PERSITENT ORGANOCHLORINE POLLUTANTS: A RISK FACTOR FOR TYPE 2 DIABETES

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Abstract

Persistent organochlorine pollutants (POP), have in several cross-sectional studies shown strong associations with type 2 diabetes. Reversed causality can however not be excluded. The aim of this case-control study was to evaluate whether POP concentration is a risk factor for type 2 diabetes.
The study was performed within a cohort of women, 50-59 years, from Sweden. Biomarkers for POP exposure, 2,2',4,4',5,5'-hexachlorobiphenyl (CB-153) and 1,1-dichloro-2,2-bis (*p*-chlorophenyl)-ethylene (p,p'-DDE) were analyzed in stored serum samples, which were collected at the baseline examination when the cohort was established. For 107 out of the 371 cases, serum samples were stored at least three years before their type 2 diabetes was diagnosed.
CB-153 and p,p'-DDE were not associated with an increased risk to develop type 2 diabetes. However, when only the cases (n=39) that were diagnosed more than six years after the baseline examination and their controls were studied, the women in the highest exposed quartile showed an increased risk to develop type 2 diabetes (OR of 1.6 [95% 0.61, 4.0] for CB-153 and 5.5 [95% CI 1.2, 25] for p,p'-DDE).
The results confirms that p,p'DDE exposure can be a risk factor for type 2 diabetes. Thus, the importance of environmental pollutants must not be neglected.

Introduction

The incidence of type 2 diabetes is rapidly increasing world-wide [1]. The main factors identified as responsible for the disease are an aging population with a genetic predisposition for diabetes, change in lifestyle such as low physical activity, obesity and smoking. In addition, multiple reports corroborate the association between persistent organochlorine pollutants (POPs) such as polychlorinated biphenyls (PCB), dioxins and dichloro-diphenyl-trichloroethane (DDT) and type 2 diabetes.
Surprisingly strong associations have been shown between serum concentrations of POPs and type 2 diabetes [2-13]. If these associations reflect a true effect of environmental exposures on the incidence of diabetes, then this is the largest public health effect observed for POPs so far. The majority of recent studies are cross-sectional however, and a direct cause has so far not been shown.
The aim of the present case-control study, performed within a well-defined cohort of women from the Southern part of Sweden, was to elucidate to what extent POP exposure may have contributed to the development of type 2 diabetes.

Materials and methods

During 1995-2000 a generic survey based on a questionnaire, physical examinations, and laboratory assessments were completed on 6 917 women (corresponding to 64% participating rate) aged 50–59 years and living in the five municipalities in the Lund area, located in Southern Sweden (the Women's Health In the Lund Area cohort - WHILA) [14].
Women with the metabolic syndrome features (positive, n=3144) underwent a baseline Oral Glucose Tolerance Test (OGTT), one to four weeks later. By linkage with the Swedish in-patient and out-patient

registers, women from the WHILA cohort who had developed type 2 diabetes before 31 December 2006, were identified. A randomly selected subgroup (n=221) of women without the metabolic syndrome features, also underwent OGTT, and the results corroborated the very low prevalence of previously unknown diabetes among women outside the group. Women with previously confirmed diabetes (n=139) were excluded from further studies. In total, 410 women were diagnosed with type 2 diabetes after the baseline examination. A case-control control study was performed within the WHILA cohort. Blood samples were obtained from all participating women at the baseline examination and were stored at -70^{o}C until the present POP analyses were run.

Cases

Out of 410 incident diabetic women (cases) 39 were not eligible for the current study due to lack of serum samples. Background characteristics for the remaining 371 cases are presented in Table 1. Fifty-six percent were diagnosed with type 2 diabetes within one year after baseline examination.

Controls

For each case, one control was randomly selected from the WHILA cohort, matched for age, calendar-year, body mass index (BMI), and according to positive or negative selection criteria for OGTT at the baseline examination, i.e. presence or not of any features of the metabolic syndrome.

Biomarkers of exposure

In the present study 2,2',4,4',5,5'-hexachlorobiphenyl (CB-153) and 1,1-dichloro-2,2-bis (*p*-chlorophenyl)-ethylene (p,p'-DDE) have been used as biomarkers for POP exposure. The chemical analyses have recently been described in detail [15].

Statistical analyses

The association between POP exposure and risk of developing type 2 diabetes was evaluated by conditional logistic regression (EGRET), given odds ratios (OR) as the risk measure with 95% confidence intervals (CI). The exposure variables (CB-153 and p,p'-DDE) were analyzed as continuous variables as well as categorized into quartiles and tertiles, respectively, based on the distributions among all controls. Women with serum concentrations in the highest quartile (or tertile) were considered as exposed. In addition, separate analyses were performed for the set of cases and controls where the cases had their type 2 diabetes diagnosed at least one, three, five and seven years after the base-line examination, respectively.

Results

The mean concentrations of CB-153 and p,p'-DDE was equally distributed among all cases and controls (Table 2).

For the set of cases and controls where the cases had type 2 diabetes diagnosed at least seven years after the baseline examination (n=39), the cases had a 22% higher mean concentration of CB-153 (1560 and 1280 pg/mL) and a 46% higher mean concentration of p,p'-DDE (5680 and 3890 pg/mL) compared with the controls.

When all individuals were included in the analyses, the women in the highest exposure quartile showed no increased risk to develop type 2 diabetes as compared to women in the three lower quartiles, irrespectively if investigating the concentrations for CB-153 or p,p'-DDE (OR 0.99 and 1.1, respectively.

The corresponding ORs increased gradually, i.e. the longer time that had passed between the baseline examination and the time to diagnose. If the cases were diagnosed at least seven years after the baseline examination, OR of 1.6 (95% 0.61, 4.0) for CB-153 and 5.5 (95% CI 1.2, 25) for p,p'-DDE were obtained (Table 2).

Discussion

Among women from the general population, the present study indicate that high serum concentrations of p,p'-DDE is a strong risk factor for developing type 2 diabetes later in life. A five-fold statistically significant increased risk was observed among the individuals with the longest follow-up. This finding is in accordance with the results from previous cross-sectional studies [2-13]. Although less pronounced, similar pattern was observed for CB-153. Thus, our data support that POP exposure can be a risk factor for type 2 diabetes and the importance of environmental pollutants must not be neglected.

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Table 1 Background characteristics for 371 women from the Southern part of Sweden who were diagnosed for type 2 diabetes after the baseline investigation (cases) and a corresponding number of matched control women.

	Controls (n=371)	Cases (n=371)
Variables	*Median (Min, Max)*	*Median (Min, Max)*
Calendar-year at baseline[a]	1998 (1995, 2000)	1998 (1995, 2000)
Age at baseline (years)[a]	57.6 (50.7, 63.8)	57.3 (51.1, 63.8)
BMI at baseline (kg/m^2)[a]	28.5 (18.2, 43.8)	28.3 (17.9, 47.0)
BMI at 25 years of age (kg/m^2)	21.7 (15.8, 33.7)	21.4 (15.4, 34.6)
Time between baseline and T2DM diagnosis (years)		0.23 (0.01, 10.5)
	Percent	*Percent*
Family history of T2DM[b]	17	18
Born in Sweden	91	91
Education		
Compulsory school	29	32
Senior high school	44	45
University	27	23
Smoking history at baseline		
Ex smoker	20	22
Current smoker	12	16
Moderate/High alcohol intake[c]	9	16
Hormone replacement therapy at baseline	30	34
Low leisure time exercise[d]	64	66
Low physical activity at work[e]	33	35

[a] Matching variable
[b] First-degree relatives
[c] More than 84 gram alcohol per week.
[d] Less than one hour of strenuous training session per week.
[e] Mostly sedentary work

Table 2 Odds ratios (OR) with 95% confidence intervals (CI) obtained from conditional logistic regressions. Figures are given when all women were included in the analyses, as well as separately for the set of cases and controls were the cases had their type 2 diabetes diagnosed at least three or seven years after the baseline investigation.

	OR	95% CI
CB-153 (pg/mL)		
>1790 vs ≤1790 (ref)[a]		
All (371 sets[b])	0.99	0.71 – 1.4
> 1year (163 sets[b])	1.1	0.66 – 1.9
>3 years (107 sets[b])	1.4	0.72 – 2.6
>5 years (74 sets[b])	1.4	0.67 – 3.1
>7 years (39 sets[b])	1.6	0.61 – 4.0
p,p'-DDE (pg/mL)		
>4600 vs ≤4600 (ref)[a]		
All (371 sets[b])	1.1	0.76 – 1.5
> 1year (163 sets[b])	1.3	0.78 – 2.2
>3 years (107 sets[b])	1.5	0.80 – 2.8
>5 years (74 sets[b])	2.5	0.97 – 6.4
>7 years (39 sets[b])	5.5	1.2 – 25

[a] The cut-off level corresponding to the 75th percentile among all women.
[b] n Sets= n cases + n controls