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Environmental cadmium exposure, adverse effects and preventive measures in Japan

Koji Nogawa, Etsuko Kobayashi, Yasushi Okubo & Yasushi Suwazono
Department of Occupational and Environmental Medicine, Graduate School of Medicine (A2), Chiba University, 1-8-1 Inohana, Chuohku, Chiba 260-8670, Japan

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Abstract

In Japan the most heavily cadmium (Cd)-polluted region is the Jinzu river basin, where Itai-itai disease is endemic and the Kakehashi river basin is the second most polluted region.. The village average Cd concentrations in rice were distributed in the range between 0.02 μg/g and 1.06 μg/g in the Jinzu river basin and 0.11 μg g and 0.67 μg g in the Kakehashi river basin. Severe renal damage has occurred widely in the Jinzu river basin. Even after Cd exposure had ceased, renal dysfunction became worse. Dose-response relationships between Cd exposure and health effects were clearly demonstrated in both regions. The allowable limits (according to the present authors' assessment) of Cd concentrations in rice were estimated to be 0.08 μg g to 0.13 μg g and approximately 2 g for total Cd intake. Renal dysfunction caused by exposure to Cd was associated with an increased mortality in both regions. The increased total Cd intake and high concentration of Cd in rice also exerts an adverse influence on life prognosis.

Introduction

In Japan, several areas have been recognized by the government as being environmentally cadmium (Cd)-polluted. Of these, the Jinzu River basin, where Itai-itai disease is endemic, is the most heavily Cd-polluted region and the Kakehashi River basin is the second most polluted area.

In the Jinzu River basin Cd contamination originates from an upstream mine and gave rise to the development of Itai-itai disease, which represents the most severe stage of chronic Cd intoxication in many of the inhabitants of this region since World War II (Nogawa & Kido 1996). Most Itai-itai disease patients are elderly postmenopausal women with renal and bone damage. The Japanese word 'itai' means 'ouch' or 'painful' in English. The pain results from unusual changes in bone i.e. osteomalacia with osteoporosis. In May 1968 the Japanese Ministry of Health concluded that Itai-itai disease developed from osteomalacia with simultaneous renal dysfunction from chronic Cd poisoning, and was under the influence of factors such as pregnancy, lactation, hormonal disorders, aging, calcium deficiency and others (Ministry of health and Welfare 1972).

The Kakehashi River basin about 70 km distance from the Jinzu River basin was also polluted by Cd from another upstream mine.

We have continued to undertake studies in the Jinzu River basin and the Kakehashi River basin. We analyzed results mostly obtained from large-scale health examinations conducted in 1967 and 1968 among the entire population of age >30 years of the Jinzu River basin. Total number is 13283 (6155 men, 7028 women), with a participation rate of 90.3%, and from 3508 persons (1574 men, 1934 women; participation rate 91.0%,) aged >50 years in the Kakehashi River basin who received health examinations conducted in 1981 and 1982.

Environmental Cd exposure levels

Cd concentration in rice paddy soil

In the Jinzu River basin Cd concentration of 1498 samples of rice paddy soil (upper layer to 15 cm) were measured from 1971 to 1974 (Toyama Prefecture Department of Health 1976). Cd concentrations in soil, which were less than 1.00 μg/g were 63% and 1.00–1.99 μg/g was 30.6%. The maximum concentration of Cd in paddy soil was 6.88 μg/g.

Cd concentration in rice

In the Jinzu River basin Cd concentrations in unpolished non-glutinous rice were analyzed from 1971 to 1976 (Toyama Prefecture Department of Health 1976). The area was divided into about 2500 sub-areas, each being 2.5 ha. A sample of mature rice on the stalk was taken in the center of each sub-area, and its Cd concentration analyzed by atomic absorption spectrophotometry after wet ashing and extraction with DDTC/MIBK. The mean Cd concentration in rice of each hamlet was calculated from concentrations measured in 2446 samples. The mean Cd concentrations of 78 hamlets were distributed in the range between 0.02 μg/g and 1.06 μg/g.

In the Kakehashi River basin rice was collected from the farmers in all of the polluted hamlets, divided into 23 groups according to location, and 35451 rice bags were stored in warehouses in 1974 (Nakashima 1997). Random samples from the bags of rice from each polluted hamlet were extracted and mixed well before being analyzed for Cd. Cd concentrations in these rice were in the range 0.11 μg/g to 0.67 μg/g.

Cd concentration in urine

In the Kakehashi River basin the health examination was conducted from1981 to 1983 and urinary Cd concentrations were measured (Hayano *et al.* 1996). Mean Cd concentration in Cd-polluted areas was 4.56 μg/g creatinine (cr.) in 1574 men (mean values of 4.15–6.44 μg/g cr. according to age divided by decade, and 7.15 (6.76–8.13) μg/g cr. in 1934 women, in contrast to 2.12 (2.00–2.80) μg/g cr. in 133 men and 3.12 (2.92–3.51) μg/g cr. in 161 women in non- polluted areas.

Health effects of cadmium exposure

Itai-itai disease

The main clinical picture of Itai-itai disease is combination of renal and bone effects (Nogawa 1981) Renal damage consists of both proximal tubular and glomelurar dysfunction. Bone damage is the combination of osteomalacia and osteoporosis. Normochromic anemia and low blood pressure were often observed. The long-term administration of large doses of vitamin D is effective for the treatment of bone symptoms. The patients were found only in the areas around the Jinzu River basin, where its water is used for irrigation of rice fields. No patients were found in areas where rice fields are irrigated by water from other rivers.

The number of patients recognized as having Itai-itai disease amounted to 184 persons (3 men, 181 women) and the number of patients suspected as having Itai-itai disease amounted to 114 persons (17 men, 97 women) as of the end of March 2001.

Renal effects

In 1967 and 1968 health examinations of the Jinzu River basin, the prevalence of proteinuria with glucosuria (cut-off value is 10 mg/l for proteinuria and 1/32% for glucosuria) was 13.4% in 1562 males and 18.5% in 1531 females who were residing over 30 years in the same hamlet and were being over 50 years of age. The values in the controls were in 348 males 3.7% and 4.4% in 317 females.

In 1981 and 1982 health examinations of the Kakehashi River basin was performed..The prevalence of β_2-MG-uria (cut-off value is 1000 μg/g cr.) in Cd-polluted areas was 14.3% in 1574 men(mean values of 4.8–52.3% according to age divided by decade, and 18.7 (4.9–61.8)% in 1934 women. This is in contrast to 6.0 (0.0–26.9)% in 133 men and 5.0 (0.0–21.4)% in 161 women found in non- polluted areas (Hayano *et al.* 1996).

In 1976 urinary samples were collected from 596 inhabitants (275 men and 321 women) aged over 5 years in the 9 hamlets of most heavy polluted areas in the Jinzu River basin (Kobayashi 1982). β_2-MG-uria ($\geq$ 4 mg l) was first found at the age of 20th decade and the prevalence increased with increasing age. The prevalence of β_2-MG is 100% in men and 90.5% in women over 70 years of age. In the control group (152 men and 267 women) β_2-MG-uria were only found at the age of 70th decade (6.1% for men and 7.9% for

Table 1. Relationship between rice cadmium concentration and urinary abnormality rate in hamlet and the allowable concentration of cadmium in rice in the Jinzu River basin (People living in the same hamlet over 30 years and aged over 50 years).

	Number of hamlets	Prevalence rate of urinary findings	Correlation coefficient	Regression line	Allowable concentration of Cd in rice (μg/g)
Male	56	Proteinuria	0.707***	Y=65.17X+ 9.10	0,08
		Glucosuria	0.409**	Y=27.59X+17.25	0,19
		Proteinuria with glucosuria	0.677***	Y=41.84X− 1.09	0,11
Female	61	Proteinuria	0.672***	Y=72.46X+13.21	0,13
		Glucosuria	0.673***	Y=47.13X+11.44	0,18
		Proteinuria with glucosuria	0.751***	Y=56.22X− 0.65	0,11
Total	76	Proteinuria	0.638***	Y=58.72X+15.02	0,05
		Glucosuria	0.582***	Y=37.73X+13.90	0,20
		Proteinuria with glucosuria	0.680***	Y=45.11X+ 0.76	0,08

women) and 60th decade (4.2% for men). This demonstrated that severe renal damage has occurred widely in the Jinzu River basin.

Progress of renal effects

The progress of renal tubular dysfunction was examined during the 5-year periods using urinary β_2-MG in 74 inhabitants in the Kakehashi River basin (Kido *et al.* 1988). In case where the level of β_2-MG in urine was 1000 μg/g cr. or greater, almost all individuals showed deterioration of β_2-MG-uria, whereas in the case where the excretion of β_2-MG into urine was less than 1000 μg/g cr., no significant changes were observed.

In the Kakehashi River basin serum creatinine and arterial blood pH of 21 inhabitants were measured annually for 8–14 year (Kido *et al.* 1990). Even after Cd exposure ceased, mean serum creatinine increased significantly and arterial blood pH values decreased significantly during these periods.

Dose-response relationship between Cd exposure level and health effects

Dose-response relationship between Cd concentration in rice or total Cd intake and renal dysfunction

We investigated the association between the Cd concentration in rice mentioned in exposure section and renal dysfunction in individuals received 1967 and 1968 health examinations of the Jinzu River basin, using a logistic regression analysis (Watanabe *et al.* 2002). In the cases of logistic regression analysis for both people (1) who had either resided in the present hamlet since birth or who had moved there from a non-polluted area (3678 men and 3153 women), and for those (2) who had resided in the present hamlet since birth (2850 men and 1150 women), except for glucosuria in males, all partial correlation coefficients between the Cd concentration in rice and occurrence of abnormal urinary findings were statistically significant in both sexes. The allowable level of Cd concentration in rice was calculated, by substituting the abnormality rates of urinary findings of the controls into the logistic regression formula for people (2). The value for subjects aged 50 years was 0.13 μg/g and 0.17 μg/g for males and females, respectively, with regard to proteinuria, and 0.15 μg/g and 0.10 μg/g for males and females, respectively, with regard to proteinuria + glucosuria.

To use another statistical analysis, the inhabitants of the same population residing in the current hamlet for a total of $\geq$30 years and aged $\geq$50 years were also divided into four groups according to the mean Cd concentration in rice found in their hamlet, namely: 0.00–0.09, 0.10–0.39, 0.40–0.59, and $\geq$0.60 μg/g (Osawa *et al.* 2002). Thereafter we calculated correlation coefficients between the Cd concentration in rice and the urinary abnormality rate in each hamlet, and when statistical significance was noted, determined regression lines. The urinary abnormality rates of the control group were substituted in these lines, and the allowable limits of the Cd concentration in rice were estimated. The value was 0.08 μg/g and 0.13 μg/g for males and females, respectively, with regard to pro-

Table 2. Correlation coefficients between average concentration of Cd in rice and the prevalences of abnormlities in several urinary indicators in the people of the hamlet polluted with Cd and the allowable concentration of Cd in rice in the Kakehashi River basin.

		Correlation coefficients		Alowable concentration of Cd in rice (μg/g)	
		Men	Women	Men	Women
β_2-MG	(μg l)	0.519*	0.509*	0,14	<0.00
MT	(μg l)	0.562**	0.466*	0.34	0.24
Protein	(mg l)	0.204	0.410	–	–
Glucose	(mg l)	0.426*	0.555**	0.03	0.25
Protein + glucose	(mg l)	0.286	0.581**	–	0.19
Amino-N	(mg l)	0.153	0.045	–	–
β_2-MG	(μg g cr.)	0.517*	0.407	0.05	–
MT	(μg g cr.)	0.585**	0.554**	0.26	0.13
Protein	(mg g cr.)	0.355	0.417*	–	0.23
Glucose	(mg g cr.)	0.344	0.436*	–	0.23
Protein + glucose	(mg g cr.)	0.343	0.458*	–	0.26
Amino-N	(mg g cr.)	0.638**	0.344	0.29	–

Table 3. Analysis of urinary β_2-MG concentration difference, related to mortality, using proportional hazard model of Cox in the Kakehashi River basin.

	Regression coefficient	SE		Hazard ratio	χ^2	
Males						
Age	0,1192	0,0074	3,29	(x+10)/x	261,77***	
β_2-MG (1)	0,2357	0,1582	1,27	+/–	2,22	
β_2-MG (2)	0,3884	0,1572	1,47	++/–	6,11*	
β_2-MG (3)	0,5273	0,2305	1,69	+ + +/–	5,23*	
Females						
Age	0,1144	0,0076	3,14	(x+10)/x	224,75***	
β_2-MG (1)	0,4600	0,1718	1,58	+/–	7,17**	
β_2-MG (2)	0,7127	0,1665	2,04	++/–	18,33*	
β_2-MG (3)	0,8879	0,1987	2,43	+ + +/–	19,98*	
				β_2-MG (1)	β_2-MG (2)	β_2-MG (3)
(–) = <300 μg/g cr.			0	0	0	
(+) = 300- <1000 μg/g cr.			1	0	0	
(++) = > 1000- <10000 μg/g cr.			0	1	0	
(+ + +) = >10000 μg/g cr.			0	0	1	

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

teinuria, and 0.11 μg/g for both males and females, with regard to proteinuria + glucosuria (Table 1).

We selected 1703 inhabitants (832 men and 871 women) who had lived in the same hamlet for at least 30 years from the participants of 1981 and 1982 health examination in the Kakehashi River basin (Nakashima *et al.* 1997 The correlation coefficients between Cd concentration in rice mentioned before and several urinary abnormality rates (β_2-MG, MT, protein, glucose and amino-N) were significant. When allowable values for Cd concentrations in rice were calculated, the highest value was 0.29 μg/g in amino-N (mg g cr.) for men (Table 2).

The allowable concentrations of Cd in rice calculated in both Cd-polluted areas were lower than the 0.4 μg/g provisionally adopted by the Japanese government.

Moreover we calculated total Cd intake from the Cd dose ingested from rice and other foods in the polluted region and the Cd dose ingested during the period of residence in a non-polluted region, and demonstrated a dose-response relationship exists between total Cd intake and health effect indices. Partial regression coefficients of total Cd intake obtained from logistic regression analysis showed statistically significant in the both males and females who had resided in the present hamlet since birth with and without subjects moved from non-polluted areas, and with or without the control group. The allowable levels of total Cd intake were calculated substituting the abnormality rates of urinary findings of the controls in 40, 50, 60 and 70 years old into the logistic regression formula. The allowable levels of total Cd intake were less than 1.58 g for both sexes and each age group using proteinuria with glucosuria.

In the Kakehashi River basin we also reported that even using different health effect indices (β_2-MG-uria, MT-uria) and different statistical methods when calculating the safe value for total Cd intake, that value was found to be approximately 2 g (Nogawa *et al.* 1989; Kido *et al.* 1991). It was suggested that there were mostly no margin between the allowable level of total Cd intake obtained in these studies and total Cd intake of the control subjects in Japan.

Dose-response relationship between Cd concentration in urine and renal dysfunction

In highest Cd-polluted 9 hamlets in the Jinzu River basin as earlier described, 542 inhabitants (293 males and 335 females) over 20 years of age were selected as the target group to study of the relationship between Cd concentration in urine and renal dysfunction (Nogawa *et al.* 1979). Prevalence rates of indices of renal effects (proteinuria with glucosuria, β_2-MG-uria, RBP-uria and prolinuria) increased proportionally with increasing Cd concentration in urine and probit linear regression lines could be calculated between them. The urinary Cd concentrations corresponding to 1% prevalence rate of β_2-MG-uria were calculated 3.2 μg Cd/g cr. for men and 5.2 μg Cd/g cr. for women.

In the Kakehashi River basin, dose-response relationship between Cd concentration in urine and prevalence rate of β_2-MG-uria was investigated using 2 methods for statistical analysis, probit linear regression analysis and logistic regression analysis (Hayano *et al.* 1996; Ishizaki *et al.* 1989). In both methods dose-response relationship between Cd concentration in urine and prevalence rate of β_2-MG-uria was demonstrated. When probit linear regression analysis was used, urinary Cd concentrations corresponding to the prevalence rates of β_2-MG-uria among non-exposed subjects (5.3–6.0% for men and 4.3–5.0% for women) were calculated using the regression lines and the resulting values were 3.8–4.0 μg/g cr. for men and 3.8–4.1 μg/g cr. for women. When logistic regression analysis was used, urinary Cd concentration corresponding to the prevalence rates of β_2-MG-uria in the non-polluted population was calculated 1.6–3.0 μg/g cr. for men and 2.3–4.6 μg/g cr. for women. These results obtained from the different methods suggested that only a slight margin of Cd exposure exists between the allowable level and the non-exposed level and that there may be people with renal dysfunction induced by exposure to environmental Cd even in non-polluted areas in Japan. Therefore, our study group undertook an epidemiological study on renal effects of Cd exposure on people living in a non-polluted area (Suwazono *et al.* 2000). In three non-polluted areas blood and urine samples were collected from 2753 subjects (1105 men and 1648 women) aged over 50 years. Cd in blood or urine was employed as indicators of internal dose, and urinary total protein, β_2-MG and NAG were used as an indicator of renal dysfunction. Multiple regression analysis and logistic regression analysis were performed to clarify the dose-effect and dose-response relationship between blood or urinary Cd concentration and indicators of renal dysfunction. Multiple regression analysis demonstrated a significant dose-effect relationship between Cd in blood and urine and indicators of renal dysfunction. Logistic regression analysis also showed that the probability that individual subjects would have abnormal values of the renal variables was significantly related to Cd in blood and urine.

Association between Cd-exposure and mortality

Association between renal dysfunction and mortality

A follow-up study was performed for 6128 days from August 1, 1967 to May 10, 1984 on 5725 inhabitants (men 2858, women 2867) who received 1967 health examination conducted mainly in the heavily polluted region of the Jinzu River basin to determine the influence of environmental Cd exposure on mortality (Matsuda *et al.* 2002). Standardized mortality ratios (SMRs) investigated according to urinary findings (protein, glucose and protein+glucose) were significantly low in the urinary protein, glucose and protein+glucose negative groups. SMRs calculated after dividing urinary protein and glucose positive status into two levels were lowest in the proteinuria and glucosuria negative groups and tended to be high in the higher positive groups. Cox's hazard ratios were significantly higher for men and women in the urinary protein, glucose and protein+glucose positive groups. In the same analysis where the urinary protein and glucose positive subjects were divided into 2 levels, mortality was demonstrated to be higher in the groups with the greater degrees of proteinuria and glucosuria.

A 9-year follow-up survey of 3178 inhabitants aged $\geq$50 years was performed in the Cd-polluted Kakehashi River basin (Nakagawa *et al.* 1993). SMRs were high in the subjects with positive β_2-MG (defined as $\geq$1000 μg/g cr.). Moreover the subjects into four groups, according to β_2-MG concentration (i.e., <300 μg/g cr., 300–999 μg/g cr., 1000–9999 μg/g cr. and $\geq$10000 μg/g cr.) and when compared with the group with β_2-MG <300 g/g cr., mortality ratios were found to increase as urinary β_2-MG excretion increased. The greater the amount of urinary β_2-MG excreted the higher the mortality risk ratios. Thus even a slight increase of β_2-MG excretion in urine, which is thought to be reversible, induces an increasing mortality.

Association between Cd concentration in rice or total Cd intake and mortality

The follow-up survey was also conducted to 2101 inhabitants (1566 men, 535 women) who had resided in their present hamlet since birth (Ishihara *et al.* 2001). The mean Cd concentration in rice of each hamlet was used as an index of external exposure of the entire population of that hamlet, and the hamlets were divided into two groups, with one showing a Cd concentration in rice of <0.30 μg/g and the other $\geq$0.30 μg/g. The influence on mortality exerted by the Cd concentration in rice was analyzed using a Cox's proportional hazards model. Hazard ratios were higher in both the male and female $\geq$0.30 μg/g groups as compared to the respective <0.30 μg/g groups, with the respective hazard ratios being 1.42 and 1.10 (significant in the men). Combining the sexes, hazard ratio was 1.36 in the $\geq$0.30 μg/g group as compared to the <0.30 μg/g one, with statistical significance found. Considering that the mean Cd concentration in rice in each hamlet is closely related to the development of renal injury, in regions with high Cd concentrations in rice, the development of renal injury induced by Cd is surmised to be the causative factor underlying this worsened prognosis of life.

The follow-up survey was also conducted to 3236 inhabitants (1835 men, 1401 women) who had either resided in their present rural community since birth or who had moved into the area from a non-polluted one were selected as the subjects of the present study (Matsuda *et al.* 2003). The hamlets were divided into two groups, one with a total Cd intake of <2.0 g and the other $\geq$2.0 g. The influence of total Cd intake on mortality was analyzed using standardized SMRs and a Cox's proportional hazards model. In both sexes SMRs and hazard ratios tended to be greater in the $\geq$2.0 g group as compared to <2.0 g group. In the Jinzu River basin, the increased total Cd intake exerts an adverse influence on life prognosis.

Countermeasures

Japanese government prohibits selling rice, which contains more than 0.4 μg g Cd. According to the law Cd-polluted paddy field soil was taken away and other soil was brought into the field. This restoration work has been carried out to clean 6626 ha field polluted by Cd and 80% of the Cd-polluted areas was cleaned until 2001.

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