ASSOCIATIONS OF LOW LEVELS EXPOSURE TO DIOXINS WITH PREVALENT DIABETES IN JAPANESE GENERAL POPULATION

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Abstract

To evaluate the associations of exposure levels of dioxins with prevalent diabetes in Japanese general population, a cross-sectional study was performed through 2002 – 2005 on 1083 participants aged 15 - 73 years who were not occupationally exposed to dioxins. Seven polychlorinated dibenzo-*p*-dioxins (PCDDs), ten polychlorinated dibenzo-furans (PCDFs), 12 co-planar polychlorinated biphenyls (co-PCBs), and hematological and biochemical factors were determined in fasting blood. A questionnaire survey on life-style was also performed. Linear and multiple regression analyses were used to determine the factors that may explain the variabilities in the toxicity equivalents (TEQs) of dioxins. We also tested the associations of the TEQs of dioxins with prevalent diabetes in logistic regression analyses. Multiple regression analyses revealed that plasma HbA1c was one of the determinants for the TEQs in blood. Logistic regression analyses revealed that the highest quantile of co-PCBs and total dioxins had adjusted odds ratios of 7.53 and 3.58 compared to the referent (second) quantile and showed graded associations. When the subjects with poor liver or renal function were removed from the analysis, the results did not substantially alter. These findings confirm a linking of dioxins, especially co-PCBs, to diabetes in Japanese general population.

Introduction

Polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs and co-planar polychlorinated biphenyls (co-PCBs) are lipophilic and prone to bioaccumulation, and are widely persistent in the environment. Various biological and toxic actions are induced by low-level exposure to these chemicals. Recently, low levels exposure to dioxins has been reported to have a possible link with increased risk of diabetes [1,2]. However, it is not yet elucidated whether similar associations exist in Japanese general population with very

low lifetime exposure to dioxins. For elucidating this question, a cross-sectional study was performed in Japanese general population with no known occupational exposure to dioxins.

Materials and Methods

This study was performed from 2002 to 2005 on 1083 participants aged 15 - 73 years in Japan. The whole of Japan was divided to five regional blocks. One prefecture was selected from each regional block every survey year, and approximately 50 individuals who had no known occupational exposure to dioxins were recruited in each prefecture. In this recruitment, almost 20 were from urban areas, almost 15 were from farming village and almost 15 were from fishing village areas, almost equally in age and gender among the three areas. A written informed consent was obtained from each participant. Seven PCDDs, 10 PCDFs and 12 co-PCBs were determined in fasting blood by isotope dilution high-resolution gas chromatography/mass spectrometry (GC/MS), after liquid/liquid extraction and gel clean-up. To express the toxic potency of the mixture of dioxin congeners, the 1998 WHO toxic equivalency factor was used [3]. If the level of the pollutant was below the limit of detection, zero was used as its concentration. Nineteen hematological and biochemical factors in blood including HbA1c were also determined. Each participant was requested to complete a questionnaire on individual characteristics including past history of diseases and treatments. Prevalent diabetes was assessed as followed criteria; 1) self-report answer of a history of physician-diagnosed diabetes, or 2) plasma HbA1c > 6.1%.

The values of dioxins on the basis of TEQ were analyzed statistically after logarithmic transformation. When necessary, results of hematological or biochemical tests in blood were also log-transformed. The differences in the TEQs of dioxins by the clinical characteristics were evaluated by Wilcoxon rank-sum test or Kruskal-Wallis test. Multiple regression analysis was performed to determine the factors that may explain the variabilities in the TEQs of dioxins. In this analysis, variables which showed P-values < 0.1 in simple correlation were included in the model as independent variables. We also tested the associations of the TEQs of dioxins with prevalent diabetes in logistic regressions, with non-adjusted and adjusted for age, gender, regional block, residential area, survey year and body mass index. The TEQs of PCDDs, PCDFs, co-PCBs and total dioxins were divided to quantiles, and second quantiles were as the referents. We reanalyzed these associations excluding the subjects with poor liver or renal function who might have impaired ability to metabolize and excrete one or more of these chemicals. All statistical analyses were performed with the SAS software package (version 8.2). All *P* values are two-tailed and those less than 0.05 were considered statistically significant.

Results and Discussion

The median of the TEQs of total dioxins were 21.0 pg TEQ/g lipid in men and 21.0 pg TEQ/g lipid in women, with no gender difference. The TEQs of total dioxins as well as those of PCDDs + PCDFs and co-PCBs progressively increased with advancing age category and were highest in the fishing village areas (data not shown). In multiple regression analyses, age, eicosapentaenoic acid (EPA) and HbA1c were the common determinants for the TEQs of PCDDs + PCDFs, co-PCBs and total dioxins (data not shown). Of the 1083 subjects, 55 subjects (5.1 %) (36 male and 19 female) were diagnosed as diabetes. In logistic regression analyses, the highest quantile of co-PCBs and total dioxins had adjusted odds ratios of 7.53 (95%CI 2.34 - 24.23) and 3.58 (95%CI 1.35 - 9.52) compared to the referent quantile (Table 1). When the subjects with poor liver or renal function were removed from the analysis, the results did not substantially alter (data not shown).

Multiple regression analyses showed that HbA1c was a main determinant for the TEQs of dioxins in blood in Japanese general population. Logistic regression analyses further revealed significant graded associations of the TEQs of co-PCBs and total dioxins with prevalent diabetes, and these associations persisted when the subjects with poor liver or renal function were removed from the analysis. These findings confirm a linking of dioxins, especially co-PCBs, to diabetes in Japanese general population.

Acknowledgments

References

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Table 1. Non-adjusted and adjusted associations of the accumulated TEQs of PCDDs, PCDFs, co-PCBs and total dioxins with prevalent diabetes.

	Odds ratio	
	Non-adjusted (95%CI)	Adjusted[a] (95%CI)
PCDDs (pg TEQ/g lipid)		
< 4.89	0.09 (0.01 - 0.69)	0.12 (0.01 - 0.97)
≥ 4.89 and < 7.80	referent	referent
≥ 7.80 and < 11.40	1.02 (0.43 - 2.38)	0.79 (0.32 - 1.95)
≥ 11.40	3.13 (1.54 - 6.34)	1.92 (0.86 - 4.28)
PCDFs (pg TEQ/g lipid)		
< 3.00	——	——
≥ 3.00 and < 4.70	referent	referent
≥ 4.70 and < 6.90	2.17 (0.96 - 4.88)	1.58 (0.67 - 3.71)
≥ 6.90	3.25 (1.50 - 7.06)	1.76 (0.73 - 4.28)
Co-PCBs (pg TEQ/g lipid)		
< 4.70	0.25 (0.03 - 2.27)	0.34 (0.04 - 3.23)
≥ 4.70 and < 7.90	referent	referent
≥ 7.90 and < 13.00	3.11 (0.98 - 9.91)	2.77 (0.83 - 9.22)
≥ 13.00	9.86 (3.48 - 27.98)	7.53 (2.34 - 24.23)
Total (pg TEQ/g lipid)		
< 13.00	——	——
≥ 13.00 and < 21.00	referent	referent
≥ 21.00 and < 31.00	2.10 (0.83 - 5.35)	1.76 (0.64 - 4.79)
≥ 31.00	5.33 (2.33 - 12.21)	3.58 (1.35 - 9.52)

[a] Logistic regressions adjusted for age, gender, regional block, residential area, survey year and body mass index.