A 30 years follow-up study in the cadmium former polluted area in Japan: the relationship between cadmium exposure and β2-microglobulin in the urine of Japanese

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Research Article

Keywords: Urinary cadmium, urinary β2-microglobulin, Kakehashi river basin, cadmium-polluted regions

Posted Date: July 22nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1809674/v1

Abstract

Cadmium (Cd) is an environmental pollutant. Long-term exposure to Cd may lead adverse health effects in humans. Our epidemiological studies showed that urinary Cd (U-Cd) concentrations increased from 2008 to 2014, although they were reduced from 1986 until 2008. This aim of this study was to elucidate the long-term effects of the changing trend of cadmium exposure levels (U-Cd) on residents' renal function within 30 years after Cd-exposure ceased. In 2016, urine samples were collected from each participant by visiting 20 elderly Japanese (9 female and 11 male) living in the Kakehashi river basin; a previously Cd-polluted area in Ishikawa, Japan. The geometric means of the β_2-microglobulin (β_2-MG) and urinary Cd (U-Cd) continued increase to 2014 until 2016. Furthermore, Cd concentration and β2-MG in urine were still higher than those in the non-polluted areas in Japan. Significant correlations were found among age, U-Cd and β_2-MG, and these were clearer in females than in males. In summary, we propose that three decades after Cd-exposure ceased, age has been more strongly associated with β_2-MG than Cd body burden. Moreover, renal tubular dysfunction is irreversible and worsens after exposure to Cd, with females being more sensitive to exposure.

1. Introduction

Cadmium (Cd) is one of the most toxic metals and causes environmental pollution. Long-term exposure leads to chronic Cd poisoning and Cd-related diseases, such as renal tubular dysfunction and bone disease (Lu etal., 2021; Kido et al., 1988; Kido et al., 2003; Nordberg et al., 2007).

In Japan, rice is the main food take daily and widely by the general population, and it has a significant role as the main source of Cd exposure (Nordberg et al., 2007; Tsukahara et al., 2003). In 1980, the cadmium-contaminated rice soil was removed from the Kakehashi River Basin, in Ishikawa Prefecture, Japan, which was one of the Cd-polluted areas, and uncontaminated soil was added to the rice field (Kido et al., 2001). Therefore, the concentration of rice cadmium (R-Cd) decreased from 1980 (Kido et al., 2001). However, the concentration of R-Cd in this region was still higher than in other countries (Friberg et al., 1985; Nordberg et al., 2007; Osawa et al., 2001). On the other hand, the Cd is known to have a long biological half-life (10–30 years) and induces the renal dysfunction (Kido et al., 1988; Kido et al., 1990; Kido et al., 2003; Nordberg et al., 2007; Suwazono et al., 2009). Therefore, we think that conducting a health checkup for residents after Cd cessation was extremely necessary.

Our previous epidemiological studies in the Kakehashi River basin have shown that it took approximately 20 years till Cd concentrations in the body of inhabitants reduced to half of them (Sato et al., 2013), and other follow-up studies have also found that cadmium exposure levels of inhabitants in Cd-polluted areas gradually decrease over time (Arisawa et al., 2007a, 2007b; Cai et al., 2001; Liu et al., 2001) or no significant change over time (Zhang et al., 2014). However, our follow-up study involving 28-year observation showed that Cd concentration in urine (U-Cd) increased recently and urinary β_2-microglobulin (β_2-MG) increased continuously (Phuc et al., 2016). Furthermore, the geometric means (GMs) of U-Cd and β_2-MG were still higher than those in non-Cd- polluted areas in Japan (Phuc et al., 2016; Suwazono et al., 2000). Therefore, the aims of this 30 years follow-up study were to elucidate the effect of long-term exposure to Cd on renal function by evaluating the correlation between Cd and β_2-MG.

2. Materials And Methods

2.1. Selection of study population:

In this follow-up study, after connecting data from 1986 to 2016, twenty elderly subjects (9 females and 11 males) living in Kakehashi river basin who participated in our all seven studies for 30 years (1986, 1991, 1999, 2003, 2008, 2014 and 2016) (Kido et al., 2001, Sato et al., 2010, 2013, Phuc et al., 2016). The mean age of the subjects was 75.8 ± 11.1 years (range: 62–98 years) for males and 76.7 ± 6.4 years (range: 66–85) for females. The mean residence times for males and females were 70.9 ± 13.5 (range: 47–94 years) and 54.7 ± 12.3 years (range: 35–79 years), respectively.

2.2. Sample collection and analysis:

All samples were collected between November and December in 2016 by visiting each family in the hamlet of the Kakehashi river basin. Spot urine samples were collected from the participants and kept in a cool box. Urine samples were kept frozen (-20°C) until analysis. U-Cd concentrations were determined by flameless atomic absorption spectrophotometry (Honda et al., 1989). The latex immunoassay was used to analyze the β_2-MG (Bernard et al., 1981), and Jaffe's method was used to determine urinary creatinine levels (Bonsnes and Taussky, 1945). A questionnaire was used to collect basic information from subjects, including age, sex, health condition, medical treatment, and period of residence.

2.3. Calculation and statistical analysis:

The Cd, β_2-MG concentrations in urine were adjusted by creatinine (μg/g creatinine). Continuously, U-Cd and β_2-MG concentrations were log 10 transformed to improve normality before using statistical tests. The normal distribution was determined by using the Shapiro–Wilk test. Pearson's correlation coefficient and Spearman's rank correlation coefficient were used according to variables with a normal or non-normal distribution, respectively. Finally, multiple linear regressions were performed to associate among U-β_2-MG as a dependent variable and age, sex as independent variables.

The data were analyzed by JMP 12 @ statistical software package (SAS Institute, Cary, NC, USA) and Excel 2010 (Microsoft, Redmond, WA, USA). A significant difference was determined with a p-value of $\leq$ 0.05. Data were shown as GMs with geometric standard deviations (GSDs).

3. Results

The trend in U-Cd concentration of three decades shows in Table 1. In combined data U-Cd concentrations decreased significantly from 1986 (GM = 6.696 μg/g.creatinine) to 2008 (GM = 2.860 μg/g.creatinine), but U-Cd concentration tended to increase from 2008 (GM = 2.860 μg/g.creatinine) to 2016 (GM = 4.863 μg/g.creatinine). In males, significant differences were found between 1986 (GM =

5.770 μg/g.creatinine) and 2008 (GM = 2.360 μg/g.creatinine) (P = 0.005); between 1991 (GM = 4.499 μg/g.creatinine) and 2008 (GM = 2.360 μg/g.creatinine) (P = 0.029). In females, no significant differences among U-Cd concentrations for seven times were found.

Table 2 shows that urinary β_2-MG concentrations increased from 1999 both sexes. Significant differences were found between 1986 (GM = 93.69 μg/g.creatinine) and 2014 (GM = 519.8 μg/g.creatinine) (P = 0.034) or 2016 (GM = 848.3 μg/g.creatinine) (P = 0.009), and between 1999 (GM = 50.73 μg/g.creatinine) and 2008 (GM = 408.1 μg/g.creatinine) (P = 0.008), 2014 (GM = 519.8 μg/g.creatinine) (P = 0.011) or 2016 (GM = 848.3 μg/g.creatinine) (P = 0.002) and between 2003 (GM = 192.9 μg/g.creatinine) and 2016 (GM = 848.3 μg/g.creatinine) (P = 0.041). In males, significant differences were found between 1986 (GM = 60.67 μg/g.creatinine) and 2016 (GM = 434.03 μg/g.creatinine) (P = 0.035) or 1991(GM = 81.35 μg/g.creatinine) and 2016 (GM = 434.03 μg/g.creatinine) (P = 0.01), and between 1999 (GM = 14.87 μg/g.creatinine) and 2003 (GM = 101.5 μg/g.creatinine) (P = 0.015), 2008 (GM = 173.7 μg/g.creatinine) (P = 0.004), 2014 (GM = 271.5 μg/g.creatinine) (P = 0.006) or 2016 (GM = 434.03 μg/g.creatinine) (P = 0.003), respectively. No significant differences for seven times were found in females.

Table 3 shows simple correlations between U-Cd and β_2-MG concentrations by sex for the period from 1986 to 2016. There were significant correlations between U-Cd and β_2-MG concentrations in 1986, 2003 and 2008 in females (Pearson correlation). Significant correlations were observed in 2008 for males (Pearson correlation). Significant correlations were observed from 1986 to 2016 (Pearson correlation for 1986, 2003 and 2014; Spearman correlation for 1991, 2008 and 2016) except for 1999 (Pearson correlation) (borderline significant) in combined data.

Tables 4 shows the association between β_2-MG and age, U-Cd, and sex. β_2-MG was used as a dependent variable, and age, U-Cd, and sex were used as independent variables. Only significant association were found between β_2-MG and age from 2003 to 2016 (2003: β = 0.449, P = 0.044; 2008: β = 0.393, P = 0.041; 2014: β = 0.559, P = 0.031; 2016: β = 0.559, P = 0.013). No significant associations were found between β_2-MG and U-Cd or sex.

4. Discussion

Our follow-up study is one of the longest epidemiological observations research projects. The former 28-year follow-up study (1986–2014) showed that U-Cd increased from 2008 to 2014, while decreasing during 22 years from 1986 until 2008. We considered two hypotheses why U-Cd showed increasing tendency since 2014. One is the accuracy of the U-Cd determination. Another is the possibility of re-exposure of Cd 22 years after Cd pollution has improved. In this study, the U-Cd concentration still showed the increasing trend from 2014 to 2016 (Table 1). Therefore, our first hypothesis about the accuracy of U-Cd determination is deemed reliable.

As another hypothesis, we worried about re-exposure in the formerly contaminated area. Because previous follow-up studies have found a gradual decrease or no significant change in U-Cd or blood Cd

(B-Cd) concentrations of inhabitants in Cd-polluted areas over time (Arisawa et al., 2007a, 2007b; Cai et al., 2001; Liu et al., 2001; Zhang et al., 2014). Moreover, we found the geometric mean of U-Cd (5.52 µg/g.creatinine and 4.19 µg/g.creatinine for females and males, respectively) in the previously Cd-polluted area were approximately 4 times higher than those in inhabitants in non-polluted areas (U-Cd: 1.00 µg/g Cr and 1.8 µg/g Cr for females and males, respectively) in Japan (Ikeda et al., 2011; Suwazono et al., 2000). However, it is well known that even when cadmium exposure is cessation, Cd remains in the body for a long time (halving the original level from 10 to 30 years) (Kido et al., 1988; Kido et al., 1990; Kido et al., 2003; Nordberg et al., 2007; Suwazono et al., 2009). On the other hand, R-Cd is an indicator of external Cd exposure in Japan (Nordberg et al., 2007; Tsukahara et al., 2003) and the Cd concentration in the B-Cd was used as an indicator to evaluate Cd exposure for short term in the resident (Lauwerys et al., 1979; Kjellström and Nordberg., 1978; Nordberg et al., 2007). The above results suggest that the cadmium concentration in rice and blood needs to be analyzed in the future study to assess whether the area was re-exposed to cadmium.

This study found that the fluctuated of β_2-MG from 1986 to 1999 and increasing tendency until 2016 (Table 2). Furthermore, we observed a significant simple correlation between U-Cd and β_2-MG in the combined data from 1986 to 2016, except for 1999 ($P = 0.053$) (Table 3). Thus, these results support our opinion that U-Cd concentration is still associated with the biomarker of renal tubular function and the process of deteriorating kidney function is irreversible caused by Cd exposure (Kido et al., 2001; Phuc et al., 2016, 2017; Sun et al., 2021). In addition, we found a significant association between age and β_2-MG using univariate regression analysis and multiple regression analysis (Tables 3 and 4). These results indicated that age is associated with β_2-MG more strongly than Cd body burden, which is consistent with our previous studies (Phuc et al., 2016, 2017). The reason for these results may be that when people are exposed to cadmium, several organs tend to accumulate the element, and as subjects become older, the internal organs of the body gradually become atrophic, and Cd is released into the blood and excreted into the urine, resulting in elevated U-Cd concentrations. The increase of U-Cd concentration led to the increase of β_2-MG. At the same time, the function of the kidneys decreases with age. Therefore, organ atrophy and renal function decline in subjects with age may be the main reasons for the increase in β_2-MG.

In this study, the correlations of U-Cd and β_2-MG were observed closer in females rather than males (Tables 3). This may be explained by the menstrual period and fertility in women, leading to iron deficiency due to anemia, which may increase the absorption of Cd as well as iron (Berglund et al., 1994; Nogawa et al., 1978). Also, some men moved to non-polluted areas for work, and the amount of Cd uptake was reduced; meanwhile, the women still lived in contaminated areas and absorbed Cd continuously. The increased absorption of Cd and longer exposure time led to higher Cd levels stored in the internal organs of women more than in men. Our analysis in this survey is consistent with previous epidemiological studies in polluted areas and they provided that the effects of Cd toxicity in females were higher than those in males (Ewers et al., 1985; Kido et al., 2001; Nishijo et al., 2004; Phuc et al., 2016, 2017; Tsuritani et al., 1992) and long-term exposure to Cd leads to higher morbidity and mortality of kidney disease in females than in males (Nogawa et al., 2017, 2018).

Although our follow-up study is one of the longest epidemiological observational studies, there are some limitations. First, the death of some participants during the 30-year follow-up survey in this study resulted in a small number of participants. Second, there is no control group in this study. Third, participants living in cadmium-contaminated areas should undergo regular physical examinations to determine the cause of the increase in cadmium. However, except for this study, no research has been performed until now. Therefore, we believe that it is necessary to clarify the reasons for the increase in Cd through follow-up investigations.

5. Conclusion

Our 30-year follow-up research is one of the longest observational studies about the effects of Cd to human health. U-Cd and β_2-MG concentrations showed increasing trend from 2008 and 1999 until 2016, respectively. Moreover, U-Cd concentrations in inhabitants living in Cd-polluted areas were higher than those in non-polluted areas more than three decades after cessation of Cd exposure. The correlations among age, U-Cd and β_2-MG concentrations were clearer in females than in males. Age was more strongly associated with β_2-MG concentration than Cd body burden. Moreover, after exposure to Cd, the renal tubular dysfunction is irreversible and worsens, with women being especially sensitive to this effect. Therefore, our research in this Cd-polluted region should be continued.

Abbreviations

Cd
Cadmium
β_2-MG
urinary β_2-microglobulin
B-Cd
blood cadmium
R-Cd
rice cadmium
U-Cd
urinary cadmium
GMs
geometric means
GSDs
geometric standard deviation.

Declarations

Ethics approval and consent to participate

All participants in this study were volunteers, and personal information was kept confidential. This research was approved by the Kanazawa University bioethics committee (approval No. 512).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

This research was funded by the Japanese Ministry of the Environment.

Authors' contributions

Xian liang Sun, Hoang Duc Phuc & Rie Okamoto: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft. Teruhiko Kido: Conceptualization, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition. Nguyen Thi Phuong Oanh, Ho Dung Manh, Le Thai Anh & Akie Ichimori: Writing - review & editing. Kazuhiro Nogawa, Yasushi Suwazono & Hideaki Nakagawa: Conceptualization, Resources, Writing - review & editing, Project administration. All authors read and approved the final manuscript.

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Tables

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