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Selenium, Cadmium, Zinc, Copper, and Iron Concentrations in Heart and Aorta of Patients Exposed to Environmental Cadmium

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Selenium (Se) is an essential trace element for humans and is well known as a modifying factor in the toxicity of heavy metal compounds such as cadmium (Cd) (Magos and Webb 1980; Högberg and Alexander 1986). Animal experiments have also indicated interactions between Se and Cd, including prevention of some acute toxicities of Cd exposure by Se. In rats, maintenance of physiologic Se concentrations reduces Cd-induced renal and testicular damage (Xiao et al. 2002, Katakura and Sugawara 1999) and antagonizes Cd-induced increases in systolic pressure (Perry et al. 1980). However, there is no information on the interaction between Cd and Se in humans chronically exposed to Cd. In previous reports we had found no evidence of interactions between post-mortem tissue concentrations of Se and Cd in humans chronically exposed to high concentration of environmental Cd. (Kido et al. 1988).

In this report we continue the evaluation of interactions between physiologic trace elements and Cd in post-mortem tissue samples of heart and aorta from subject exposed to environmental Cd and from nonexposed controls. Several reports indicate a correlation between hypertension and lowered concentration of Se in whole blood and plasma (Momcilo et al. 1998). In addition, long-term exposure to high concentration of environmental Cd is associated with lowered blood pressure in humans (Nogawa and Kawano 1969). The goal of this study was to determine if post-mortem tissue concentrations of Se, Zinc (Zn), Copper (Cu) or Iron (Fe) would be affected by Cd exposure in heart and aorta and evaluate potential correlations between hypotension and altered trace elements concentrations on Cd-exposed and nonexposed subjects.

MATERIALS AND METHODS

Post-mortem tissue samples were obtained from 9 patients with Itai-itai disease (severe Cd poisoning, 1 male, 8 females), from 24 patients suspected of Itai-itai disease (6 males, 18 females), and from 20 nonexposed subjects (7 males, 13 females). Itai-itai disease is the most severe case of chronic Cd poisoning and had been endemic in the Cd-polluted areas of the Jinzu River basin in Toyama Prefecture, Japan. The patients with Itai-itai disease or the patients suspected of the disease had been officially recognized by the Department of Health, Toyama

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Prefecture. All nonexposed subjects resided in Toyama Prefecture or Ishikawa Prefecture. Individual records including age, sex, occupation, smoking habits, course of disease, weight of sampling organs and pathological findings were obtained from their medical records. All the subjects were autopsied at the Department of Pathology, Kanazawa Medical University and at the Department of Pathology, Toyama Medical and Pharmaceutical University during 1980 and 1983.

The causes of death of the subjects were as follows: infectious disease (25) (pneumonia, 13; infections of the genito-urinary tract, 5; meningitis, 1; tuberculosis, 4; others, 2), cancer at various sites (15) (stomach, 4; liver, 5; pancreas, 1; others, 5), gastric ulcer (5), heart disease (3), cerebrovascular disease (1), accident (1) and others (3). All patients with Itai-itai disease and those suspected of Itai-itai disease had morphological changes in the renal tubules characteristic of chronic cadmium poisoning and indicators of renal disorder including moderately increased excretion of total protein (0.1-1.5 g/dl) and significantly increased excretion of β_2-microglobulin (5-82 mg/l).

Post-mortem tissue samples (1-2g) from the anterior wall of the left ventricle and from the aortic arch were put into polyethylene tubes immediately after autopsy and kept frozen (-20℃). For analysis, a weighed portion of the tissue was placed in a Kjeldahl flask and underwent 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 and Cu 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 and Cu in the samples. A deuterium background correction was used in the flame AAS method. In the case of the electrothermal AAS, Cd and Cu in the samples were analyzed after extraction with ammonium pyrrolidine dithiocarbamate-methylisobutyl ketone (APDC-MIBK). The Zn and Fe concentrations were measured by the flame ASS method only.

For Se, a definite wet weight sample (1 g as standard) was placed in a Kjeldahl flask and wet-ashed with nitric and perchloric acids (ashing temperature 110℃). After diluting the digested solution to a definite volume with deionized and distilled water, Se was measured by the diaminonaphthalene fluorimetric method (Watkinson 1966) (Hitachi, MPF-4). The reagent blanks and standard solutions were treated in a manner identical to that for samples. All materials were soaked in 10% nitric acid overnight and rinsed with deionized and distilled water.

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, Cu, Zn, Fe (5 determinations) and Se (4 determinations) were 1.8%, 2.7%, 2.3%, 1.5% and 6.43%, respectively.

RESULTS AND DISCUSSION

Although animal experiments have indicated interaction between Cd and Se, there is little information on interaction between Cd and Se in humans chronically exposed to Cd. We previously reported significantly lower tissue concentrations of Se, Cu, Zn concentrations in autopsied kidney of 21 Cd-exposed subjects, including 8 patients with Itai-itai disease, 13 subjects who were suspected of Itai-itai disease, and 15 controls. In contrast, liver Se concentrations were similar in the exposed and nonexposed groups, and liver Se concentrations were significantly correlated only with Cu in the Cd-exposed group (Kido et al. 1988). These data suggested that Se had a different and unique distribution in the kidney (the primary target organ for Cd toxicity), than in other organs.

In this study we extend the examination of relationships between Cd and other trace elements in extrarenal tissues of patients with chronic Cd exposure and nonexposed controls.

Geometric means and standard deviations of concentrations of Se, Cd, Zn, Cu and Fe in heart and aorta are shown in Table 1 for the Cd-exposed group and the nonexposed control group. The average ages of every group are also provided.

Table 1. Concentrations of selenium, cadmium, zinc, copper and iron in heart and aorta of Cd-exposed and nonexposed subjects (unit: μg/g)

		Males				Females			
		Nonexposed subjects(n=7)		Exposed subjects(n=7)		Nonexposed subjects(n=13)		Exposed subjects(n=26)	
		GM	GSD	GM	GSD	GM	GSD	GM	GSD
Age*		68.4	11.3	81.7	7.1a	73.6	7.1	79.6	5.3b
Heart	Se	0.24	1.18	0.22	1.36	0.21	1.30	0.21	1.19
	Cd	0.32	1.87	1.71	1.61c	0.39	2.13	0.79	1.73b
	Zn	26.73	1.09	24.66	1.14	26.73	1.19	24.49	1.19
	Cu	2.86	1.31	2.59	1.15	2.67	1.21	2.73	1.11
	Fe	50.70	1.68	45.29	1.37	44.46	1.15	47.42	1.18
Aorta	Se	0.17	1.18	0.17	1.59	0.16	1.18	0.16	1.20
	Cd	0.94	2.17	3.16	1.52b	0.90	1.78	2.97	1.38c
	Zn	21.73	1.15	16.37	1.23a	19.01	1.18	17.06	1.23
	Cu	1.10	1.15	0.70	1.42a	0.91	1.19	0.89	1.26
	Fe	9.57	1.99	10.40	1.51	10.77	2.17	9.38	1.43

Age: Arithmetic mean and arithmetic standard deviation.
GM: Geometric means GSD: Geometric standard deviations
The exposed group include Patients with Itai-itai Disease and suspected subjects
Significant difference, compared with nonexposed subjects by t-test
(a: $P < 0.05$, b: $P < 0.01$, c: $P < 0.001$).

Cd concentrations in heart and aorta of Cd-exposed subjects were significantly higher than those of nonexposed controls in both sexes. Se and other trace element concentrations in heart and aorta were not significantly different between Cd-exposed subjects and nonexposed controls in both sexes except for Zn and Cu concentrations in aorta of Cd-exposed male subjects.

Correlation coefficients among trace elements in heart for the exposed and nonexposed control groups are shown in Table 2, and those in aorta are shown in Table 3.

Table 2. Correlation coefficients among selenium, cadmium, zinc, copper and iron in heart of Cd-exposed and nonexposed subjects (unit: μg/g).

	Males			Females		
Correla-tion	Nonexposed subjects	Exposed subjects	All subjects	Nonexposed subjects	Exposed subjects	All subjects
Se/Cd	-0.178	-0.677	-0.350	-0.091	-0.337	-0.216
Se/Zn	0.004	0.569	0.436	-0.464	-0.154	-0.248
Se/Cu	0.016	0.202	0.121	0.597*	0.134	0.391*
Se/Fe	-0.359	0.413	0.049	-0.434	-0.036	-0.181
Cd/Zn	-0.760*	-0.421	-0.572*	0.176	0.058	-0.022
Cd/Cu	0.224	-0.069	-0.140	-0.038	0.102	0.058
Cd/Fe	-0.152	-0.365	-0.234	0.057	0.066	0.146
Zn/Cu	-0.331	0.603	0.159	-0.304	0.243	-0.023
Zn/Fe	-0.171	0.579	0.214	0.481	-0.161	-0.024
Cu/Fe	0.617	0.879**	0.686**	0.186	0.128	0.154

*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

Table 3. Correlation coefficients among selenium, cadmium, zinc, copper and iron in aorta of Cd-exposed and nonexposed subjects (unit: μg/g).

	Males			Females		
Correla-tion	Nonexposed subjects	Exposed subjects	All subjects	Nonexposed subjects	Exposed subjects	All subjects
Se/Cd	0.340	-0.682	0.031	0.979*	0.071	0.193
Se/Zn	0.100	-0.683	-0.106	0.296	-0.702**	-0.607**
Se/Cu	0.051	-0.472	-0.178	0.761	-0.294	-0.174
Se/Fe	-0.265	0.967*	0.235	0.813	0.345	0.340
Cd/Zn	0.273	-0.734	-0.540*	-0.019	0.404*	-0.088
Cd/Cu	0.461	0.724	-0.290	0.723**	0.210	0.165
Cd/Fe	-0.309	-0.547	-0.183	0.232	0.202	0.029
Zn/Cu	0.650	-0.297	0.430	0.402	0.513**	0.488**
Zn/Fe	-0.220	0.228	-0.074	-0.136	-0.225	-0.125
Cu/Fe	-0.192	-0.374	-0.221	0.002	0.149	0.082

*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

Correlations between Cd and Se concentrations were significant only in aorta from nonexposed controls. Correlation coefficients between Cd and Se in heart and aorta of Cd-exposed subjects were not significant in either sex. Therefore it can be concluded that high exposure to Cd did not affect the distribution of Se in heart and aorta. This result was similar to results in the previously reported studies of Cd, Se, Cu Zn and Fe in liver samples from the same subjects, but different from findings in kidney samples. Additionally, although Zn concentration significantly increased and Cu concentration significantly decreased in liver in the previous study, all trace element concentrations in heart, except for Cd, showed no changes, and Zn and Cu concentrations tended to decrease significantly in aorta in this study.

These data suggest that Cd and trace elements distributions may vary between different tissues. Variations in Se concentration of heart and aortic tissues do not appear to explain the association between chronic exposure to environmental Cd and hypotension. Further studies on the distribution of Se and other trace elements in Cd-exposed subjects are necessary, since it is difficult to explain the meaning of correlation among trace elements concentrations in heart and aorta of the Cd-exposed subjects.

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