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Renal dysfunction of cadmium-exposed workers residing in a cadmium-polluted environment

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Abstract

Human exposure to cadmium may occur in both occupational and general environments. We were interested in determining whether a combination of occupational and environmental exposure to cadmium results in different levels of severity of renal dysfunction relative to that arising from environmental or occupational exposure alone. We selected 44 residents, who once were employed in a smelter and lived in a cadmium-polluted area, as group A. Another 88 subjects, who never worked in the plant, but lived in the same area, were selected as group B. Group C consisted of 88 subjects who had no history of occupational exposure to cadmium and lived in a non-cadmium-polluted area. Statistical analysis demonstrated that there was no significant difference in age or gender among the three groups, nor were there significant differences in smoking habits. The prevalence of renal dysfunction as indicated by increased excretion of β2-microglobulin (B2M), *N*-acetyl-β-D-glucosaminidase (NAG) and albumin (ALB), was higher in group A than in group B. This finding suggests that exposure to cadmium both occupationally and environmentally results in a higher prevalence of renal dysfunction, relative to those who are exposed to cadmium only in the general environment. Therefore, this specific population, who once were occupationally exposed to cadmium and lived in polluted areas, should be identified. Furthermore, health examinations of this population should be conducted in time to prevent further health damage induced by cadmium exposure.

Introduction

The health effects of cadmium were first documented in cadmium-exposed workers (Friberg 1948). In the 1950s and 1960s, cadmium intoxication was considered to be a specific occupational disease (Friberg 1985). Concerns about the effects of cadmium on the health of the general population did not begin until the recognition of itai-itai disease (ostemalacia) and concurrent kidney disease in Japan in the 1960s (Hagino & Yoshiola, 1961). Since then, an increasing number of studies have focused on the effects of long-term exposure of the general populations in cadmium-polluted areas.

Human exposure to cadmium may occur in both occupational and general environments (Nordberg 1996). In occupational settings, workers become exposed to cadmium mainly by inhaling cadmium fumes or dusts, i.e. cadmium enters the body via the respiratory route. In the general environment, cadmium exposure arises predominantly from contaminated food or drinking water, i.e., the general population is exposed mainly through the gastrointestinal tract. It is well documented that the critical effect of long-term exposure to cadmium is renal dysfunction, regardless of whether the exposure occurs in an occupational or environmental setting. In the present study, we aimed to find out whether a combination of occupational and environmental exposure to cadmium results in different levels of severity of renal dysfunction, relative to those that occur after solely environmental or solely occupational exposure.At the same time, we analyzed

urinary β2-microglobulin (B2M) and *N*-acetyl-β-D-glucosaminidase (NAG), which have been suggested as sensitive indicators of renal tubular dysfunction induced by cadmium (Bernard 1988, Nogawa *et al.* 1986; Kawada *et al.* 1989), as indices of renal effects. In addition, we also detected urinary albumin (ALB) as an indicator of renal glomerular function.

Materials and methods

Study population and exposure

The study population consisted of three groups (A, B, C). Two of the groups (the two exposed groups) were from a cadmium-polluted area, and the other (the control group) from a non-cadmium-polluted area. The polluted study area is near the smelter, which is located in southeastern China. The smelter began operating in 1961 and discharged cadmium-polluted wastewater into the nearby river, the water of which was used to irrigate rice fields. Historical data from the local industrial health inspector shows that the cadmium concentration in the air of the workplace was in the range 0.026–3.623 mg/m^3 (the average concentration was 0.655 mg/m^3). A survey in 1995 showed that the average cadmium concentration in the rice produced in this area was 3.7 mg/kg, which is a level that was 18-fold higher than the State hygienic standard. Rice is the main food of the local residents. We selected 44 residents, who once were employed for some periods by the smelter and lived in this cadmium-polluted area, to be group A. They were exposed to cadmium both from their food and general environment and by inhalation of cadmium-polluted air in their workplace. The average work age of group A was 8.5 years (from 1 to 15 years). Another 88 subjects were selected as group B: they had never worked in this plant, but they lived in the same area and were exposed to cadmium mainly by contaminated food. Group C consisted of 88 subjects who had no any occupational history of exposure to cadmium and lived in a non-cadmium-polluted area where the cadmium concentration in rice was found in 1998 to be 0.05 mg/kg. The living customs, social and economic conditions, and lifestyles of these three groups were similar. All participants were over 36 years in age; the average ages of groups A, B, and C were 48.8, 48.6, and 50.3 years, respectively. Statistical analysis showed that there were no significant differences in age or gender among the three groups. The proportion of smokers in groups A, B, and C was 31.8, 38.6, and 43.2%, respectively. There were no significant differences in the smoking habits among the three groups and, thus, smoking habits should not affect the present results.

Each participant was interviewed by a trained and supervised interviewer and filled out a detailed questionnaire, Meanwhile, each subject provided blood and urine samples for biological measurement.

Sampling procedures and bioanalytical methods

Urine samples were collected from all participants, and were kept frozen at -20 °C until analysis. Urinary cadmium concentrations were measured by graphite-furnace atomic absorption spectrometry (AAS). UB2M was measured by means of RIA. Urinary albumin was measured by ELISA and NAG and its isoforms were measured (Bernard et al., 1995). Creatinine was measured by the Jaffe reaction method. All urinary parameters were adjusted for creatinine in urine. It has been described in detail by Jin *et al.* (2002).

Calculation of cadmium uptake

We performed estimations of cadmium uptake as described by Cai *et al.* (1998). Total cadmium uptake (TCd) = occupational uptake + environmental uptake. Cadmium intake from occupational exposure was calculated on the basis of the historical average cadmium concentration in the workplace. The fractional uptake of cadmium from the respiratory tract was assumed to be 0.03, which is a number based on 10% deposition and 30% absorption of inhaled cadmium from air (Nordberg *et al.* 1985). Occupational uptake = average cadmium concentration in workplace $\times$ total inhaled volume (efficiency ventilation volume per hour $\times$ working time per year $\times$ working age in smelter) $\times$ 0.03.

Rice is the main food in these areas and its consumption is considered to be the major source of environmental cadmium intake. The life long cumulative uptake of cadmium from the general environment was calculated based on rice consumption, taking an age-related weighting factor into account (0–9 years, 0.413; 10–19 years, 0.885; 20–59 years, 1.000; $\geq$60 years, 0.823). The fractional uptake of cadmium from food was assumed to be 0.05. Environmental uptake of cadmium = daily cadmium intake (daily rice consumption $\times$ average rice Cd concentration) $\times$ 365 $\times$ weighting factor $\times$ years $\times$ 0.05.

Table 1. Geometric means (G.M.) of total cadmium intake (TCd), blood (BCd), and urinary cadmium (UCd) with respect to different areas and genders

	Total			Female			Male		
	n	G.M.	(range)	n	G.M.	(range)	n	G.M.	(range)
TCd (mg)									
Group A	44	683.9*$^{\Delta}$	(548.7–976.0)	11	731.1*$^{\Delta}$	(685.7–854.4)	33	668.3*$^{\Delta}$	(601.3–976.0)
Group B	88	540.8*	(456.8–582.1)	22	543.3*	(530.2–577.1)	66	539.5*	(456.8–582.0)
Group C	88	19.7	(12.7–33.9)	22	17.8	(14.1–22.6)	66	20.4	(12.7–33.9)
BCd (μg/l)									
Group A	44	9.66*	(2.13–44.75)	11	13.27*$^{\Delta}$	(3.63–35.38)	33	8.69*	(2.13–44.75)
Group B	88	7.82*	(0.75–32.88)	22	8.51*	(2.75–32.88)	66	7.59*	(0.75–32.38)
Group C	88	1.53	(0.00–8.00)	22	1.63	(0.00–3.63)	66	1.50	(0.13–8.00)
UCd (μg/g creatinine)									
Group A	44	11.86*$^{\Delta}$	(1.69–55.72)	11	18.97*$^{\Delta}$	(5.52–55.72)	33	10.30*	(1.69–42.19)
Group B	88	9.51*	(2.06–42.99)	22	10.84*	(5.03–42.99)	66	9.12*	(2.06–28.97)
Group C	88	1.81	(0.09–5.72)	22	1.55	(0.09–4.76)	66	1.91	(0.29–5.72)

*Compared with group C: $p < 0.05$
$^{\Delta}$Compared with group B: $P < 0.05$

Smoking is an important means of cadmium exposure, especially for general populations not residing in cadmium-polluted areas, but no tobacco is produced in the particular area we studied, in which only commercial cigarettes are smoked. As mentioned above, there was no statistically significant difference in the rate of smoking among the three groups and, thus, we do not consider that smoking is a significant source of the total cadmium uptake of the participants in this study. The total cumulative cadmium uptake of group A occurs from both occupational and environmental intake; the uptakes of groups B and C were calculated only on basis of environmental factors.

Statistical analysis

Data were entered into a database on a microcomputer using Epi-info (Version 6.04b). The mean test, the χ^2 test, the χ^2 trend test, and other statistical tests are provided in the Epi-info program package. For comparisons between more than two groups, we used a one-way analysis of variance (ANOVA). We performed regression and correlation analyses using the SPSS program. Distributions of the biological measurements were normalized by logarithmic transformations.

Results

The levels of total cadmium uptake, blood cadmium, and urine cadmium in the three groups

Table 1 presents the geometric means of total cadmium uptake (TCd), blood cadmium (BCd), and urinary cadmium (UCd) with respect to different areas and genders. Regardless of gender, the estimated average total cadmium uptakes in groups A and B were significant higher that that in group C, and the TCd of group A was significantly higher than that of group B. A similar result was found for urinary and blood cadmium concentrations of residents among the three groups. Most of the BCd values of group C were less than or around 2 μg/L both for males and females, but most of the BCd values of groups A and B were >5 μg/L. Table 1 also shows that BCd and UCd values for females were higher than those of males in the two exposed groups. Further correlative analysis showed that the correlative coefficients of TCd/BCd, TCd/UCd, and BCd/UCd were 0.62 ($p < 0.001$), 0.64 ($p < 0.001$), and 0.55 ($p < 0.001$), respectively.

The levels of urinary B2M, NAG, and ALB among the different groups and genders

Table 2 lists the geometric means of the levels of urinary B2M, NAG, and albumin among the different groups and genders. For both males and females, there is a statistically significant increase in the levels

Table 2. Geometric means (G.M.) of the levels of urinary B2M, NAG, and ALB with respect to different areas and genders

	Total			Female			Male		
	n	G.M.	(range)	n	G.M.	(range)	n	G.M.	(range)
B2M (mg/g creatinine)									
Group A	44	0.521*$^{\Delta}$	(0.097–6.219)	11	0.729*	(0.144–6.219)	33	0.466*	(0.097–3.442)
Group B	88	0.346*	(0.040–4.590)	22	0.431*	(0.012–4.590)	66	0.321*	(0.040–2.952)
Group C	88	0.170	(0.014–2.385)	22	0.154	(0.014–1.444)	66	0.176	(0.024–2.385)
NAG (U/g creatinine)									
Group A	44	10.35*$^{\Delta}$	(0.36–47.66)	11	10.67*$^{\Delta}$	(2.10–47.70)	33	10.26*	(2.13–47.66)
Group B	88	7.10*	(0.09–131.82)	22	8.71*	(0.78–50.64)	66	6.64*	(0.09–131.82)
Group C	88	2.20	(0.05–45.03)	22	1.82	(0.05–25.05)	66	2.43	(0.10–45.03)
ALB(mg/g creatinine)									
Group A	44	6.4*	(1.1–85.3)	11	8.6*	(2.0–85.3)	33	5.8*	(1.1–34.4)
Group B	88	5.0	(0.4–96.2)	22	4.9	(0.5–48.0)	66	5.1	(0.4–96.2)
Group C	88	2.9	(0.1–37.8)	22	2.8	(0.1–24.4)	66	3.1	(0.1–37.8)

*Compared with group C: $p < 0.05$
†Compared with group B: $P < 0.05$

of excretion of these three urinary indicators of renal function upon increasing cadmium exposure. When comparing groups A and B, increases of urinary B2M and NAG were significant in some instances. The urinary albumin values in group A was significant higher than those in group C.

Prevalence of B2Muria, NAGuria, and ALBuria in three groups

We define the cut-off points (abnormal values) for the criterion variables (B2M, NAG, and ALB) as the 95% upper limit values, which we calculated from group C (control group). The cut-off values of B2M, NAG, and ALB were 0.8 mg/g creatinine, 15 U/g creatinine, and 20 mg/g creatinine, respectively. The prevalence of B2Muria, NAGuria, and ALBuria were calculated and are presented in Figure 1, which indicates that the prevalence of B2Muria, NAGuria, and ALBuria in groups A and B was higher than that in group C. Meanwhile, the prevalence of B2Muria, NAGuria, and ALBuria in group A was higher than that in group B. To further analyze the reasons for the increased prevalence of B2Muria, NAGuria, and ALBuria, all the members of the three groups were pooled together and then divided into five subgroups according the their values of UCd and BCd, respectively. We studied the relationship between exposure and response and obtained results similar to those reported by Jin *et al.* (2002).

Discussion

The current estimation of cadmium uptake, based on empirical data and theoretical considerations (Nordberg *et al.* 1985), reflected the total amount of cadmium uptake of the subjects in this study. The total cadmium uptake of workers who were exposed to cadmium both occupationally and environmentally was significantly higher than that of subjects who were exposed to cadmium only environmentally. We have found a significant correlation between the total cadmium uptake and the levels of blood or urinary cadmium. As mentioned in a previous study (Jin *et al.* 2002), the level of blood cadmium, as well as urinary cadmium, is a good indicator of the extent of cadmium exposure. In long-term exposure, blood cadmium also can reflect the body burden of cadmium. The present study shows that both groups A and B had relatively high levels of exposure to cadmium. Table 1 also indicates that a higher level of cadmium exposure is found in group A, relative to group B. The additional occupational cadmium exposure in group A resulted in higher levels of BCd and UCd.

It has been well documented that urinary B2M and NAG can be used as early indicators of renal dysfunction induced by cadmium (Nogawa *et al.* 1986; Bernard 1988; Kawada *et al.* 1989; Bernard *et al.* 1992). The present study demonstrates that the levels of urinary B2M and NAG of two of the exposed groups (A and B) were higher than those of group C. The relationship that exists between exposure indicators and

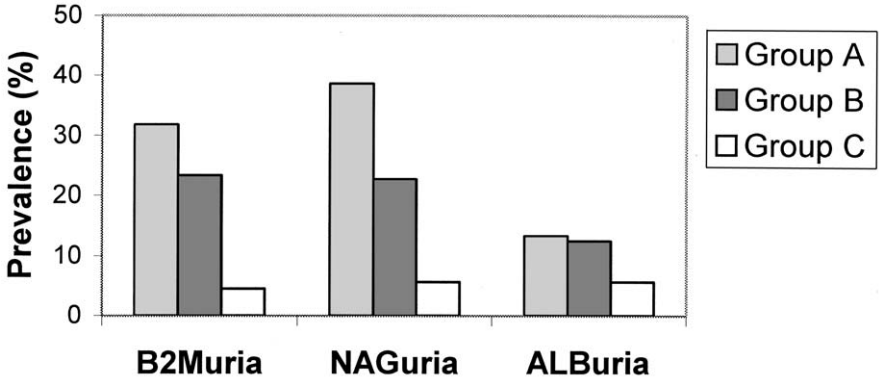

Fig. 1.

indices of renal effect (this study, and Jin *et al.* 2002) proves that the two indicators are sensitive biomarkers of renal dysfunction induced by cadmium. Explanations for the observation of increased urinary albumin in cadmium-exposed populations are still to be formulated. In this study, we have shown that when urinary cadmium reaches a relatively higher level ($\geq$20 μg/g creatinine), the excretion of urinary albumin is increased significantly. A possible explanation is that an increased penetration of the renal glomerular membrane is induced by cadmium. This explanation partly suggests that high-level exposure to cadmium might give rise to renal glomerular damage.

Although different exposure pathways exist between workers and the general population, it is well known that renal dysfunction is one major critical effect induced by long-term exposure to cadmium, regardless of whether it occurs occupationally or environmentally (Nordberg 1992). The same possible mechanisms of renal dysfunction have been suggested (Nordberg 1996).

In the present study, the prevalence of B2Muria and NAGuria in group A was higher than that in group B. This finding suggests that exposure to cadmium both occupationally and environmentally results in a higher prevalence of renal dysfunction in these workers, relative to persons who exposure to cadmium occurs only in the general environment. Because age and gender distributions in these two groups were similar, the total amount of cadmium uptake from environmental exposure in group A was close to that of group B. This observation suggests that the additional occupational exposure to cadmium results in the higher prevalence of renal dysfunction in group A. Therefore, this specific population, who once were exposed occupationally to cadmium and lived in polluted areas, should be identified. In addition to renal effects, other health effects should be studied further, such as bone effects and reproductive effects. Furthermore, health examination of this population should be conducted in time to prevent further health damage induced by cadmium exposure. It has been suggested that lung cancer could be another critical effect of long-term inhalation exposure (Nordberg 1996). A continued follow-up study of these workers should be taken into account.

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