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ORIGINAL ARTICLE

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Effects of aging on cadmium and tubular dysfunction markers in urine from adult women in non-polluted areas

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Abstract ***Objectives***: The objectives of the present analyses were to examine if Cd and tubular dysfunction marker levels in urine show age-dependent changes among women who lived in areas with no known cadmium (Cd) pollution in Japan, and if the trends would be further modified by correction of analyte concentration in terms of urinary creatinine (CR or cr) or urine specific gravity (SG or sg). ***Methods***: The results of urinalysis for Cd, α_1-microglobulin (α_1-MG), β_2-microglobulin (β_2-MG), and N-acetyl-β-D-glucosaminidase (NAG) concentrations together with CR and SG were cited from previously established databases. A majority of urine samples were collected in 2000–2002 from adult women (mostly at 40–60 years of age) in various areas in Japan, and the collection was supplemented by cases of ≧60-year-old women in 2003. In total, 11,090 never-smoking cases were subjected to statistical analysis. The values as observed (e.g., Cd_{ob}), together with after correction for CR (e.g., Cd_{cr}) or SG (e.g., Cd_{sg}), were examined by linear regression analysis after logarithmic conversion. ***Results***: The geometric mean (GM) values for Cd were 1.10 μg/l (as observed) or 1.32 μg/g cr (after correction for creatinine concentration). No increases were found in the levels of α_1-MG, β_2-MG or NAG on a group basis, in agreement with the conditions that there was no known environmental pollution with Cd in the sampling areas. There were almost linear increases in logarithm of Cd, α_1-MG, β_2-MG and NAG concentrations as age advanced. As CR, and to a lesser extent SG, also decreases steadily throughout life (Ikeda et al. 2005; Moriguchi et al. 2005), the correction of the analyte concentrations for urine density induced substantial increases in the analyte values; i.e., the correction by CR and SG induced amplification of the increases by two- and 1.4-times, respectively, compared with the increase in non-corrected observed values. ***Conclusions***: There were age-related increases in Cd and tubular dysfunction markers in urine among women in areas with no known Cd pollution. The increase was amplified two- or 1.4-times when CR or SG correction was applied, respectively. The observation suggests that care should be practiced in applying CR or SG correction, especially when evaluation of Cd exposure and resulting health effects is made among elderly populations.

Keywords Aging · Cadmium in urine · General population · Japan · Middle-aged women · Tubular dysfunction

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Introduction

Cadmium (Cd) is a toxic element ubiquitous in the environment, and long-term exposures to this element through the general environment might elevate the risk of renal tubular dysfunction (International Programme on Chemical Safety 1992a, 1992b). In the practice of epidemiological studies on health effects of Cd exposure among general populations, β_2-microglobulin (β_2-MG) has been most popularly employed as a marker of renal tubular dysfunction (Kawada 1995), and attention has also been paid to other markers of tubular dysfunction, such as α_1-microglobulin (α_1-MG) (Tohyama et al. 1986; Kawada 1995) and N-acetyl-β-D-glucosaminidase (NAG) (Nogawa et al. 1986; Kawada et al. 1992; Stengel et al. 1999). It has been a common practice (World

Health Organization 1996; American Conference of Governmental Industrial Hygienists 2003) to correct urinary marker levels in terms of either concentration of creatinine [CR (or cr)] or specific gravity [SG (or sg)] (e.g., β_2-MG_{cr} or β_2-MG_{sg}).

Experiences among Cd-polluted areas have shown that the Cd-induced tubular dysfunction would be more evident after exposures for many years and therefore among elderly populations (International Programme on Chemical Safety 1992a, 1992b). Previous analyses (Ikeda et al. 2005; Moriguchi et al. 2005) have shown that both urinary CR and SG decrease substantially as a function of age above 30 years, and that the decrease is more marked for CR than for SG. It is the purpose of the present analysis to examine if Cd and tubular dysfunction marker levels in urine show age-dependent changes among women in Cd-nonpolluted areas in Japan, and if such trends would be further modified by the correction for CR or SG. The possible implication of correction-induced changes in evaluation of Cd exposure-associated tubular dysfunction is also discussed.

Materials and methods

Populations surveyed

Three databases were employed in combination for present analyses, as elsewhere described in detail (Moriguchi et al. 2005). In short, three databases, one established in 2000–2001 on 10,883 adult women (aged mostly from 40 to 60 years; Ezaki et al. 2003) the second one established in 2002 on 1,482 adult women (mostly at the ages of 35–60 years; Tsukahara et al. 2003), and an additional collection of data on 1,274 women volunteers (mostly of ≧60 years of age; Ikeda et al. 2005) were combined for the present analyses. All participants provided informed consents. Data on Cd, α_1-MG, β_2-MG, NAG, CR and SG in urine and data on social habits were sorted from the combined databases. After adjustment of the duplicate registration, selection for never-smoking women gave 11,090 cases in total.

Urinalysis for Cd, tubular function markers, CR and SG

The methods of urinalyses and the programs of quality assurance were as previously detailed (Ezaki et al. 2003; Moriguchi et al. 2003). In essence, Cd was measured by graphite furnace atomic absorption spectrometry, α_1-MG and β_2-MG by RIA, NAG by ELISA, CR by colorimetry and SG by refractometry, respectively. The quality of urinalysis for Cd was validated by the 31st and 32nd Round Robin external quality assurance programs (organized by German Society of Occupational Medicine and Environmental Medicine; Schaller et al. 2002).

Statistical analysis

Urinary analyte levels (e.g., Cd in urine) were expressed in some instances after correction for CR concentration (Jackson 1966) (expressed, e.g., as Cd_{cr}), and also after correction for a urine SG of 1.016 (Buchwald 1964; Rainsford and Lloyd Davies 1965) (e.g., Cd_{sg}), in addition to the values as observed (e.g., Cd_{ob}). In statistical analysis, SG was expressed in terms of factor G, which was defined by the equation that factor G = (SG−1.000)×1,000 (Levine and Fahy 1945) for practical convenience.

A log-normal distribution was assumed for Cd, α_1-MG, β_2-MG and NAG (Ikeda et al. 1995, 2000), and the distribution was expressed in terms of a geometric mean (GM) and a geometric standard deviation (GSD), whereas the age, CR and SG distributed almost normally (Moriguchi et al. 2005), and the distribution was expressed in terms of an arithmetic mean (AM) and an arithmetic standard deviation (ASD). Accordingly, regression analyses between the age and urinary analytes were conducted after logarithmic conversion of Cd, α_1-MG, β_2-MG and NAG.

Results

Urinary analyte levels in the group studied

GMs and GSDs for Cd, α_1-MG, β_2-MG and NAG are summarized in Table 1, together with AM and ASD for age, CR and SG. The GM values for Cd as observed was 1.10 μg/l, and it was 1.32 μg/g cr when corrected for CR.

Table 1 Basic parameters of the group studied

Parameter (unit)	AM/GM	M[a]	SD[a]
Number of cases[b]		11,090	
Age (years)	AM	50.0 (Min. 20, Max. 86)	9.8
Urine			
Cd_{ob} (μg/l)	GM	1.10	2.42
Cd_{cr} (μg/g cr)	GM	1.32	2.10
Cd_{sg} (μg/l)	GM	1.10	2.09
α_1-MG_{ob} (mg/l)	GM	2.14	2.43
α_1-MG_{cr} (mg/g cr)	GM	2.58	2.01
α_1-MG_{sg} (mg/l)	GM	2.15	1.98
β_2-MG_{ob} (μg/l)	GM	100.2	1.98
β_2-MG_{cr} (μg/g cr)	GM	120.8	1.87
β_2-MG_{sg} (μg/l)	GM	100.7	1.75
NAG_{ob} (unit/l)	GM	3.01	2.07
NAG_{cr} (unit/g cr)	GM	4.10	1.68
NAG_{sg} (unit/l)	GM	3.23	1.69
CR[c] (g/l)	AM	0.99	0.57
Factor G[c,d]	AM	17.4	6.52

[a] *M* for arithmetic or geometric mean, and *SD* for arithmetic and geometric standard deviation
[b] 11,090 non-smoking women all over Japan, except for NAG, which was studied in 2,115 cases
[c] Cited from Moriguchi et al. (2005)
[d] Factor G = (specific gravity−1.000)×1,000

In agreement with the estimation that subjects were from non-polluted areas, the GM values for α_1-MG, β_2-MG and NAG were, e.g., 2.6 mg/g cr, 121 μg/g cr and 4.1 units/g cr, respectively, indicating that the participants did not show tubular dysfunction on a group basis.

Age-dependent increases in Cd, and three tubular dysfunction markers

The relation of Cd (in μg/l or μg/g CR) with age (in years) was examined after logarithmic conversion of Cd values (Table 2). The slopes were positive (i.e., >0) and correlation coefficient was statistically significant ($P<0.01$) irrespective of correction for urine density. The relation of log $Cd_{cr}$with age is presented in Fig. 1A together the regression line for visual understanding. The observation as a whole suggested that Cd most probably increased steadily throughout the age ranges studied.

Similar analyses for the age-dependency were conducted with three tubular dysfunction function markers; i.e., α_1-MG, β_2-MG and NAG (Table 2, Fig. 1B–D). The results showed that these parameters with positive slopes and significant ($P<0.01$) correlation coefficients (irrespective of correction) also increased as a function of the age throughout life. The correlation coefficients for β_2-MG (0.031–0.279), however, tended to be smaller than the corresponding values for α_1-MG (0.078–0.318) and NAG (0.063–0.454), as examined by Wilcoxon's signed rank test for paired samples ($P \fallingdotseq 0.10$).

The age-dependent decreases in CR and SG (being more marked in CR) was confirmed in the present study (Table 2) as observed in previous analyses (Moriguchi et al. 2005), and similarly age-dependent increase was observed for Cd and three tubular dysfunction markers in the present analyses (Table 2). In order to evaluate the two changes of the different direction in combination, the analyte levels at two separate ages of 30 and 80 years were estimated taking advantage of the regression equations given in Table 2. The results of the calculation are summarized in Table 3, in which I and II show the estimated level at the ages of 30 and 80 years, respectively.

It is clear from Table 3 that the ratios for the three tubular dysfunction markers were generally greater than 1, and that the lower limits of the 95% confidence range were all >1 except for NAG_{ob} irrespective of correction for urine density. It was also possible to note that the ratios were larger for Cd than for three dysfunction markers, i.e., 3.16–6.31 in cases of Cd, and it was 1.12–3.16 for three dysfunction markers ($P \fallingdotseq 0.10$ for comparison of Cd with α_1-MG, β_2-MG or NAG by Wilcoxon's signed rank test and $P \fallingdotseq 0.01$ for comparison of Cd with a combination of α_1-MG, β_2-MG or NAG by Mann–Whitney's *U*-test for unpaired samples).

In a further analysis to compare whether the ratios for CR-corrected values were larger than that for SG-corrected values, the relative ratio was calculated taking the ratio for observed (ob) values as 1 [i.e., the relative ratio = (the ratio for CR-corrected or SG-corrected values)/(the ratio for OB values)], and the relative ratios were compared between CR-corrected values and SG-corrected values. Comparison by Wilcoxon's signed rank test showed that the 80/30 years old ratios for CR-corrected values were significantly ($P \fallingdotseq 0.01$) larger than the ratios for SG-corrected values.

Table 2 Age-dependent increases in Cd, α_1-MG, β_2-MG and NAG in urine. The figures are parameters of a regression line in which $Y = \alpha + \beta X$, where X is age (in years) and Y is the parameter given in the table after logarithmic conversion (e.g., log Cd-U_{ob})

Y in the equation (unit)	Regression line parameters[a]				
	α	β	Corrlation coefficient		
			r[b]	95% LL[c]	95% UL[c]
Cd_{ob} (μg/l)	−0.438	0.010	0.239	0.222	0.257
Cd_{cr} (μg/g cr)	−0.696	0.016	0.489	0.475	0.503
Cd_{sg} (μg/l)	−0.592	0.013	0.382	0.366	0.398
α_1-MG_{ob} (mg/l)	0.178	0.003	0.078	0.059	0.096
α_1-MG_{cr} (mg/g cr)	−0.008	0.010	0.318	0.301	0.334
α_1-MG_{sg} (mg/l)	0.024	0.006	0.205	0.187	0.222
β_2-MG_{ob} (μg/l)	1.955	0.001	0.031	0.013	0.050
β_2-MG_{cr} (μg/g cr)	1.696	0.008	0.279	0.262	0.296
β_2-MG_{sg} (μg/l)	1.800	0.004	0.161	0.145	0.182
NAG_{ob} (unit/l)	0.339	0.001	0.063	0.021	0.106
NAG_{cr} (unit/g cr)	0.212	0.007	0.454	0.420	0.487
NAG_{sg} (unit/l)	0.269	0.004	0.267	0.227	0.306
CR[d] (g/l)	1.786	−0.016	−0.273	−0.291	−0.256
Factor G[d,e]	23.957	−0.130	−0.196	−0.214	−0.178

[a] 11,090 cases were studied for Cd, α_1-MG, β_2-MG, CR and Factor G, of which NAG was studied in 2,115 cases
[b] Correlation coefficients; all correaltion coefficients are statistically significant ($P<0.01$)
[c] The lower or upper limit of the 95% confidence interval
[d] Cited from Moriguchi et al. (2005)
[e] Factor G = (specific gravity−1.000)×1,000

Discussion

In the present analysis, only women were studied, because they are potentially at higher risk than men with regard to health effects due to Cd exposure (Sartor et al. 1992). In addition, the smoking rate among the Japanese population is substantially lower in women (about 16% for those in their 20s, with a gradual age-dependent decrease to 3% at 70 and above) than that in men (58–59% in their 20s to 40s, with a decrease to 29% at ≥70 years; Ministry of Health, Labour and Welfare 2003), indicating better opportunity of having never-smokers among women than men; never-smokers were selected in the present analysis because smoking is a known confounder in estimation of environmental exposure to Cd (Ikeda 1992). In the present analysis, urine samples were collected only once. Nevertheless, high reproducibility in analysis results after repeated urine sampling among populations with no apparent

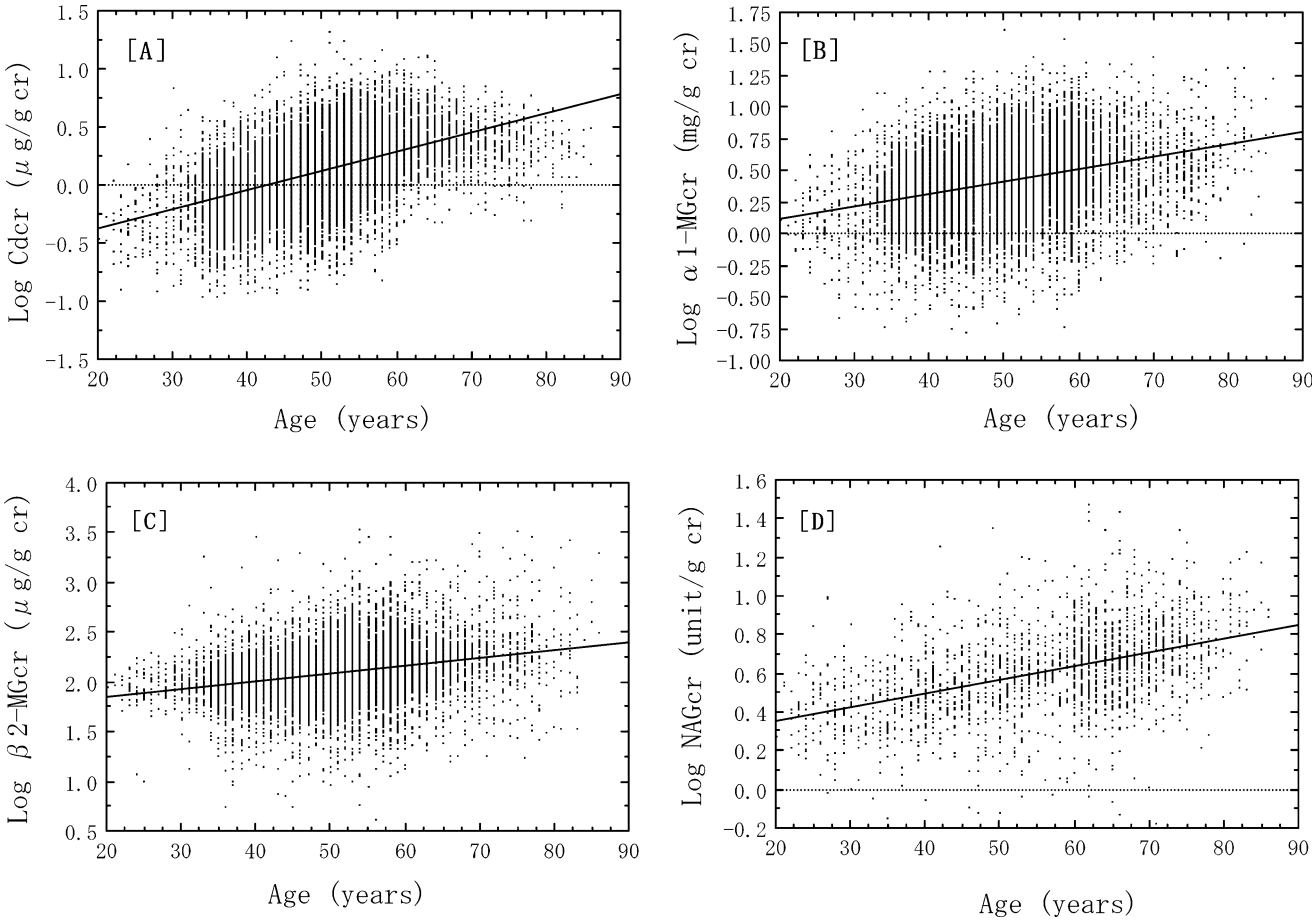

Fig. 1 Age-dependent changes in **A** Cd_{ob}, **B** α_1-MG_{sg}, **C** β_2-MG_{cr} and **D** NAG_{ob}. Each *dot* represents one case (11,090 cases in **A**, **B** and **C**, and 2,115 cases in **D**), and the line is drawn with an assumption of linear relation. For the regression equations, see Tables 1, 2, 3

Cd-induced health effects has been confirmed for Cd, α_1-MG and β_2-MG (Ikeda et al. 2005) as well as for NAG (Stengel et al. 1999).

It appears that the age-dependent changes in urinary Cd levels have been studied only on limited occasions. According to Sartor et al. (1992), who studied men and women (2,327 subjects in total, and in a age range of about 20–80 years) in Belgium, Cd in 24-h urine samples increased from 0.34 μg/day at the age of slightly above 20 years to reach a peak of 1.12 μg/day in men and 0.87 μg/day in women at the age of around 60 years, followed by decreases to 0.96 μg/day (men) or 0.67 μg/

Table 3 Ratio of estimates at the ages of 80 years over those at 30 years: Cd, α_1-MG, β_2-MG and NAG

Y in the equation[a] (unit)	I [b]	II [c]	II/I ratio[d]			Relative ratio[f]
	At 30 years	At 80 years	Ratio	95% LL[e]	95% UL[e]	
CR (g/l)	1.31	0.51	0.39	0.36	0.42	
Factor G	20.1	14.2	0.70	0.68	0.73	
Cd_{ob} (μg/l)	0.73	2.30	3.16	2.90	3.45	1.00
Cd_{cr} (μg/g cr)	0.61	3.84	6.31	5.89	6.76	2.00
Cd_{sg} (μg/l)	0.63	2.81	4.47	4.14	4.82	1.41
α_1-MG_{ob} (mg/l)	1.85	2.62	1.41	1.29	1.55	1.00
α_1-MG_{cr} (mg/g cr)	1.96	6.19	3.16	2.93	3.41	2.24
α_1-MG_{sg} (mg/l)	1.60	3.19	2.00	1.87	2.13	1.42
β_2-MG_{ob} (μg/l)	97	108	1.12	1.05	1.20	1.00
β_2-MG_{cr} (μg/g cr)	86	217	2.51	2.38	2.66	2.24
β_2-MG_{sg} (μg/l)	83	132	1.58	1.49	1.69	1.42
NAG_{ob} (unit/l)	2.34	2.62	1.12	0.98	1.28	1.00
NAG_{cr} (unit/g cr)	2.64	5.92	2.24	2.07	2.42	2.00
NAG_{sg} (unit/l)	2.45	3.88	1.58	1.43	1.76	1.42

[a]The values are estimated by use of the regression equations given in Table 2
[b]The estimate for the age of 30 years
[c]The estimate for the age of 80 years
[d]The ratio of the estimate for the age of 80 years over that for the age of 30 years
[e]The lower or upper limit of the 95% confidence interval
[f]The relative ratio is calculated taking the 80 years/30 years ratio with observed values as 1

day (women) at the ages of above 80 years. It was not possible, however, to detect such bi-phasic changes in the present study, probably because a linear regression was considered. Although smaller correlation coefficients for log β_2-MG compared with those for log α_1-MG or log NAG might be related to this possibility of bi-phasic relation, a quadratic regression between age and log β_2-MG (with or without correction for CR or SG) did not show the presence of a local maximum (data not shown). The lack of decrease in Cd in urine at higher age in the present analysis may be associated with the fact that dietary exposure to Cd was substantially higher in the late 1960s (e.g., 50–95 μg/day) in Japan compared with the level at present (25–35 μg/day) even among general populations in areas where no environmental pollution with Cd was known (Ikeda et al. 2004). In this connection, it should be added that the general population exposure to Cd has been almost exclusively via foods (>99.5%), with essentially no contribution from atmospheric air (Ikeda 1992).

Reports on the relation of tubular dysfunction marker levels with age appear to be very limited. In an early report, Nomiyama et al. (1983) observed that both β_2-MG and NAG increased age-dependently among the elderly populations (60s–90s) in an area with no known Cd pollution in Japan. In addition, they observed that such increases were however not accompanied by other changes of kidney function markers such as creatinine clearance or tubular re-absorption of phosphorus.

Age-dependent increase in Cd and tubular function markers may be further amplified when the levels were corrected for CR or SG (Table 3), because both CR and SG decrease as a function of age. Although it has been a common practice in Cd epidemiology (World Health Organization 1996; American Conference of Governmental Industrial Hygienists 2003) to correct urinary analyte concentration by CR concentration; Berlin et al. (1985), for example, did not find any advantage of CR correction over the use of observed values, although Mason et al. (1998) observed that CR correction might reduce intra-individual variation when multiple samples were collected from the same individuals.

Assuming that the problem associated with different urine density will be overcome by the determination of a large number of samples, and thus findings with the observed values can be considered as most reliable, the correction with CR concentration will induce amplification by two times and that with factor G (or SG) by 1.4 times in evaluating the changes in Cd as well as tubular dysfunction markers (Table 3). Thus, care should be practiced in evaluating these marker levels especially among the populations with ages in wide ranges.

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References

American Conference of Governmental Industrial Hygienists (2003) Documentation of the TLVs and BEIs. ACGIH, Cincinnati

Berlin A, Alessio L, Sesana G, Dell'Orto A, Ghezzi I (1985) Problems concerning the usefulness of adjustment of urinary cadmium for creatinine and specific gravity. Int Arch Occup Environ Health 55:107–111

Buchwald H (1964) The expression of urine analysis results—Observations on the use of a specific gravity correction. Ann Occup Hyg 7:125–136

Ezaki T, Tsukahara T, Moriguchi J, Furuki K, Fukui Y, Ukai H, Okamoto S, Sakurai H, Honda S, Ikeda M (2003) No clear-cut evidence for cadmium-induced tubular dysfunction among over 10,000 women in the Japanese general population; a nationwide large-scale survey. Int Arch Occup Environ Health 76:186–196

Ikeda M (1992) Biological monitoring of the general population for cadmium. In: Nordberg GF, Herber RFM, Alessio L (eds) Cadmium in the human environment: Toxicity and carcinogenicity. International Agency for Research on Cancer, Lyon, pp 65–72

Ikeda M, Moon C-S, Zhang Z-W, Iguchi H, Watanabe T, Iwami O, Imai Y, Shimbo S (1995) Urinary α_1-microglobulin, β_2-microglobulin and retinal-binding protein levels in general populations in Japan with reference to cadmium in urine, blood, and 24-hour food duplicates. Environ Res 70:35–46

Ikeda M, Zhang Z-W, Moon C-S, Shimbo S, Watanabe T, Nakatsuka H, Matsuda-Inoguchi N, Higashikawa K (2000) Possible effects of environmental cadmium exposure on kidney function in the Japanese general population. Int Arch Occup Environ Health 73:15–25

Ikeda M, Ezaki T, Tsukahara T, Moriguchi J, Furuki K, Fukui Y, Okamoto S, Ukai H, Sakurai H (2003) Bias induced by the use of creatinine-corrected values in evaluation of β_2-microglobulin levels. Toxicol Lett 145:197–207

Ikeda M, Ezaki T, Tsukahara T, Moriguchi J (2004) Dietary cadmium intake in polluted and non-polluted areas in Japan in the past and in the present. Int Arch Occup Environ Health 77:227–234

Ikeda M, Ezaki T, Tsukahara T, Moriguchi J, Furuki K, Fukui Y, Ukai H, Okamoto S, Sakurai H (2005) Reproducibility of urinary cadmium, α_1-microglobulin, β_2-microglobulin levels in health-screening of general population. Arch Environ Contam Toxicol 48:135–140

International Programme on Chemical Safety (1992a) Environmental health criteria 134 cadmium. World Health Organization, Geneva

International Programme on Chemical Safety (1992b) Environmental health criteria 135 cadmium—environmental aspects. World Health Organization, Geneva

Jackson S (1966) Creatinine in urine as an index of urinary excretion rate. Health Phys 12:843–850

Kawada T (1995) Indicators of renal effects of exposure to cadmium: N-acetyl-β-D-glucosaminidase and others. J Occup Health 37:69–73

Kawada T, Shinmyo R, Suzuki S (1992) Urinary cadmium and N-Acetyl-β-D-glucosaminidase excretion of inhabitants living in a cadmium-polluted area. Int Arch Occup Environ Health 63:541–546

Levine L, Fahy JP (1945) Evaluation of urinary lead concentrations. I. The significance of the specific gravity. J Ind Hyg Toxicol 27:217–223

Mason HJ, Williams NR, Morgan MG, Stevenson AJ, Armitage S (1998) Influence of biological and analytical variation on urine measurements for monitoring exposure to cadmium. Occup Environ Med 55:132–137

Ministry of Health, Labour and Welfare, the Government of Japan (2003) National nutritional survey in Japan, 2001(in Japanese). Dai-ichi Shuppan Press, Tokyo

Moriguchi J, Ezaki T, Tsukahara T, Furuki K, Fukui Y, Okamoto S, Ukai H, Sakurai H, Shimbo S, Ikeda M (2003) Comparative evaluation of four urinary tubular dysfunction markers, with special references to the effects of aging and correction for creatinine concentration. Toxicol Lett 143:279–290

Moriguchi J, Ezaki T, Tsukahara T, Fukui Y, Ukai H, Okamoto S, Shimbo S, Sakurai H, Ikeda M (2005) Decreases in urine specific gravity and urinary creatinine in elderly women. Int Arch Occup Environ Health 78. DOI 10.1007/s004-0597-z

Nogawa K, Yamada Y, Kido T, Honda R, Ishizaki M, Tsuritani I, Kobayashi E (1986) Significance of elevated urinary N-acetyl-β-D-glucosaminidase activity in chronic cadmium poisoning. Sci Total Environ 53:173–178

Nomiyama K, Yotoriyama M, Nomiyama H (1983) Urinary β_2-microglobulin and renal functions in elderly people in an area with no known cadmium pollution (Japan). Arch Environ Contam Toxicol 12:143–146

Sartor FA, Rondia DJ, Claeys FD, Staessen JA, Lauwerys RR, Bernard AM, Buchet JP, Roels HA, Bruaux PJ, Ducoffre GM, Lijnen PJ, Thijs LB, Amery AK (1992) Impact of environmental cadmium pollution on cadmium exposure and body burden. Arch Environ Health 47:347–353

Rainsford SG, Lloyd Davies TA (1965) Urinary excretion of phenol by men exposed to vapour of benezene; a screening test. Br J Ind Med 22:21–26

Schaller KH, Angerer J, Drexler H (2002) Quality assurance of biological monitoring in occupational and environmental medicine. J Chromatogr B 778:403–417

Stengel B, Watier L, Chouquet C, Cenee S, Philippn C, Hemon D (1999) Influence of renal biomarker variability on the design and interpretation of occupational or environmental studies. Tox Lett 106:69–77

Tohyama C, Kobayashi E, Saito H, Sugihara N, Nakano A, Mitane Y (1986) Urinary α_1-microglobulin as an indicator protein of renal tubular dysfunction caused by environmental cadmium exposure. J Appl Toxicol 6:171–178

Tsukahara T, Ezaki T, Moriguchi J, Furuki K, Fukui Y, Ukai H, Okamoto S, Sakurai H, Ikeda M (2003) No significant effect of iron deficiency on cadmium body burden or kidney dysfunction among women in the general population in Japan. Int Arch Occup Environ Health 76: 275–281

World Health Organization (1996) Biological monitoring of chemical exposure in the workplace. Cadmium and β_2-microglobulin, vol 1. World Health Organization, Geneva