers becoming pre-diabetic, which can lead to diabetes, we investigated the associations between HOMA-IR related factors (e.g., age, gender, and BMI) and Mets-related risk factors and finally defined the insulin resistance of inhabitants living in the vicinity of the deserted PCP factory. Our findings may provide a further linkage between dioxins and Mets-related risk factors in non-diabetic and diabetic participants. Finally, we also examined the associations between the prevalence of metabolic syndrome, high insulin resistance (HOMA-IR), high serum PCDD/Fs concentrations, and their potential interaction.

Materials and Methods

This cross-sectional study was done from July, 2005 to August, 2007 through a district health center near the deserted PCP factory. The only recruitment criteria was the residents who living in the Hsien-Gong, Lu-Erh, or Ssu-Tsao Lis, three small municipal administrative units, near the deserted PCP factory. After signing an informed consent form, each participant provided 80 mL of venous blood. Information obtained from the questionnaire included personal characteristics and life style habits. After exclusion of 36 individuals who had not fasting before blood sampling, the final recruited subjects were 1444. Serum insulin was measured using a radioimmunoassay. In addition, enzymatic colorimetric test for fasting glucose (FG), high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) were carried in the pathology laboratory of National Cheng Kung University Hospital. In each participant, the degree of insulin resistance was estimated at the baseline using a HOMA-IR value[5]. A lower HOMA-IR value indicates high insulin sensitivity, whereas a higher HOMA-IR value indicates insulin resistance. In addition, the European Group for the Study of Insulin Resistance (EGIR) defines insulin-resistance as a fasting insulin or HOMA-IR value > 75th percentile for the reference population. The definitions of metabolic syndrome (MetS) adopted in this study was according to the MetS criteria for Taiwanese (MetS-TW) which is modified from Adult Treatment Panel III (ATP III)[6]. According to MetS-TW criteria, the MetS was diagnosed in the presence of any three of the following: waist circumference greater than 90 cm in men and greater than 80 cm in women, triglycerides of 150 mg/dl or more, HDL cholesterol less than 40 mg/dl in men and less than 50 mg/dl in women, blood pressure of 130/85 mm Hg or higher, or fasting glucose of 100 mg/dl or higher. We also defined a MetS score as the number of these traits in a given patient. Factor analysis were initially carried out with all subjects including nondiabetic and diabetic subjects. At first, principle factor

analysis was used to identify the initial set of uncorrelated factors. And then the number of components to be retained was based on Scree plot analysis and eigenvalue criteria (1.0).

Results and Discussion:

Quantitative aspects of MetS and insulin resistance

One thousand, four hundred and forty-four residents (750 men, 694 women), ranging from 25 to 92 years of age (mean: 56.0 years) were recruited for this study. From the total study subjects, 532 patients (36.8%) had three or more MetS traits and therefore fulfilled the criteria for the MetS-TW. The prevalence of diabetes mellitus increased with an increasing MetS score from 0.4% in patients with no MetS risk factor through 68.8% in patients with five MetS risk factors ($P < 0.001$). BMI and concordant with MetS-TW criteria for the diagnosis of the MetS, waist circumference, triglycerides, and systolic as well as diastolic blood pressures significantly increased, and HDL cholesterol significantly decreased through the categories of the MetS score ($P < 0.001$ for all). Overall, the increase in HOMA-IR from subjects with zero through patients with five MetS traits was observed in patients with diabetes (HOMA-IR, 2.9± 0.7, 3.2± 0.9, 3.4± 0.8, 3.9± 0.8, 4.2± 0.9, and 3.5± 0.9, respectively; $P < 0.001$). Serum PCDD/F levels in subjects were significantly with zero MetS traits through subjects with five MetS traits (serum PCDD/F levels, 28.4± 36.7, 40.5 ± 56.4, 43.8± 47.0, 48.3± 51.7, 41.9± 31.1, and 65.5± 120.2 pg WHO_{98}-TEQ_{DF}/g lipid, respectively; $P < 0.001$) (Table 1). This increasing severity of insulin resistance with an increasing number of markers of the MetS reflects and confirms the pathophysiological rationale behind the ATP III criteria for the diagnosis of the MetS. Moreover, the similar trend was also observed between serum PCDD/F levels and MetS score which disclosure that PCDD/Fs could make some contribution in the cause of Mets.

Factor analysis in nondiabetic and diabetic individuals

In factor analysis, three factors with an eigenvalue >1 could accounted for 60.6% of the variance in the original 8 variables in nondiabetic individuals (Table 2). These three factors can be interpreted as representing lipidemia, blood pressure, and glycemia. On the hand, four factors with an eigenvalues >1 could accounted for 74.3% of the variance in diabetic participants. Thus, similar to results in nondiabetic individuals, results in diabetic participants can be interpreted as representing body size, lipidemia, blood pressure, and glycemia. In our study, factor analysis was used to investigate the clustering of variables that are thought to be important components of metabolic syndrome including PCDD/Fs. Because many of these risk factors cluster together, it has been hypothesized that they may reflect a limited number of etiological metabolic abnormalities or perhaps even a single abnormality. However, the present factor analyses did not identify a single factor underlying the correlation structure in the variables included. However, the present analyses gave discordant results in diabetic and nondiabetic individuals, and these results were consistent using different procedures for factor rotation. In Lee's study[7], OC pesticides were positively and significantly associated with four of the five risk factors of Mets, especially elevated triglycerides and high fasting glucose, but not high blood pressure. In addition, PCBs were significantly associated with waist circumference, triglycerides and impaired fasting glucose. While PCDD/Fs showed small but significant associations only with high blood pressure. In our study, PCDD/Fs were also interrelated with blood pressure in nondiabetic participants. Experimental data suggest that that TCDD may produce insulin resistance and compensatory hyperinsulinemia and hence predispose to hypertension through effects on the renin-angiotensin-aldosterone system[8]. On the other hand, TCDD will decrease expression of the insulin-responsive glucose transporter Glut 4[9]. In our study, PCDD/Fs were also interrelated with triglycerides in diabetic and systolic blood pressure in nondiabetic participants. Similar to an animal study, TCDD exposure may contribute to the acceleration of atherosclerotic plaque development in ApoE-null mice and then result in a significant elevation of triglycerides and LDL plasma levels. TCDD treatment led to an increase in both blood pressure and atherogenic lipids[10]. Thus, the results of most factor analyses, including the present study, suggest that relationships among the variables typically proposed as constituting the metabolic syndrome are best explained as resulting from multiple physiological processes and that the attempt to reduce these to a single entity will result in a substantial loss of information about these metabolic processes.

Interaction between serum PCDD/F levels and insulin resistance

In the groups with lower serum PCDD/F levels and higher Log HOMA-IR value was related to a higher risk of

metabolic syndrome compared to lower Log HOMA-IR value after adjusting for age, gender and BMI (adjusted OR = 2.76, 95% CI = 1.80- 4.22) (Table 3). Moreover, participants with higher serum PCDD/F levels and higher Log HOMA-IR value had the highest the risk of metabolic syndrome compared to the other three groups (adjusted OR = 5.28, 95% CI = 3.45- 8.15). However, these data show that PCDD/Fs exposure did not impact the relation between insulin resistance and metabolic syndrome (*P* for interaction =0.124). Therefore, it may be important to consider PCDD/Fs exposure as a possible effect modifier of the association between insulin resistance and metabolic syndrome. The present study established the relationship between increased insulin resistance and PCDD/Fs body burden after adjustment for age, gender, and BMI. Previous studies have reported a correlation between Mets and OC pesticides exposure. The present study further suggest a possible effect modification of PCDD/Fs exposure between the insulin resistance and the prevalence of metabolic syndrome. Further study is needed to confirm these findings in other PCDD/Fs-exposed individuals. Long-term health implications should be promptly delivered to persons diagnosed with abnormality of Mets risk factors so that they could prevent themselves from developing Mets.

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Table 1 Baseline characteristics by Mets score

	MetS score[a]					
	0	1	2	3	4	5
No. of subjects	240	310	362	301	167	64
Age (yr) [b, *]	47.0± 8.5	53.3± 12.1	58.8± 14.4	59.2± 13.2	60.3± 14.0	61.3± 12.8
Male gender (%) [c, *]	109 (45.4%)	180 (58.1%)	204 (56.4%)	152 (50.5%)	78 (46.7%)	27 (42.2%)
Diabetes (%) [c, *]	1 (0.4%)	28 (9.0%)	65 (18.0%)	90 (29.9%)	78 (46.7%)	44 (68.8%)
Smoking (%) [c, *]	61 (25.4%)	113 (36.5%)	145 (40.1%)	105 (34.9%)	53 (31.7%)	27 (42.2%)
Drinking (%) [c]	35 (14.6%)	59 (19.0%)	78 (21.6%)	58 (19.3%)	32 (19.2%)	12 (18.8%)
Systolic BP (mm Hg) [b, *]	109.5± 10.2	123.6± 19.0	136.5± 23.9	139.7± 22.2	144.0± 20.1	149.9± 22.6
Diastolic BP (mm Hg) [b, *]	69.4± 7.6	74.5± 10.0	77.2± 11.5	80.4± 11.9	81.0± 12.7	85.0± 11.7
Body mass index (kg/m^2) [b, *]	22.3± 2.6	23.5± 3.6	25.1± 3.5	26.9± 3.7	27.5± 3.2	27.9± 4.0
Waist circumference (cm) [b, *]	75.4± 7.5	80.9± 9.4	87.0± 9.3	92.1± 9.9	93.4± 9.1	96.7± 10.2
Fasting glucose (mg/dl) [b, *]	87.4± 6.2	96.9± 30.3	105.9± 40.0	116.4± 47.4	128.0± 44.5	154.8± 52.6
Triglycerides (mg/dl) [b, *]	79.3± 27.9	95.8± 42.7	131.6± 132.8	166.6± 119.7	256.2± 388.5	374.8± 336.5
Total cholesterol (mg/dl) [b, *]	195.2± 37.9	202.5± 44.0	204.9± 45.8	204.1± 41.5	207.8± 49.9	220.3± 44.7
HDL cholesterol (mg/dl) [b, *]	63.3± 15.5	58.2± 15.6	53.3± 15.4	47.2± 13.5	42.7± 11.3	36.7± 6.7
HOMA-IR [b, *]	2.9± 0.7	3.2± 0.9	3.4± 0.8	3.9± 0.8	4.2± 0.9	4.6± 0.9
PCDD/Fs [b, *] (pg WHO_{98}-TEQ_{DF}/g lipid)	28.4± 36.7	40.5± 56.4	43.8± 47.0	48.3± 51.7	41.9± 31.1	65.5± 120.2

[a] :The MetS score is defined as the number of MetS traits. [b]: One-way ANOVA. [c]: Chi-squared test. [*]:P<0.05

Table 2 Factor loadings for original variables with rotated factors in nondiabetic and diabetic participants

	Nondiabetic			Diabetic			
	Lipidemia	Blood pressure	Glycemia	Body size	Lipidemia	Blood pressure	Glycemia
Body weight	0.33	0.08	0.26	**-0.45**	-0.03	0.03	0.00
Waist circumference	0.32	-0.08	0.14	**-0.41**	-0.02	-0.07	-0.02
HDL	**-0.44**	-0.05	0.32	0.20	-0.39	-0.24	0.21
Systolic BP	-0.08	**-0.56**	-0.01	0.08	0.01	**-0.62**	-0.10
Diastolic BP	0.01	-0.38	0.18	-0.17	-0.02	**-0.48**	0.13
Triglycerides	0.30	0.05	-0.18	-0.05	**0.54**	0.04	0.21
Fasting glucose	-0.19	-0.06	**0.64**	0.02	-0.05	0.01	**0.90**
PCDD/Fs	-0.04	**-0.44**	-0.50	0.20	**0.54**	-0.17	-0.18
Variance (%)	25.8	19.9	14.9	25.9	17.3	17.8	13.3

Factor loadings with an absolute value ≧0.4, which indicates that the variable can be considered a major constituent of the factor, are shown in bold. Each factor is named according to the variables which are its major constituents. The percentage of the variance represents the proportion of variance in the original 8 variables accounted for by each factor.

Table 3 Odds ratios (ORs) of metabolic syndrome with low to high serum PCDD/Fs levels by their presence of insulin resistance

PCDD/Fs levels [†]	Log HOMA-IR[‡]	Mets (−) (n)	Mets (+) (n)	Adjusted OR [§]	95% CI
≦median	≦75 percentile	448	121	1	
≦median	>75 percentile	65	85	2.76	1.80- 4.22**
>median	≦75 percentile	345	169	1.09	0.77- 1.54
> median	> 75 percentile	54	157	5.28	3.45- 8.15**

[†]: Serum PCDD/F levels indicate that 1. ≦ median: ≦ 27.9 pg WHO_{98}-TEQ_{DF} /g lipid;
2. > median: > 27.9 pg WHO_{98}-TEQ_{DF}/g lipid;

[‡]: Log HOMA-IR indicate that 1. ≦ 75th percentile: ≦ 4.13; 2.> 75th percentile: > 4.13

[§]: Adjusted for age, sex, BMI; *: p<0.05; **: p<0.01 *P* for interaction = 0.124