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doi: 10.1007/s00128-010-9947-6

Seventeen-Year Observation on Urinary Cadmium and β_2-Microglobulin in Inhabitants after Cessation of Cadmium-Exposure in Japan

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Abstract The purpose of this study is to clarify the change and relationship of urinary cadmium (Cd) and β_2-microglobulin (β_2-MG) concentrations of inhabitants in Cd-polluted areas after soil restoration. The urinary Cd and β_2-MG concentrations of 25 males and 28 females did not show a significant change, 22 years after the Cd-polluted soil was restored. Once exposed to Cd, it was found to remain in the body, 22 years after the Cd -polluted soil was restored. However, this did not influence renal tubular dysfunction in most of the younger generation compared with elders heavily exposed to Cd.

Keywords Urinary-Cadmium, Urinary-β_2-Microglobulin, Biological half life, Soil restoration

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Cadmium (Cd), atomic No 48, atomic weight 112 is a mineral found in mines. Cd is a by-product that is released to the environment when zinc is refined from the mines (Wada 1986). Residents in mining areas have been exposed to chronic Cd poisoning for long periods of time, for example the Kakehashi river basin (Ishikawa Prefecture) population were exposed for about 100 years. Kakehashi river basin inhabitants use the river water that Cd is released into for farming vegetables, rice etc. Hence, people were directly exposed by consuming farming foods as well as fish from the river. This oral exposure resulted in kidney dysfunction, osteomalacia, osteoporosis, liver injury and hypertension (Kasuya. 1985; Saito et al. 1993). The most common characteristic of Cd exposure is renal tubular dysfunction. An indicator of renal tubular dysfunction is urinary β_2-microglobulin (β_2-MG), a low molecular weight protein which is used as an indicator and judged by the limit 1000 μg/gCr (Nogawa et al. 1983; Aoshima et al. 1988; Kubota et al. 1985). Due to Cd being released to the Jinzu river (Toyama Prefecture, Japan), inhabitants in the surrounding areas have been exposed for a long time. Itai-itai disease is the severest disease cause by chronic Cd poisoning. The direct translation of the Japanese phrase “Itai-itai” is based on the patient’s response “Ouch-ouch” to the many fractures in their bodies by osteomalacia (Aoshima, Kasuya 1993). The ministry of Health in Japan and Welfare recognized Itai-itai disease as the first mining-related illness in April 1968 (Matsunami 2006). There are six Cd-polluted areas in Japan. The largest Cd polluted area is Jinzu

river basin, followed by Kakehashi river basin (Nakagawa, Nishijo 1999).

In 1981 the Ishikawa Prefecture Government decided to restore the soil in the most Cd-polluted Kanehira areas around Kakehashi river basin (Ishikawa Prefecture 1975) and performed a physical examination on Kakehashi river basin inhabitants of over 50 years of age (Ishikawa Prefecture South Kaga Public Health 1997). It was evident from the results obtained that the biological half–life of Cd is 10-30 years (Friberg 1985) and Cd concentration increased with age (Aoshima, Kasuya 1993). The results showed that 14.3% men and 18.7% women were over the 1000 μg/g.Cr limit of urinary β_2-MG. However, only 6% men and 5% women were over the limit in the control area. This shows a significant difference (Kido 1995). In 1986, five years after soil restoration (Kido et al. 2002) were apprehensive about the effects of Cd on inhabitants 50 years and under, who were not examined in 1981 by Ishikawa Prefecture Government. Further tests were performed 4 times over a 17 year period from 1986 to 2003, in inhabitants of most Cd -polluted area of Kakehashi River basin. The purpose of this study is to clarify the change and relationship of urinary Cd and β_2-MG concentrations of inhabitants in Cd- polluted areas after soil restoration.

Materials and Method

In 1981 the Ishikawa Prefecture Government restored the soil in the most Cd-polluted area in the Kakehashi river basin. Five years after soil restoration in 1986, investigations were carried out to determine the influence of Cd on the inhabitant health, and 3 further tests were carried out in 1991, 1999 and 2003, over 17 years. The subjects were 53 inhabitants who received physical examinations 4 times during 17 years. The 53 inhabitants (50 years and under in 1986) included 25 men and 28 women. The mean age of the subjects was 40.2 years old (men: 38.5, women: 42.1) in 1986.

The research process was spread into two parts; 1) Urinary test 2) Questionnaire. The urinary test involved measuring concentration of urinary creatinine (Cr), Cd and β_2-MG in early morning urine. The concentration of urinary indicators was then corrected by Cr. Urinary β_2-MG, Cd and Cr were measured by Radioimmunoassay (RIA), Flameless Atomic Absorption Spectrophotometry (Honda et al 1989) and Jaffé methods respectively. The questionnaire involved obtaining basic data from subjects by gender, age, period of residence and Brinkman index.

Urinary Cd and β_2-MG concentrations were converted into a logarithm scale. The results were statistically analyzed using the one-way layout ANOVA, t-test, Pearson correlation coefficient, and multiple regression analysis. The significant difference was $p \leq 0.05$ The software used for analysis was SPSS12.OJ for Windows.

Subject participation in this research was voluntary. An agreement was signed regarding this matter. The examination performed in 1999 and 2003 were accepted by the Kanazawa Medical University Bioethical committee. To protect privacy of the individual, only numbers (no names) were used during examination.

Results and Discussion

Table 1 shows that there is no significant difference in urinary Cd concentration (μg/g.Cr) for men and women during a 17 year period, even though both of them showed decreasing tendency. It can be seen from table 2 that there is significant difference (p=0.000) in men during 1991-1999 and 1999-2003. However, in women there is no significant difference during a 17 year period. It can be seen from table 3 that there is a significant difference in 1986 (p=0.000), 1991 (p=0.002), 1999 (p=0.003) and 2003 (p=0.000), when comparing the urinary Cd concentration between men and women. On the other hand, urinary β_2-MG concentration shows a significant difference between men and women in 1986 (p=0.000), 1999 (p=0.022) and 2003 (p=0.003), but there is no significant difference in 1991 (p=0.174). In both cases it can be clearly seen that the geometric mean is higher in females than males, except for mean urinary β_2-MG concentration in 1991. Table 4 shows that in 25 males there is a significant correlation with urinary Cd and β_2-MG concentrations in 1999 (p=0.044). On the other hand, in 28 females there is a significant correlation between urinary Cd and β_2-MG concentration in 1986 (p=0.010) and 2003 (p=0.033). Urinary Cd and β_2-MG concentrations showed significant relationship in 2003. Fig 1 shows that only two subjects were found to exceed the critical urinary β_2-MG limit (1000 μg/g.Cr) in 2003. Table 5 shows that there is no significant regression between urinary β_2-MG and urinary Cd, age, period of residence, Brinkman index in 25 males and 28 females, except for significant association in females between urinary β_2-MG and age (p=0.036) as well as Brinkman index (p=0.040) in 2003.

As shown in table 1 there is no significant difference in urinary Cd concentration in 25 males and 28 females, 22 years after cessation of Cd exposure (soil restoration in 1981, first investigation 5 years after in 1986 until 2003). This shows that once exposed to Cd it remains in the body for a long time. This agrees with the biological half life of Cd which is 10-30 years (Nordberg 1985). This shows that once exposed to Cd, irreversible injury (renal tubular dysfunction) was noted to occur when urinary β_2-MG excretion exceeded 1000 μg/g.Cr (Cai 2001; Iwata et al. 1993; Kido et al. 1988).

As shown in table 2 in males there is no significant difference in urinary β_2-MG concentration over 17 years. However, between 1991-1999 and 1999-2003 (p=0.000) there is a significant decrease and increase respectively. At the moment there is no plausible reason for this “V” shaped curve. But the geometric means of urinary β_2-MG concentration during 17 years were within the normal range. This can be explained by the physiological changes of the human body. Urinary β_2-MG is a sensitive indicator of renal tubular dysfunction (Nogawa et al. 1983; Aoshima et al. 1988; Kubota et al. 1985). Previous studies have shown that there is a significant relationship between urinary Cd and β_2-MG (Kido et al. 1988; Honda et al. 1982). It can be seen from table 3 that females have a higher geometric mean urinary Cd and β_2-MG concentration relative to males (Kido et al. 2001).This study shows that urinary Cd still remain in the body 22 years after cessation of exposure. Moreover, urinary β_2-MG remains in the body for the same period of time as Cd (Tables 1 and 2). Therefore, there is a significant correlation between urinary Cd and β_2-MG concentration in males in 1999 (p=0.004) and in females in 1986 (p=0.010) and 2003 (p=0.033) (Table 4). In multiple regression analysis with urinary β_2-MG, urinary Cd, age, period of residence and Brinkman index are contributing factors for Cd exposed subjects. The results in table 5 show

that in 2003 there is a significant relationship between urinary β_2-MG and age (p=0.036) and also Brinkman index (p=0.040) in females. Even though Cd remained in the body for 22 years after cessation of Cd exposure it did not influence renal tubular dysfunction. This is because when the first investigation was conducted in 1986, 5 years after cessation of Cd exposure, the ages of all 53 subjects were under 50 years. At this time their exposure to Cd was less than that of inhabitants 50 years and over. Only four subjects were found to exceed the critical urinary β_2-MG limit (1000 μg/g.Cr) during 17 years, as shown in figure 1.

Recently, not many long term epidemiological studies have been performed internationally. So it is imperative that long term epidemiological studies should be carried out such as our investigation. This study has thoroughly examined urinary Cd and β_2-MG in inhabitants after cessation of Cd exposure. In Cd-polluted areas of Japan, this is the first report that shows inhabitants having no adverse health effects. Countermeasure of replacement of Cd-polluted soil might contribute to younger inhabitants rather than the elder people in the former Cd-polluted areas. Even though the seventeen year observation data shows no significance in relationships between urinary Cd and β_2-MG due to the aforementioned reasons, further investigations will be carried out to confirm these present results.

This manuscript can be concluded by the following points:

i) The change of urinary Cd and β_2-MG concentrations in 25 males and 28 females were not significant during 17 years after the Cd-polluted soil was restored even though they showed decreasing tendency.

ii) The comparison with urinary Cd and β_2-MG concentrations between men and women showed a significant difference during a 17 year period (1986, 1991, 1999 and 2003), except for urinary β_2-MG concentrations in 1991. The geometric mean was higher in females than males.

iii) Once exposed to Cd, it was found to remain in the body, 22 years after the Cd-polluted soil was restored. However, this did not influence renal tubular dysfunction generally..

Acknowledgements The authors would like to thank the inhabitants of the Kanehira area, who had to endure physical examinations over a period of 17 years. We sincerely wish the inhabitants of the Kanehira area to be well.

Table 1 Change in urinary Cd concentration (μg/g.Cr) in males and females (one- way layout ANOVA)

	Males (N=25)		Female (N=28)	
Year	GM	GSD	GM	GSD
1986	3.02	2.14	5.50	2.19
1991	2.75	2.00	5.50	2.30
1999	2.19	1.66	3.80	2.09
2003	1.95	1.74	4.27	2.00

GM: Geometric Mean GSD: Geometric Standard Deviation

Table 2 Change in urinary β_2-MG concentration (μg/g.Cr) in males and females (one-way layout ANOVA)

	Males (N=25)			Females (N=28)	
Year	GM	GSD		GM	GSD
1986	30.20	8.32		83.18	4.07
1991	89.13	2.51	p=0.000	128.83	2.95
1999	12.88	6.46		51.29	10.23
2003	57.54	2.24	p=0.000	131.83	3.02

GM: Geometric Mean GSD: Geometric Standard Deviation p: p-value

Table 3 Comparison with urinary Cd and β_2-MG concentration (μg/g.Cr) in 25 males and 28 females (t-test)

		urinary Cd (μg/g.Cr)			urinary β_2-MG (μg/g.Cr)		
Year	Gender	GM	GSD	p-value	GM	GSD	p-value
1986	M	3.05	2.16	p=0.000	29.90	8.36	p=0.000
	F	5.52	2.19		83.12	4.09	
1991	M	2.79	2.01	p=0.002	88.19	2.47	p=0.174
	F	5.47	2.27		128.94	2.94	
1999	M	2.17	1.66	p=0.003	12.84	6.49	p=0.022
	F	3.79	2.10		50.90	10.15	
2003	M	2.00	1.73	p=0.000	57.50	2.20	p=0.003
	F	4.30	2.00		133.05	3.01	

GM: Geometric Mean GSD: Geometric Standard Deviation

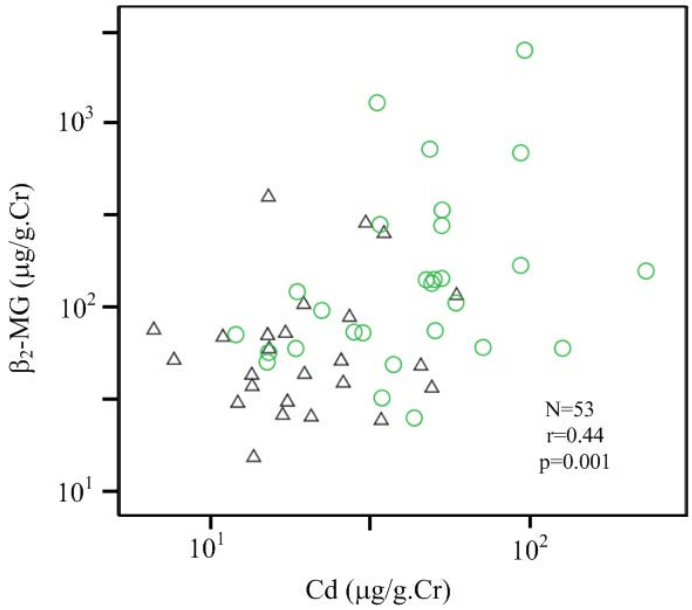

Figure. 1 Scatter plot of correlation between urinary Cd and β_2-MG concentration for 28 females (○) and 25 males (△) in 2003 (Pearson correlation method; r: Pearson correlation coefficient).

Table 4 The correlation coefficient between urinary Cd and β2-MG concentration in females and males (Pearson correlation method)

	1986	1991	1999	2003
Males	r=0.202	r=0.183	r=0.349	r=0.155
(N=25)	p=0.167	p=0.191	p=0.044	p=0.229
Females	r=0.435	r=0.241	r=0.093	r=0.351
(N=28)	p=0.010	p=0.108	p=0.320	p=0.033

r : Pearson correlation coefficient p : p-value

Table 5 Multiple regression analysis of urinary β_2-MG and Age, urinary Cd, period of residence, Brinkman index in males and females

Males (N=25)								
	1986		1991		1999		2003	
	β	p-value	β	p-value	β	p-value	β	p-value
Age	-0.142	0.682	-0.037	0.914	-0.174	0.501	-0.073	0.804
Cd	0.174	0.593	-0.114	0.775	0.268	0.284	0.038	0.907
Period of residence	0.145	0.651	0.241	0.426	0.137	0.632	0.254	0.425
Brinkman index	0.125	0.674	0.444	0.132	0.401	0.119	0.118	0.689
R^2	0.055		0.140		0.232		0.056	

Females (N=28)								
	1986		1991		1999		2003	
	β	p-value	β	p-value	β	p-value	β	p-value
Age	0.111	0.684	0.247	0.410	0.301	0.177	0.426	0.036
Cd	0.294	0.327	-0.056	0.858	-0.181	0.386	0.015	0.941
Period of residence	0.112	0.625	9.225	0.340	0.397	0.053	0.244	0.208
Brinkman index	-0.037	0.847	-0.083	0.676	-0.211	0.237	-0.346	0.040
R^2	0.435		0.134		0.322		0.435	

β: Standardized partial regression coefficient R^2: Coefficient of determination

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