Chemosphere 145 (2016) 25–33

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

Effects of dioxin-related compounds on bone mineral density in patients affected by the Yusho incident

Jun-ichi Fukushi [a, *], Shoji Tokunaga [b], Yasuharu Nakashima [a], Goro Motomura [a], Chikage Mitoma [c], Hiroshi Uchi [c], Masutaka Furue [c], Yukihide Iwamoto [a]

[a] Department of Orthopaedic Surgery, Graduate School of Medical Sciences, Kyushu University, Maidashi3-1-1, Higashi-ku, Fukuoka 812-8582, Japan
[b] Medical Information Center, Kyushu University Hospital, Maidashi3-1-1, Higashi-ku, Fukuoka 812-8582, Japan
[c] Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Maidashi3-1-1, Higashi-ku, Fukuoka 812-8582, Japan

HIGHLIGHTS

- Dioxin-related compounds may result in adverse effects on bone metabolism.
- The effect of dioxins on bone mineral density (BMD) in Yusho disease was studied.
- The blood level of 1,2,3,4,6,7,8-HpCDD was negatively associated with BMD in women.
- No congeners were negatively associated with BMD in men.

ARTICLE INFO

Article history:
Received 23 January 2015
Received in revised form
10 November 2015
Accepted 22 November 2015
Available online 1 December 2015

Handling editor: Andreas Sjodin.

Keywords:
Bone mineral density
Dioxins
PCB
Yusho

ABSTRACT

Exposure to dioxin-related compounds results in many adverse health effects. Several studies have examined the effects of dioxin-related compounds on human bone metabolism with inconsistent results. In Japan in 1968, accidental human exposure to rice oil contaminated with dioxin-related compounds led to the development of Yusho oil disease. The aim of this study was to determine whether exposure to dioxin-related compounds was associated with bone mineral density in Yusho patients. In 2010, 262 women and 227 men underwent dual-energy X-ray absorptiometry bone scans as part of the nationwide Yusho health examination. Serum levels of polychlorinated dibenzo-*p*-dioxin, polychlorinated dibenzofurans, and non-ortho polychlorinated biphenyls were measured using high-resolution gas chromatography and high-resolution mass spectrometry. When adjusted for prefecture, 1,2,3,4,7,8-HxCDD and 2,3,7,8-TCDF were significantly positively associated with Z-scores in men. No congeners were positively associated with Z-scores in women. After adjustment for prefecture and body mass index, one congener, 1,2,3,4,6,7,8-HpCDD, was negatively associated with Z-scores in women. In contrast, no congeners remained significant in men after adjusting for body mass index. This may suggest that 1,2,3,4,6,7,8-HpCDD has a negative effect on bone mineral density in women; however, the findings should be interpreted carefully, because no increase in the serum level of this congener was observed in patients with Yusho disease.

1. Introduction

Polychlorinated biphenyls (PCBs), polychlorinated dibenzo-*p*-dioxin (PCDDs), and polychlorinated di-benzofurans (PCDFs) are a group of persistent organochlorine compounds that are widespread in the environment. These highly lipophilic compounds accumulate in food chains and are detectable in human tissue. Exposure to these molecules, especially dioxins and dioxin-related compounds, results in many adverse health effects, including developmental defects (Walkowiak et al., 2001; Ayotte et al., 2003), immunotoxicity (Weisglas-Kuperus et al., 2000), reproductive toxicity (Tsukimori et al., 2008), and endocrine dysfunction (Pluim et al., 1993).

In Western Japan in 1968, over 1900 people were accidentally exposed to rice oil contaminated with PCBs and their pyrolytic byproducts, PCDFs and PCDDs. This food poisoning caused various

* Corresponding author.
E-mail address: fukushi@med.kyushu-u.ac.jp (J.-i. Fukushi).

http://dx.doi.org/10.1016/j.chemosphere.2015.11.091

clinical symptoms, including systemic, dermatological, and ophthalmological manifestations, and was referred to as Yusho oil disease (Furue et al., 2005; Yoshimura, 2012). A recent study showed that the sum of the toxic equivalent concentrations of PCDDs, PCDFs, and non-ortho PCBs in the blood of Yusho patients in 2006 was 3.3 times higher than that in normal controls. Among PCDF congeners, which are now considered to be the primary causative agents of Yusho, 2,3,4,7,8-pentaCDF had the highest concentration, about 10 times that found in controls (Todaka et al., 2009). Thus, dioxin-related compounds persisted for a long time in Yusho patients.

Dioxin-related compounds exert a variety of endocrine effects, including estrogenic, anti-estrogenic, and anti-androgenic effects (Ahlborg et al., 1995; Gray, 1998). Given the central role of estrogen in the development of post-menopausal osteoporosis (Deroo and Korach, 2006), dioxin-related compounds that can interact with estrogen receptors or alter estrogen metabolism may affect bone metabolism. Studies in populations with environmental exposure to dioxin-related compounds have shown inconsistent results regarding the effect on bone mineral density (BMD). In 153 Inuit women with long-term exposure to high levels of organochlorine compounds due to their traditional seafood diet, univariate analyses showed that plasma concentrations of PCB153 were inversely correlated with quantitative ultrasound parameters at the heel bone. However, this association was not significant after adjusting for confounding variables (Cote et al., 2006). In a population living close to both the Baltic coast and a river contaminated by PCBs, PCB118 was inversely associated with BMD in men and positively associated with BMD in women, suggesting sex-specific effects of PCBs on bone metabolism (Hodgson et al., 2008). Very recently, Eskenazi et al. reported no significant negative association between serum tetrachlorodibenzodioxin (TCDD) concentrations and BMD in women in Seveso, where people were highly exposed to TCDD due to an industrial explosion in 1976 (Eskenazi et al., 2014).

It was reported that 3 of 12 infants with congenital Yusho who were born to mothers with Yusho had natal teeth, spotty calcification of the skull bones, and open fontanelles at birth, suggesting impairment of calcium metabolism (Miller, 1985). In a cohort of Yucheng disease in Taiwan, a similar large-scale food poisoning occurred in 1979, natal teeth and open fontanelles were also reported in 11 of 127 children (Rogan et al., 1988). In a follow-up study of Yucheng children, no differences in BMD were observed when compared with controls (Guo et al., 1994). The aim of the current study was to examine whether exposure to dioxin-related compounds was associated with BMD in Yusho patients.

2. Materials and methods

2.1. Subjects

A nationwide Yusho health examination has been conducted annually in Japan since 1986 to monitor the health status of chronic Yusho patients (Furue et al., 2005). Officially registered Yusho patients are those registered by the prefecture office and the Ministry of Health, Labour and Welfare. The examination is open not only to officially registered Yusho patients but also to those who were exposed to the contaminated rice oil and who regard themselves as potential victims.

In 2010, 543 individuals participated in the nationwide health examination, and 14 underwent the same health examination at Kyushu University hospital. Of these 557 potential subjects, we included those who were born before the onset of the Yusho accident. Therefore, 489 subjects were eligible for the analysis. These included 262 women and 227 men with mean ages of 66.3 years in women and 66.9 years in men. The officially registered Yusho patients comprised 161 (61.5%) women and 158 (69.6%) men. The majority of the study subjects lived in Nagasaki ($n = 207$, 42%) and Fukuoka ($n = 158$, 32%), and the rest lived in Kanagawa, Aichi, Osaka, Tottori, Hiroshima, Yamaguchi, and Kochi. We obtained written informed consent from all subjects prior to drawing blood and conducting an interview. The Institutional Ethics Committee approved the study design (No. 25-166, Kyushu University).

2.2. Clinical and biological parameters

Body height and weight were recorded, and body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Data on osteoporosis were obtained either through face-to-face interviews by trained nurses ($n = 304$, 83.3%, Nagasaki and Fukuoka) or mailed questionnaires ($n = 61$, 16.7%, other regions). The questions about osteoporosis addressed history of osteoporosis and history of medications for osteoporosis.

BMD was measured at the distal radius of non-dominant arms using a dual-energy X-ray absorptiometry (DXA) method. Participants were 66 men and 100 women in Fukuoka, 90 men and 112 women in Nagasaki, and 41 men and 39 women in other regions. Four different devices were used: DCS-600EX (Aloka, Tokyo, Japan, $n = 173$, Fukuoka, Osaka, and Kochi), DTX-200 (Osteometer Meditech Inc. CA, $n = 191$, Nagasaki), Discovery Wi (Hologic, Inc. MA, $n = 20$, Hiroshima, Tottori), and Delphi (Hologic, Inc., $n = 12$, Kanagawa). These devices are used worldwide, and quality assurance procedures have been performed (Hangartner, 2007; Hans et al., 2008). Z-scores, which are the number of standard deviations away from the average of the age-matched reference BMD values, were used for analysis.

The clinical characteristics of the study subjects are shown in Table 1.

2.3. Measurements of PCBs and dioxin-related compounds

The serum levels of dioxin-related compounds were measured during the nationwide Yusho health examination (Todaka et al., 2009). Briefly, 10-ml blood samples were collected, and the levels of PCDDs, PCDFs, and non-ortho PCBs in the blood were measured using high-resolution gas chromatography and high-resolution mass spectrometry at the Fukuoka Institute of Health and Environmental Sciences (Todaka et al., 2003). Twenty-nine different congeners were measured: 7 PCDDs, 10 PCDFs, and 12 PCBs. Of the 12 PCBs, 4 congeners detected in more than half of the participants were further analyzed.

2.4. Data analysis and statistical methods

Because the incidence of osteoporosis differs significantly between women and men, we separately assessed the relationships between the concentrations of dioxin-related compounds and BMD measures for each gender expressed by Z-score. The associations between Z-score, BMI, and levels of dioxin-related compounds were analyzed using linear regression models. In cases in which concentrations of dioxin-related compounds were lower than the detection limit, a value of half the detection limit was used. Considering their highly skewed distributions, the concentrations of dioxin-related compounds were $\log_{10}$-transformed and included in the model. The regions of residency were included in the model as dummy variables for Fukuoka, Nagasaki, and other prefectures. A two-sided $P < 0.05$ was considered statistically significant in the statistical tests. All statistical analyses were performed using Stata version 13 statistical analysis software (Stata, College Station, TX, USA).