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Tissue cadmium (Cd) concentrations of people living in a Cd polluted area, Japan

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Abstract

There are more than 50 cadmium (Cd) polluted areas in Japan. The severest general environmental Cd polluted area in Japan was the Jinzu River basin in Toyama Prefecture where Itai-itai disease had been endemic. The present study aimed to compare organ Cd concentrations of inhabitants who had been exposed to different levels of environmental Cd and to clarify the health effects of the environmental Cd exposure in Japan. Since 1960 we have measured tissue Cd concentrations of inhabitants with a history of living in a different Cd polluted areas. Study population living in Cd polluted areas were 36 (1 male, 35 females) patients with Itai-itai disease, 20 (7 males, 13 females) subjects suspected of having Itai-itai disease, 8 (2 males, 6 females) inhabitants in Cd polluted areas other than the Jinzu River basin. Subjects who had lived in Cd non-polluted area were 72 inhabitants. Cd concentrations in liver, pancreas and thyroid of those living in Cd polluted areas were as high as those of patients with Itai-itai disease, and their Cd concentrations in renal cortex were as low as those of patients with Itai-itai disease. The present study demonstrated that tissue Cd concentrations of some inhabitants in Cd polluted areas other than Jinzu River basin are equal to those of the patients with Itai-itai disease and that patients with Itai-itai disease were present even in these areas.

Introduction

The severest general environmental Cd polluted area in Japan was the Jinzu River basin in Toyama Prefecture where there were many inhabitants with renal dysfunction due to exposure to Cd. Among them the severest form of chronic Cd poisoning was Itai-itai disease. One hundred and eighty seven (3 males, 184 females) subjects had been recognized to be patients with Itai-itai disease and 114 (17 males, 97 females) subjects had been recognized to be patients suspected of having Itai-itai disease. The cause has been ascribed to the inflow of effluent from zinc mine located in the upper reaches of the Jinzu River, with the Cd contained therein contaminating the surrounding rice paddies and fields, and the inhabitants then exposed to Cd by ingestion of rice and other produce grown there (Nogawa 1981). In Japan, Cd polluted areas, 50–70% of the amount of Cd ingested orally derives rise (Tsuchiya & Iwao 1978).

It is known that there are more than 50 Cd polluted areas in Japan. The Environment Agency had performed health examinations from 1976 to 1984, which had recruited 12,559 (5,657 males, 6,902 females) residents living in eight highly Cd polluted areas and 6,435 (2,782 males, 3,653 females) residents living in eight Cd non-polluted areas, and had found 202 inhabitants with renal tubular dysfunction in four Cd polluted areas (Shigematsu 1989). Other examinations reporting health effects of Cd were recognized in Kosaka town in Akita Prefecture (Saito *et al.* 1982), the Jinzu River basin in Toyama Prefecture (Nogawa 1981), the Kakehashi River basin in Ishikawa Prefecture (Kido 1987), the Ichi River basin in Hyogo Prefecture (Nogawa *et al.* 1975) and Tsushima in Nagasaki Prefecture (Saito *et al.* 1993).

We considered that tissue Cd concentrations were important as an indicator of the internal dose of environmental Cd exposure because the biological half time of Cd is quite long. Since 1960 we have measured tissue Cd concentrations of inhabitants with a history of living in Cd polluted areas. The present study aimed to compare tissue Cd concentrations of inhabitants in Cd polluted areas other than the Jinzu River basin with those of inhabitants who were recognized to be patients with Itai-itai disease in the Jinzu River basin in Toyama Prefecture and those of inhabitants in Cd non-polluted areas and to clarify the health effects and situations of the environmental Cd exposure in Japan.

Materials and methods

Study population living in Cd polluted areas from whom we could collect post-mortem tissue samples were 36 (1 male, 35 females) patients with Itai-itai disease in the Jinzu River basin in Toyama Prefecture, 20 (7 males, 13 females) subjects suspected of having Itai-itai disease, 5 (2 males, 3 females) inhabitants in the Ichi River basin in Hyogo Prefecture, 2 (females) inhabitants in the Kakehashi River basin in Ishikawa Prefecture and 1 (female) inhabitant in Annaka area in Gunma Prefecture (Table 1).

As subjects who had lived in a Cd non-polluted area 72 inhabitants aged over 60 years in Ishikawa and Toyama Prefectures were selected, since the people living in the Cd polluted areas were all over 60 years of age (Table 2).

Post-mortem tissue samples (1–2 g) were put into polyethylene tubes immediately after autopsy and kept frozen (−20 °C). For analysis, a weighed portion of the tissue was placed in a Kjeldahl flask and was subjected to wet digestion with nitric, sulphuric and perchloric acid. Ashed samples (about 0.5 ml in volume) were transferred to glass vials and diluted to 10 ml deionized and distilled water. The Cd concentrations were measured by atomic absorption spectrophotometry (AAS) by the flame AAS method (Hitachi, Model 308) and the electrothermal AAS method (Hitachi, Model 180-80) depending on the concentrations of Cd in the samples. A deuterium background correction was used in the flame AAS method. In the case of the electrothermal AAS, Cd in the samples was analyzed after extraction with ammonium pyrrolidine dithiocarbamate–methylisobutyl ketone (APDC–MIBK). The accuracy and precision of the analytical methods were tested with standard reference materials (NBS-bovine liver, No.1577, Washington D.C.). The precision for Cd (Coefficient of variation) was 1.8%.

The study was approved by the ethical review boards of the Graduate School of Medicine, Chiba University.

Results

Tissue Cd concentrations of inhabitants in Cd polluted areas were shown in Table 1 and those in Cd non-polluted areas in Table 2. The values, geometrical mean, geometric standard deviation, maximum value and minimum value were shown, which were of patients with Itai-itai disease and subjects suspected of having Itai-itai disease in the Jinzu River basin. Those of inhabitants in Cd non-polluted areas were also shown. There were no differences between tissue Cd concentrations of patients with Itai-itai disease and subjects suspected of having Itai-itai disease. The organ which showed the highest mean Cd concentration was liver amounting to about 60 μg/g (about 4.8 times higher than those of inhabitants in Cd non-polluted areas). Cd concentrations of pancreas were 40–50 μg/g (about 4.1 times higher than those of inhabitants in Cd non-polluted areas), and those of thyroid

Table 1. Tissue cadmium concentrations of the inhabitants living in the Cd polluted areas (unit: μg/g wet weight).

Area	The Jinzu River basin										The Ichi River basin		The Kakehashi River basin	Annaka area
	Itai-itai disease patients					Suspected patients					1	2		
	N	GM	GSD	Min	Max	*N*	GM	GSD	Min	Max				
Males											Case 1	Case 2		
Age*	1	94				7	80.1	4.5	73	85	83	84		
Liver	1	139.0				7	82.0	1.7	37.8	195.4	98.8	28.3		
Renal cortex	1	58.3				7	48.3	1.5	28.6	89.9	95.7	100.2		
Renal medulla	1	36.6				7	33.9	1.4	21.2	63.4	63.1	72.8		
Pancreas	1	92.0				5	57.8	1.5	35.1	91.4	29.5	30.5		
Thyroid	1	132.1				7	80.5	1.3	53.2	135.5		65.3		
Heart	1	2.9				7	1.4	1.6	0.8	2.8		1.4		
Muscle	1	16.1				7	12.6	1.4	6.9	20.1	5.9	9.2		
Aorta	1	3.9				6	3.2	1.5	1.4	4.1				
Bone	1	2.5				7	2.1	1.6	1.0	5.1	1.6	1.5		
Females											Case 1	Case 2**	Case 1**	Case 1
Age*	35	78.5	7.2	61	90	13	82.3	6.6	70	91	76	74	81	87
Liver	35	62.4	1.9	14.4	170.2	13	60.8	1.5	25.9	97.7	69.0	75.2	104.2	33.0
Renal cortex	33	25.6	1.8	9.7	112.5	13	33.0	1.5	19.4	67.6	22.1	58.2	12.2	28.7
Renal medulla	32	20.8	1.6	8.9	66.7	13	21.7	1.5	10.9	51.3	32.3	35.1	10.7	12.7
Pancreas	23	42.8	1.7	11.1	102.8	10	48.5	1.5	24.4	76.4	38.7	59.1	48.4	13.2
Thyroid	22	35.0	2.5	1.9	171.0	11	45.4	2.0	12.6	140.9	43.9	96.0	66.8	
Heart	25	0.8	2.1	0.2	4.8	12	0.9	1.8	0.4	3.5	1.0	3.7	0.4	
Muscle	25	8.5	1.5	3.5	14.6	12	9.9	1.6	3.4	19.9	8.8	19.2	7.6	
Aorta	24	2.5	1.8	0.3	4.7	12	2.5	1.5	1.0	4.4	2.7	7.3		
Bone	25	1.6	1.9	0.2	3.8	12	2.0	1.6	1.1	6.3	2.2	2.8		0.7

N, number of subjects examined; GM, geometric mean; Min, minimum value. Max, maximum value. *Arithmetic mean. **Previously reported case.

were 35–45 μg/g (about 3.0 times higher than those of inhabitants in Cd non-polluted areas). Cd concentrations of renal cortex of patients with Itai-itai disease and subjects suspected of having Itai-itai disease were 25–33 μg/g and were much lower than those of inhabitants in Cd non-polluted areas, 80 μg/g. Decrease of renal cortex Cd concentrations indicates that the kidney has lost Cd due to the advanced damage. Male Case 1 in the Ichi River basin showed higher Cd concentration in liver, 98.8 μg/g, than the mean Cd concentration of patients with Itai-itai disease. Liver Cd concentration of male Case 2 was 28.3 μg/g, which was half of the mean Cd concentration of patients with Itai-itai disease. Thyroid Cd concentration of that subject was 65.3 μg/g, which was twice the mean Cd concentration of patients with Itai-itai disease. Female Case 1 and 2 showed the same or higher liver, pancreas and thyroid Cd concentrations than the respective mean Cd concentration of patients with Itai-itai disease. Female Case 1 showed a low Cd concentration in the renal cortex which was the same as that of patients with Itai-itai disease. A case in the Kakehashi River basin showed high Cd concentrations in liver and thyroid and low Cd concentration in renal cortex compared to those of the controls. As for the female Case in Annnaka area, liver Cd concentration was half of that of patients with Itai-itai disease (about 2.5 times higher than those of inhabitants in Cd non-polluted areas), pancreas Cd concentration was one third of those of patients with Itai-itai disease (about 1.3 times higher than those of inhabitants in Cd non-polluted area) and Cd concentration of renal cortex was decreased like that of patients with Itai-itai disease.

Table 2. Tissue cadmium concentrations of the inhabitants living in the Cd non-polluted areas (unit: μg/g wet weight).

	N	GM	GSD	Min	Max
Males					
Age*	36	71.4	6.5	60	85
Liver	36	7.9	2.1	1.3	33.3
Renal cortex	36	72.1	1.7	19.4	200.0
Renal medulla	36	18.3	2.2	3.5	76.4
Pancreas	7	7.4	2.0	3.0	25.9
Thyroid	5	10.6	2.2	3.8	35.0
Heart	7	0.3	1.5	0.1	0.5
Muscle	7	1.2	2.1	0.3	3.2
Aorta	5	1.0	2.1	0.4	2.5
Bone	5	0.4	1.6	0.2	0.6
Females					
Age*	36	72.7	8.8	60	91
Liver	36	13.1	2.1	3.1	106.4
Renal cortex	35	83.9	2.2	3.9	252.9
Renal medulla	35	24.5	2.1	4.0	105.0
Pancreas	16	10.5	2.1	2.5	29.8
Thyroid	16	11.9	2.0	3.9	56.4
Heart	17	0.4	2.0	0.1	1.3
Muscle	16	2.2	2.4	0.8	12.4
Aorta	16	1.1	1.9	0.3	3.0
Bone	16	0.6	1.8	0.2	1.6

N, Number of subjects examined; GM, geometric mean; Min, minimum value; Max, maximum value. *Arithmetic mean. Age ≥ 60 y.o.

Discussion

Tissue Cd concentrations of patients with Itai-itai disease and subjects suspected of having Itai-itai disease were measured by Kuzuhara *et al.* who found that Cd concentrations in liver, pancreas and thyroid were high but much decreased in renal cortex compared to those of the subjects in Cd non-polluted areas. In the present study, mean Cd concentrations of patients with Itai-itai disease showed a similar trend and were well consistent with the mean values reported by Kuzuhara *et al.* (1997).

We previously reported five female cases in the Ichi River basin and one case in the Kakehashi River basin that showed the same clinical features as patients with Itai-itai disease (Nogawa *et al.* 1975; Kido *et al.* 1991). Among them, we already reported the clinical features and tissue Cd concentrations of Case 2 in the Ichi River basin and Case 2 in the Kakehashi River basin and clarified that those were the same as in patients with Itai-itai disease. The present study is the first report about tissue Cd concentrations in organs other than liver and renal cortex, since Cd concentrations in liver and renal cortex of those subjects were plotted on the figure in another report (Nogawa *et al.* 1986). As for female Case 1 in the Ichi River basin, we already reported that the clinical features and bone findings were the same as in patients with Itai-itai disease (Case 3 in the previous report) and it was clarified that tissue Cd concentrations were also the same as those of patients with Itai-itai disease. Male two cases in the Ichi River basin showed an increase of low molecular protein excretion in urine, but did not show obvious findings of osteomalacia in the radiographic examination of bone. Tissue Cd concentrations of the present study showed that Cd exposure levels were high in both cases. The reason for the absence of osteomalacia was thought to be that the occurrence of osteomalacia due to Cd exposure was quite rare in males like the occurrence of Itai-itai disease itself.

An autopsy in Annaka area was performed in 2003 and the case described in the present study was the first one in this area in which tissue Cd concentrations were measured. In the pathological examination there were renal tubular lesions which were particular to moderate Cd poisoning and

there was no obvious finding of osteomalacia (Kitagawa, personal communication). Liver Cd concentrations were increased by about 2.5 times fold than those of inhabitants in Cd non-polluted areas, and Cd concentrations of renal cortex were decreased like those of patients with Itai-itai disease. These findings demonstrated that the case in Annaka area could be diagnosed as chronic Cd poisoning with renal tubular dysfunction. It should be mentioned that the pathological findings of renal tubular lesions due to Cd exposure are quite unique and easy to distinguish from those of other diseases (Kitagawa 2005). Annaka area was polluted by Cd from a factory and investigations on the health effects induced by Cd were conducted on a large scale, mainly by the Gunma Prefecture Health Authority between 1960 and 1970. It was concluded that no health effects were present in inhabitants in this area .(Fukushima 1978).

Besides the target areas of the present study, minute examination of Cd pollution was performed in Tsushima, Nagasaki Prefecture. All of 11 autopsied samples showed renal tubular disorder and 9 of them were pathologically diagnosed as manifesting osteomalacia. Cd concentrations in liver were 44.2–311 μg/g, Cd concentrations in renal cortex were 18.9–73.6 μg/g and clinical and pathological findings and tissue Cd concentrations corresponded to those of Itai-itai disease (Takebayashi *et al*. 2000).

WHO/IPCS EHC document on Cd reported a summary of the survey of Cd levels in rice and health status of 14 local populations in Japan. According to this report health effects were observed in five areas (Fuchu, Ikuno, Tsushima, Kakehashi and Kosaka) and no Cd health effects, including elevated prevalence of β2-microglobulinuria, were observed in other areas with higher levels of Cd (WHO 1992). In Japan authorities recognize health effects of Cd in Jinzu River basin and in Toyama Prefecture as Itai-itai disease. Although clinical examination of subjects in other areas polluted with Cd shows the same clinical picture as those suffering from Itai-itai disease even in non-Jinzu River basin, these subjects have never been legally recognized as Itai-itai disease patients. The present study demonstrated that the past studies performed by authorities in Japan, *e.g*., by Prefecture Health Authorities or The Environment Agency limited the identification of patients with Itai-itai disease to this region. Thus, conclusions on the health effects by Cd in Japan were not completely covered. Furthermore, we would like to emphasis that it is important in Japan to continue measuring tissue Cd concentrations of inhabitants having lived not only in the Jinzu River basin but also in other Cd polluted areas since the internal dose of Cd exposure in people in all parts of Japan is still unknown.

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