DIOXIN EXPOSURE AND TYPE 2 DIABETES MELLITUS

Shaw Watanabe, M.D.
National Instittute of Health and Nutrition, 1-23-1, Toyama, Shinjuku, Tokyo, Japan

Abstract

To confirm the hypothesis that the exposure to dioxins contributes to the occurence of type 2 diabetes mellitus, well designed case-control study was carried out. Total blood dioxins (PCDD + PCDF + Co-PCB) of Control, PreDM and DM of both sex were 23.4±11.2, 30.8±11.5, 33.4±13.7 pg TEQ/g lipid and body burden was 0.61±0.32, 0.97±0.38, and 0.92±0.40 ng TEQ/kg body weight, respectively($p<0.001$). By multiregression analysis, The Exp(B) of familial history was 20.4 ($p=0.000$), Dioxin Factor 1, 2, 4, and 5 showed 2.33 ($p=0.036$), 1.67 ($p=0.066$), 2.81 ($p=0.011$), and 2.19 ($P=0.017$), respectively. Dioxin level associated with increased adipocytokines for insulin resistance, and negatively associated with adiponectin. Related papers were reviewed.

Introduction

In Japan, diabetes mellitus (DM) has rapidly increased in recent years. The total number of people who have a strong suspicion of DM and a possibility of DM was estimated to be approximate 17 millions by the National Nutrition Survey in 2002. Such an increase is considered to be due to the increased obesity and following metabolic syndrome. However, DM is a multifactorial disease and the reason of such increase has not been well understood. Exposure to 2,3,7,8-TCDD among US veterans in Vietnam War and people who exposed to BASF explosion in Seveso, Italy clarified the various health effects by chronic exposure of dioxins. Henriksen, et al. first reported a possible association between high-level TCDD exposure and DM among veterans of Operation Ranch Hand. The incidence of DM in Seveso also increased in TCDD exposure group.

We started dioxin measurement for workers in a heavily contaminated municipal waste incinerator in 1997, in which dioxin levels ranged from 13.4 to 805.8 pg TEQ/g lipid (1). We studied 740 residents in both sex in 17 areas from 1998 to 2001 and 840 workers from 60 incinerators in 24 areas from 1999 to 2005 (2-5). These cross sectional studies showed the significant correlations between blood dioxin exposure and past history of diabetes. The logistic regression analysis showed that sex, age, BMI, Co-PCB were significantly contributed to the prevalence of DM. It prompted us to confirm the risk of dioxins for DM by more sophisticated epidemiological method, and a case control study was carried out.

Design and Methods

To get 50 each of diabetic patients and controls in age 50's and 60's, 60 type 2 diabetes patients and 60 controls matched with sex and age (± 5 yrs) were selected from the list of Saku General Hospital and Health Doc

Center, Nagano. Height, body weight, body fat percentage and blood pressure were measured, and life habits and dietary habits were collected by a questionnaire. The questionnaire also included smoking and drinking habits, residential and work environment, physical activity, past history of diseases and treatments, family history, and reproductive history for females.

In addition to the routine hematological and biochemical analysis, lipokines, such as adiponectin, leptin, TNFalpha, resistin and nonesterified fatty acid were measured at the Serum Research Laboratory, Tokyo. 50 ml blood was collected to measure 7 polychlorodibenzo-p-dioxins (PCDD), 10 polychloro- dibenzofurans (PCDF), and 12 coplanar polychlorobiphenyl (PCB) at the Otsuka Lifescience Initiative, Tokushima. The exposure of the dioxins was calculated by the WHO TEF method (1997) and is expressed as TEQ/g lipid. Body burden was also calculated from the body fat percentage.

For statistical analysis, SPSS version 14.0 was used. Log transformation was done to normalize variables, If necessary. Multiple logistic regression analysis was used for evaluating the risk of dioxins for DM.

Results and Discussion

Among 72 participants received 75 g glucose OGT at the Health Doc, 12 were found to have PreDM, so the final group was consisted of 56 DM, 12 PreDM, and 49 Control. PreDM patients were obese with high body fat percent, and significantly higher leptin and lower adiponectin compared to other two groups. Regular medication was done in 64 (55.2%), in which 33 (28.4%) for diabetes, 29 (25%) for hypertension, 12 (10.3%) for hyperlipidemia, and others. Family history of DM in parents was present in 26 (22.4%), in which 3 in Control, 1 in PreDM and 22 in DM group. Average period of DM prevalence was 6.8±5.3 years. HbA1c of Control, PreDM and DM was 5.0+/-0.3, 5.2±0.2, 7.2±1.4 in males, and 4.9±0.2, 5.2±0.4 and 7.3±1.4 in females, respectively.

Total blood dioxins (PCDD + PCDF + Co-PCB) of Control, PreDM and DM of both sex were 23.4±11.2, 30.8±11.5, 33.4±13.7 pg TEQ/g lipid and body burden was 0.61±0.32, 0.97±0.38, and 0.92±0.40 ng TEQ/kg body weight, respectively($p<0.001$). Regression factor analysis of dioxin congeners yielded 5 factors. Logistic regression analysis for DM and PreDM was performed. The dependent variable was DM or Control, and independent variables were age, sex, BMI, smoking and drinking status, agriculture, familial history of DM, adiponectin, leptin and factor 1 to 5 of dioxin congeners. The Exp(B) of familial history was 20.4, Factor 1, 2, 4, and 5 showed 2.33, 1.67, 2.81, and 2.19, respectively. Only age and BMI were significant Exp(B) in the logistic regression analysis for PreDM, although family history, Factors 2 and 3 showed positive odds ratio without statistical significance.

Table Logistic regression analysis for the risk of DM

Control vs. DM	B	std. error	p	Exp (B)	95% confidece interval	
					upper	lower
age	0.103	0.056	0.065	1.108	0.994	1.236
sex	-0.485	0.964	0.615	0.616	0.093	4.069
bmi	0.145	0.112	0.196	1.156	0.928	1.440
familial history	3.013	0.821	**0.000**	**20.353**	4.074	101.692
farming	0.555	0.551	0.313	1.743	0.592	5.127
smoking	0.150	0.427	0.726	1.161	0.503	2.682
drinking	-0.320	0.325	0.324	0.726	0.384	1.373
adiponectin	-0.002	0.070	0.980	0.998	0.870	1.145
leptin	0.005	0.078	0.948	1.005	0.863	1.171
Factor 1	0.846	0.404	**0.036**	**2.330**	1.056	5.142
Factor 2	0.527	0.286	**0.066**	**1.693**	0.966	2.968
Factor 3	-0.070	0.218	0.749	0.933	0.608	1.431
Factor 4	1.033	0.405	**0.011**	**2.810**	1.270	6.219
Factor 5	0.782	0.328	**0.017**	**2.185**	1.150	4.152
constant	-9.145	4.922	0.063	0.000		

Step 1: adjusted variables are age, sex, bmi, familial history of DM, farming, smoking, drinking (none, current, quit), adiponectin, leptin, Factor 1, Factor 2, Factor 3, Factor 4 and Factor 5.

Factor 1: PCB157, 156, 189, 169, 167, 114, 118, 23478PCDF

Factor2: 12378PCDD, 123678PCDD, 2378PCDD, 123478PCDD, 123478PCDF, 123678PCDF, 1234678PCDF,

Factor 3: PCB81, 2378PCDF, PCB77, 12378PCDF, PCB126, PCB105,

Factor 4: 1234678PCDD, OCDD, PCB123,

Factor 5: 1234678PCDF

A hypothesis whether dioxin exposure would become a risk of type 2 DM was confirmed by this case control study. US veteran studies and Seveso's study only measured 2,3,7,8-TCDD, so the risk would have been underevaluated.In Japan, PCB usage was a peak in 1970s, and breast milk showed the highest dioxin concentration at that time. The babies at that time grew older into 30s and 40s, and children become 50s and 60s.

Recent report of Lee, et al. (6) also suggested the possibility that persistent organic pollutants might contribute to cause diabetes. They analyzed serum concentrations of 6 persistent organic pollutants, such as PCB153,

HpCDD, OCDD, Oxychlordane, DDE, DDT and trans-Nonachlor, with fasting plasma-glucose concentrations in a random sample of general population. They showed that the prevalence of DM was more than 5 times higher in groups with higher concentrations of PCB153, oxychlordane, or trans-nonachlor than in those with low concentrations.

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