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Brief communication

Benchmark dose for estimation of cadmium reference level for osteoporosis in a Chinese female population

Xiao Chen [a,1], Caohui Gan [a,1], Guoying Zhu [a,*], Taiyi Jin [b,*]

[a] Institute of Radiation Medicine, Fudan University, Shanghai 200032, China
[b] School of Public Health, Fudan Unversity, Shanghai 200032, China

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ABSTRACT

In this study, the reference level of cadmium in urine and blood related with bone damage was assessed using benchmark dose in a Chinese female population. Total of 338 women was recruited, and urine and blood samples were collected from each individual for determination of cadmium in urine (UCd) and blood (BCd). Bone mineral density was measured by dual energy X-ray absorptiometry. BMD and BMDL were calculated corresponding to additional risk of 5% and 10%. With benchmark response (BMR) of 5%/10%, the BMD of BCd, UCd related with osteoporosis was 1.88 μg/L/3.23 μg/L and 5.30 μg/g crea/9.06 μg/g crea, and the BMDL-05 was 1.39 μg/L/2.38 μg/L and 3.78 μg/g crea/6.36 μg/g crea; the BMD of BCd, UCd related with low bone mass was 0.95 μg/L/3.12 μg/L and 3.12 μg/g crea/5.87 μg/g crea, and the BMDL-05 was 0.72 μg/L/1.35 μg/L and 2.14 μg/g crea/3.99 μg/g crea. The BMD of UCd in people over 60 years old was much lower than that of people less than 60 years old. BMD value was related with ages and effects biomarkers. Our data showed that BMD of UCd associated with osteoporosis was lower than that previously estimated.

1. Introduction

Cadmium (Cd) is one of heavy metals commonly found in industrial workplace and the environment. It had been suggested that bone is one of target organs for Cd toxicity (WHO, 1992). It has been indicated that Cd exposure could induce bone loss, osteoporosis and high risk of bone fractures in humans and experimental animals (Wang et al., 2003; Jin et al., 2004a; Staessen et al., 1999; Brzoska et al., 2005). Recent epidemiological studies demonstrated that environmental Cd exposure which could not result in kidney damage might associate with low bone mineral density and increase the risk of bone fractures (Schutte et al., 2008; Åkesson et al., 2006; Nawrot et al., 2010). However, little information was known about the reference point of Cd related bone damage.

The benchmark dose (BMD) method has been widely used to assess the health risk of environmental contaminants (Crump, 1984; Filipsson et al., 2003). BMD represent the exposure level that corresponds to a specific change in response compared to the zero background. It has been showed that the lower 95% confidence limit of BMD (BMDL-05) could be used to replace the no observed adverse effect level (NOAEL) (Crump, 1984; Gaylor et al., 1998). Unlike NOAEL, BMDs are not constrained to one experimental dose, but utilizes the information from the whole dose–response curve. In addition, BMDs depend on less sample size compared with NOEAL. BMD is a better approach to estimate reference point than NOAEL for continuous outcome variable.

BMD method has been used to assess the reference dose of Cd damage to kidney (Suwazono et al., 2006; Kobayashi et al., 2006, 2008; Suwazono et al., 2010a, 2011). Recently, Suwazono et al. (2010b) adopted BMD to assess the reference point of Cd-induced osteoporosis in a Swedish population. Our previous study showed that body Cd level was associated with decrease of bone mineral density and increase of risk of osteoporosis after reduction of exposure in a Chinese population (Chen et al., 2009). It has been suggested that women may be more affected by Cd compared with men (Vahter et al., 2007; Chen et al., 2009). Moreover, the reference point of Cd related osteoporosis in Swedish population was lower than critical concentration previously reported. Thus, in this study, we want to know the reference point of Cd at which could decrease bone mineral density and induce osteoporosis in a Chinese female population. Meanwhile, we analyzed the influence factors which may be related with BMD calculation.

2. Materials and method

2.1. Area and study population

One control area and two Cd polluted areas were included in this present study. A Cd smelter that begun operating in 1961 was located in the polluted area and industrial wastewater was regularly discharged into the nearby river. The population living in Cd-polluted area was divided into two groups: namely heavily

* Corresponding authors. Tel.: +86 021 64431139.
E-mail addresses: chx_win@hotmail.com (G. Zhu), tyjin@shmu.edu.cn (T. Jin).
[1] These authors contributed equally to this work.

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polluted group and moderately polluted group, living 0.5 km and 12 km away from the smelter, respectively. The residents living in the polluted areas used the polluted river to irrigate their rice fields from 1961 to 1995. Rice was the main food of the local residents. Cd concentration in rice was 3.7 mg/kg and 0.5 mg/kg in 1996 in the heavily and moderately polluted areas, respectively. From 1996 onward, however, the residents living in the Cd-contaminated areas were advised to stop producing rice and shifted to eat commercial rice from non-polluted areas (0.03 mg Cd/kg). A control group was selected from a non-Cd-polluted village (Yantou) having many conditions in common with the polluted areas (social, economic conditions and living habits) but with a lower Cd concentration in its rice. More detailed information has been provided previously (Wang et al., 2003; Jin et al., 2004a; Chen et al., 2009).

A total of 338 women, aged 40 years and older were recruited in this study. The participants had no conditions known to affect bone mineral density, including a history of chronic disease, use of medications known to alter bone metabolism. The participants in the study gave their oral informed consent and completed a questionnaire including information on medical and drug history, cigarette smoking and menopause status. During this study, Declaration of Helsinki was followed. The Ethics Committees of Fudan University approved this study.

2.2. Bone mineral density measurements and definition of osteoporosis

Dual energy X-ray absorptiometry (DXA, Norland) was used to measure bone mineral density at the non-dominant wrist; measurement precision, expressed as the coefficient of variation (CV) was within 1%. The repeatability was 99.47% measured by this apparatus in the same person for 10 times. The apparatus was calibrated every day, including quality assurance and phantom scanning, and all measurements were performed by the same experienced machine operator.

The index of osteoporosis is expressed in terms of the *T*-score and *Z*-score. *Z*-score was calculated by age-adjusted and the influence of age could be eliminated. And it has been suggested that *T*-score is often used to diagnose osteoporosis for postmenopausal women. In our study, some people were premenopausal women. In addition, *T*-score does not take into account other important information such as age (Licata, 2006). Thus *Z*-score was used in this study. It was computed using the equation $Z\text{-score} = (X\mu - Xm)/\text{SD}$, where $X\mu$ is the obtained bone mineral density, Xm is the mean value for same age in the control group, and SD is the standard deviation in the same control group. In this study, four age subgroup (40-, 50-, 60-, 70-) was adopted, about 20 of subjects in each group. Osteoporosis was defined as *Z*-scores less than −2 (Consensus Development Conference, 1993; Stein et al., 1996; Jin et al., 2004a) and low bone mass was defined as *Z*-scores less than −1.

2.3. Exposure assessment

Cd content in urine (UCd) and blood (BCd) were determined by graphite-furnace atomic absorption spectrometry (GF-AAS, ShimadzuAA-670, Kyoto, Japan). For quality control purpose, reference material (lyophilised whole human blood) with two certified concentration 9.6 ± 1.7 μg/kg and 3.3 ± 0.9 μg/kg were analyzed. The obtained Cd concentration were 11.1 ± 0.2 μg/kg and 4.8 ± 0.3 μg/kg. The detection limit was the same 0.05 μg/L. Urinary creatinine was measured by Jaffe reaction method. UCd were adjusted by creatinine concentration and expressed as μg/g creatinine (μg/g crea). Both UCd and BCd were used as biomarkers of the exposure. BCd reflects Cd body burden (Diarmid et al., 1997; Jin et al., 2002), particularly in long term low level exposure and after cessation of exposure. UCd is a valid marker of past exposure, body burden and renal accumulation (Jin et al., 2002).

2.4. Statistical analysis

Database management and analysis was performed using SPSS11.5 (SPSS Inc, Chicago, IL, USA) and BMDS (Version 1.4.1c, Environmental protection agency, USA). Arithmetic means were compared by using ONEWAY-ANOVA. The data were expressed in terms of mean ± SD or geometric mean ± SD. According to our previous studies (Jin et al., 2002; Jin et al., 2004a,b; Chen et al., 2009), subjects were divided into three (BCd, 0–2, 2–5 and >5 μg/L) or four groups (UCd, 0–2, 2–5, 5–10 and >10 μg/g crea) based on the exposure level. Benchmark dose (BMD) and BMDL-05 for Cd-induced osteoporosis were calculated using logistic model. The benchmark response (BMR) was defined as 5% and 10% additional risk, above the background. The criterion significance level was set at $p < 0.05$.

3. Results

3.1. Characteristics of subjects

The characteristics of subjects are summarized in Table 1. Age, UCd and BCd of subjects living in control area were significantly different with those living in moderately and heavily polluted areas, but no such difference was found between moderately and heavily polluted areas, except for the BCd. Bone mineral density of subjects living in heavy polluted area was significantly lower than those in control and moderately polluted area. The internal dose of Cd remained high even after the cessation of Cd exposure in heavily polluted area. In addition, prevalence of osteoporosis and low bone mass were increased with the increasing of BCd and UCd level (Table 2).

3.2. BMD of UCd and BCd for osteoporosis

Next, BMD software was used to perform dose–response evaluation using the logistic model at two different levels of additional risk, BMR: 5% and 10% (Table 3). For BCd, the BMDL-05 was 1.39 μg/L and 2.38 μg/L for BMR set at 5% and 10%, respectively. For UCd, the BMDL-05 was 3.78 μg/g crea and 6.36 μg/g crea for BMR set at 5% and 10%.

3.3. BMD of UCd and BCd for low bone mass

Then, we calculated the BMD of UCd and BCd for low bone mass at two different levels of additional risk, BMR: 5% and 10% (Table 4). For BCd, the BMDL-05 was 0.72 μg/L and 1.35 μg/L for BMR set at 5% and 10%, respectively. For UCd, the BMDL-05 was 2.14 μg/g crea and 3.99 μg/g crea for BMR set at 5% and 10%.

3.4. BMD of UCd for low bone mass between people with different age

Finally, we calculated the BMD of UCd for low bone mass between people with different age at two different levels of additional risk, BMR: 5% and 10% (Table 5). The BMD and BMDL-05 of UCd of the people over 60 years old were obvious low than those of people less than 60 years old. For the people over 60 years old, the BMDL was 0.52 μg/g crea and 1.01 μg/g crea for BMR set at

Table 1
Characteristics of the study population.

	Women		
	Control ($n = 83$)	Moderately ($n = 104$)	Heavily ($n = 151$)
Age	63 ± 12[*] (40–86)	57 ± 9 (43–81)	56 ± 10 (40–84)
BMI (kg/m^2)	23.3 ± 3.7 (17–34)	24.3 ± 3.2 (16–32)	24.2 ± 3.3 (16–35)
Current smokers	0	0	0
BCd (μg/L)	0.83 ± 1.94 (0.1–2.6)	1.91[#] ± 1.86 (0.4–14)	3.44[*] ± 1.90 (0.5–17)
UCd (μg/g crea)	2.37[*] ± 2.09 (0–12)	3.89 ± 2.02 (0–17)	10.13 ± 1.99 (0–50)
Bone mineral density (g/cm^2)[**]	0.68 ± 0.01	0.64 ± 0.008	0.60 ± 0.007[a]

Data was shown as arithmetic means or geometric means (BCd and UCd). BMI: body mass index.
[#] Compared to control areas, $p < 0.05$
[*] Compared to other two areas, $p < 0.01$.
[**] Age was adjusted to 59 years for females and 61 years for males.
[a] Significant difference ($p < 0.01$) compared with control and moderately polluted areas.