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Mortality in a cadmium polluted area in Japan

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Abstract

A 15-year follow-up study of 3178 inhabitants (1424 men and 1754 women) living in the cadmium (Cd) polluted Kakehashi River basin was conducted. The results clarified effects on mortality of renal dysfunction induced by Cd indicated by urinary beta-2-microglobulin (β_2-MG), total protein, glucose, and total amino acids. This study used Cox's proportional hazard model.

The mortality risk ratio of urinary β_2-MG positive (>= 1000 μg/gCr) subjects was significantly increased in both sexes: 1.35 for men and 1.73 for women. The increased mortality ratio of the urinary protein positive (>= 10 mg/dl) subjects was also significant for both sexes, with risk ratios of 1.82 for men and 2.01 for women. Only the women showed significantly increased mortality of the urinary glucose positive (>= 20 mg/dl) subjects and amino acids positive (>= 300 μg/gCr) subjects. When the subjects were divided into four categories according to urinary β_2-MG, <300, 300–1000, 1000–10000, >= 10000 μg/gCr, the mortality risk ratios were increased in proportion to the increase of urinary β_2-MG in both sexes. These results suggest that mortality of Cd-exposed subjects increased with increasing excretion of four urinary markers of renal tubular dysfunction, and in proportion to increases in the amount of urinary β_2-MG excretion including under 1000 μg/gCr.

Introduction

The Kakehashi River basin in Ishikawa Prefecture is an environmental Cd polluted area in Japan as a consequence of upstream copper mine mining activity that began operation in the 1600s. In 1974, three years after the closure of all the mines in this area, the Ishikawa Prefectural Government determined that average Cd concentrations in the paddy soil in the Kakehashi River basin were higher than those in other areas (Health authority of Ishikawa Prefecture, 1976). Significant positive relationships between indices of Cd exposure, urinary Cd and Cd in rice, and high excretion of low molecular protein, which is a good biomarker of renal tubular dysfunction, were reported among inhabitants of this area (Nogawa *et al.* 1978, 1989; Ishizaki *et al.* 1989).

We demonstrated previously that increased excretion of urinary low molecular proteins, such as beta-2-microglobulin (β_2-MG) and retinol binding protein (RBP), increased the mortality of inhabitants of the Kakehashi River basin (Nakagawa *et al.* 1993; Nishijo *et al.* 1994; Nishijo *et al.* 1995). However, renal tubular dysfunction induced by Cd is known to engender multiple proximal tubular dysfunctions, as evidenced by low molecular protein, but also total protein, glucose, and amino acids. Therefore, the present 15-year follow-up study uses these four indices to investigate the relationship between renal tubular dysfunction induced by Cd and mortality among inhabitants of the Cd polluted Kakehashi River basin.

Moreover, urinary β_2-MG is useful in early diagnosis of renal tubular dysfunction. Reportedly, the normal value of urinary β_2-MG is under 290 μg/l in Europe (Kjellström 1977). Although renal function of subjects with urinary β_2-MG of more than 1000 μg/gCr was found to be progressive in almost all previous follow-up studies (Kasuya *et al.* 1986,

1991; Kido 1988; Jarup *et al.* 1995, 1998), outcomes of subjects with <1000 μg/gCr of urinary β_2-MG remains unclear. For that reason, we examined the relationship between mortality and amount of urinary β_2-MG excretion in inhabitants including subjects with <1000 μg/gCr.

Materials and methods

In 1981–1982, the Ishikawa Prefecture Health Authorities conducted a two-part health impact survey among inhabitants of the Kakehashi River basin aged $>=$ 50 years. For 15 years, from the day of their initial examination until 30 November 1996, 3178 inhabitants (1424 men and 1754 women), amounting to 91% of the target population of this area, were followed. At the time of the survey, morning urine specimens were measured for β_2-MG, total protein, glucose, amino acids, and Cd concentrations. Analysis was performed for β_2-MG using RIA (Phadebas β_2-microtest; Pharmacia Diagnostic AB), total protein by modified Kingsbury-Clark method, glucose by O-toluidine boric acid method, amino acids by the TNBS method. These measurements were corrected by urinary creatinine measured by the Jaffe method. Table 1 shows positive rates of these four indices by sex.

The survival status (alive or dead) and residence status (still residing in the target area or not) was determined with the cooperation of the City Municipal Office and Prefecture Public Health Office; the date of death of the subjects who died during the follow-up period was ascertained from death certificates. Relationships between mortality and indices of renal tubular dysfunction were analyzed using Cox's proportional hazard model to eliminate the influence of age.

Results

During the observation period, 140 men died (68.3%) and 199 women died (60.5%) among the β_2-MG positive subjects; among β_2-MG negative subjects, 367 men died (30.1%) and 271 women died (24.4%) (Table 2). After adjustment for age using Cox's proportional hazard model, the mortality risk ratio (hazard ratio) of the urinary β_2-MG positive subjects was increased significantly compared with β_2-MG negative subjects. The ratios were 1.35 for men and 1.73 for women, presuming the risk ratio of β_2-MG negative subjects as 1 (Table 2). Similarly, the risk of mortality of urinary protein positive subjects was increased significantly in both sexes: 1.77 for men and 1.91 for women. However, significant increases of risk ratios of urinary glucose and amino acids positive subjects were observed only in women. The risk ratio of urinary glucose positive women was 1.77, whereas that of urinary amino-acid-positive women was 1.35. (Table 2).

We investigated the relationship between urinary β_2-MG concentration difference and mortality after adjustment for age to clarify the relationship between mortality and the degree of renal tubular dysfunction. Hazard ratios of men with two urinary β_2-MG categories, 1000–10000 μg/gCr and $>= 10,000$ μg/gCr were 1.52 and 2.43, respectively. They were significantly high compared to men with urinary β_2-MG <300 μg/gCr (Table 3). Three categories of urinary β_2-MG were related to mortality with regard to women: the hazard ratios of urinary β_2-MG concentrations, 300–1000 μg/gCr, 1000–10000 μg/gCr, and more than 10000 μg/gCr were 1.94, 2.27, and 2.71, respectively (Table 3).

Discussion

Urinary low-molecular protein is a well-known early biomarker of renal tubular dysfunction. The present study targeted urinary β_2-MG measured in inhabitants of the Kakehashi River basin. Previous studies found a clear dose-related response demonstrated between the urinary β_2-MG positive rate and urinary Cd concentration, average rice Cd concentration, and residence time (Ishizaki *et al.* 1989; Nogawa *et al.* 1989). We measured not only urinary β_2-MG, but also urinary protein, glucose and amino acids concentrations. High incidence of abnormal values related to Cd exposure was found in the 1981–1982 health impact survey, a baseline survey for the present follow-up study (Kido *et al*. 1987).

The present study tracked this population for a mean of 15 years, and investigated the relation between mortality and the presence or absence of these four urinary indices of renal tubular dysfunction. Results confirmed that the prognosis of subjects with renal tubular dysfunction is unfavorable, especially for women, with respect to indices of renal tubular dysfunction other than β_2-MG. Among the men, only total protein of these 3 indices showed a significant relationship to mortality. This fact might be a consequence

Table 1. Positive rates of indices of renal tubular dysfunction in both sexes

Urinary indices of renal tubular dysfunction		Men No. subjects (%)		Women No. subjects (%)	
β2-MG	(<=1000 μg/gCr)	205	14.3	329	18.8
Total protein	(>=10 mg/dl)	88	6.2	112	6.4
Glucose	(>=20 mg/dl)	200	14	145	8.3
Total amino acids	(300 μg/gCr)	29	2	151	8.6

Table 2. Mortality risk ratios of the positive subjects, as compared with negative subjects of each marker after adjustment for age by Cox's hazard model

	No. Death (−)	No. Death (+)	Hazard ratio	(95% C.I.)
Urianry β2-MG				
Men	367	140	1.35	(1.09, 1.66)
Women	271	199	1.73	(1.42, 2.11)
Urinary total protein				
Men	446	62	1.77	(1.35, 2.33)
Women	387	83	1.91	(1.49, 2.46)
Urniary glucose				
Men	433	74	1.26	(0.98, 1.61)
Women	394	76	1.77	(1.38, 2.27)
Urinary total animo acids				
Men	490	17	1.52	(0.93, 2.46)
Women	406	64	1.35	(1.04, 1.76)

Table 3. Urinary β_2-MG concentration difference and mortality after adjustment for age by Cox's hazard model

β2-Mg (μg/gCr)	No. subjects	No. death	(%)	Hazard ratio	(95% C.I.)
Men					
<300	1011	269	(26.6)	1	
300-1000	210	99	(47.1)	1.26	(0.99–1.60)
1000–10000	160	102	(63.8)	1.52	(1.20–1.94)
>=10000	43	37	(86)	2.43	(1.71–3.47)
Women					
<300	1097	151	(13.8)	1	
300-1000	329	121	(36.8)	1.94	(1.52–2.48)
1000-10000	241	129	(53.5)	2.27	(1.77–2.90)
>=10000	87	87	(79.3)	2.71	(1.98–3.70)

of the small number of amino-acid-positive subjects and the lack of specificity of urinary glucose to renal tubular dysfunction in men.

Moreover, a significant association between mortality and urinary β_2-MG, which reflects the severity of renal tubular dysfunction was found. Increased mortality ratios were proportional to increases in the amount of urinary β_2-MG excretion. Especially in women, the mortality risk ratio of subjects with 300–1000 μg/gCr of urinary β_2-MG was significantly higher than that of subjects with less than 300 μg/gCr. These results indicate that a slight increase of urinary β_2-MG under 1000 μg/gCr may affect mortality in women.

In the present follow-up study, standardized mortality ratio (SMR) for causes of death of urinary β_2-MG positive and negative inhabitants was also investigated. Higher SMRs of urinary β_2-MG positive subjects for all causes were observed for both sexes in comparison to the general Japanese population and urinary β_2-MG negative subjects. The diseases contributing most to increased mortality were cerebrovascular diseases and heart failure in men, and heart failure, digestive diseases, and senility in women. Also, SMRs for renal diseases were significantly higher in men. These results indicate that excess mortality was mostly the result of non-specific causes of death, such as heart failure. A longer follow-up study period is necessary in the future to evaluate incidence of death in Cd polluted areas.

In conclusion, the life prognosis of the inhabitants with renal tubular dysfunction induced by Cd is unfavorable; mortality of women with increase of urinary β_2-MG at a lower level might be affected in Cd polluted areas.

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