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Evaluation of the Biological Threshold Value of Urinary Cadmium Concentration in a Group of Workers

Asuman Karakaya,[1] Sinan Süzen,[1] Nevin Vural,[1] and Gül Oflaz[2]

[1]Department of Toxicology, Faculty of Pharmacy, Ankara University, 06100, Tandoğan, Ankara, Turkey and [2]Department of Nuclear Medicine, Faculty of Medicine, Ankara University, Ankara, Turkey

Occupational exposure to cadmium occurs primarily through inhalation of dust and fume. The highest occupational exposures occur in the metallurgical industries (particularly cadmium refining), in the production of nickel-cadmium batteries, cadmium pigment and plastic stabilizers (Friberg et al. 1986; Thun et al. 1991).

The most typical feature of chronic cadmium intoxication is kidney damage. Cadmium affects reabsorption functions of the proximal tubuli and the first sign of which is usually an increase in urinary excretion of low molecular weight proteins (e.g., β2-microglobulin, retinol-binding protein, α1-microglobulin), known as microproteinuria (Friberg et al. 1986; Lauwerys and Bernard 1986; Thun and Clarkson 1986). β2-microglobulin, a major component of the low molecular weight proteins in the urine of cadmium workers, increases with renal tubular damage. Microproteinuria can be defined as β2-microglobulin in urine >300 μg/g creatinine (Roels et al. 1991). Some researchers have shown that the concentration of cadmium in urine (which reflects the renal burden of cadmium) above which the risk of occurence of microproteinuria significantly increases, is around 10 μg/g creatinine (Bernard et al. 1979; Buchet et al. 1980; Lauwerys et al. 1979). It has been also shown that cadmium induced microproteinuria is irreversible(Elinder et al. 1985; Roels et al. 1989).

Although the tubular effects of cadmium are well recognized, there is some controversy about the threshold value of urinary cadmium concentration at which nephropathy appears (Ishizaki et al. 1989) and about the significance of β2-microglobulin in combination with cadmium exposure (Chia et al. 1989; Kawada et al. 1989).

This study was carried out to investigate the dose-effect relationship between urinary cadmium and urinary β2-microglobulin concentration and to estimate the biological threshold value of urinary cadmium concentration in a group of workers exposed to cadmium fume and dust.

Send reprint requests to Dr.Karakaya at the above address

MATERIALS AND METHODS

The study was conducted on 31 male workers employed in a zinc/cadmium smelters and 4 male workers employed in a small plant plating metals with cadmium by an electrolytic process. Their ages ranged from 23 to 50 years (mean: 38.8 years) and 27 of them were smokers. The average duration of exposure to cadmium for zinc/cadmium smelters workers was 14,2 years (range 10 to 17 years), for cadmium plating workers was 4.8 years (range 1 to 10 years). The controls belonged to the same socioeconomic class as did the workers exposed, with ages ranging from 22 to 53 years (mean 34.1 years) and 11 of them were smokers.

Morning urine samples were collected in metal free polyethylene containers. Blood samples were obtained by venepuncture using cadmium free disposable syringes. All samples were kept frozen (-20 °C) until analyses were performed. For β_2-microglobulin determination, urinary pH was measured and adjusted to pH 6.0 when necessary to avoid degradation of β_2-microglobulin.

The determinations of cadmium in whole blood and urine were performed by flame atomic absorption spectrometry using atom trapping technique (Karakaya and Taylor 1989; Karakaya et al. 1992). The urinary β_2-microglobulin was measured by radioimmunoassay using β_2-microglobulin RIA kit developed by the DRG Instruments. The urinary measurements were all corrected with the urinary creatinine concentration and expressed per gram creatinine.

Student's t test and Mann Whitney U test were used to assess the significance of the differences between the controls and cadmium workers. Association between variables was evaluated by Pearson's correlation coefficients.

RESULTS AND DISCUSSION

In Table 1 the concentration of cadmium in blood and in urine, β_2-microglobulin in urine are summarized. As expected blood cadmium concentrations were significantly higher in the cadmium workers than in the controls (2.12 ν 0.69 μg/100 ml, $p < 0.001$), as was urine cadmium (5.77 ν 2.01 μg/g creatinine, $p<0.001$). The concentrations of β_2-microglobulin in urine were also significantly increased in the exposed group (266.13 ν 85.74 μg/g creatinine, $p < 0.001$).

A significant increase in blood cadmium concentrations was observed in smoker controls (mean : 0.98 μg/100 ml, n=11) compared with the non-smokers of the same group (mean : 0.55 μg/100 ml, n=19). But there was no significant difference of smokers and non-smokers of the exposed group. No differences also in urine cadmium concentrations between smokers and non-smokers of the exposed and control groups were observed.

There was no significant correlation blood cadmium and urinary cadmium concentration, urinary β_2-microglobulin and blood cadmium concentration of the exposed group. In the same group, excretion of β_2-microglobulin was well correlated urinary cadmium. Correlation

Table 1. Biological measurements of controls and cadmium workers

	Controls(n=30)			Cadmium workers (n=35)			
	Mean	Median	Range	Mean	Median	Range	p value
Blood cadmium (μg/100 ml)	0.69	0.69	0.03-1.77	2.12	1.58	0.37-6.52	<0.001
Urine cadmium (μg/g creatinine)	2.01	1.93	0.57-4.00	5.77	5.00	2.27-17.90	<0.001
Urine β_2-micro-globulin (μg/g creatinine)	85.74	50.05	8.92-377.50	266.13	168.20	20.60-1025.60	<0.001

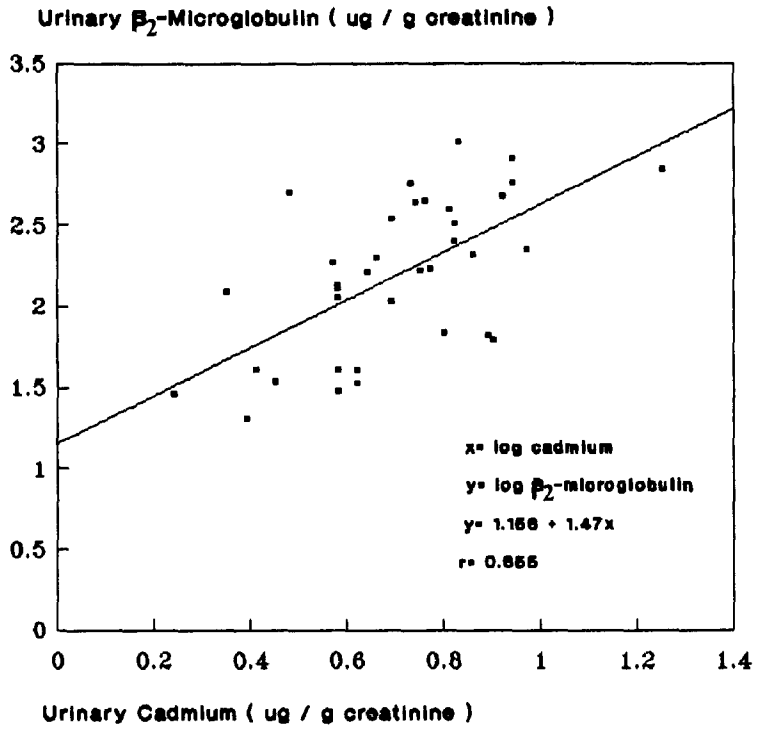

Figure 1. The relationship between log transformed urinary β2-microglobulin and urinary cadmium concentrations

coefficient was 0.655 ($p < 0.0001$). The relationship between log transformed urinary β2-microglobulin and urinary cadmium concentrations is shown in Fig.1. Urinary β2-microglobulin concentrations showed a consistent rise with increasing urinary cadmium for the control and exposed groups (Fig.2).

In the control group, a significant correlation was evident between urinary and blood cadmium concentration ($r=0.499$; $p<0.01$), urinary cadmium and β2-microglobulin concentration ($r=0.380$; $p < 0.05$). Again a weak correlation was found between blood cadmium and urinary β2-microglobulin concentration ($r=0.245$; $p<0.5$) of the same group.

We observed a significant increase in blood cadmium concentrations in smoker controls compared with the non-smokers of the same group. But there was no significant difference between smokers and non-smokers of the exposed group. Similar observations have been reported by other researchers (Buchet et al. 1980 ; Smith et al. 1976). Contrary to the results of Hassler et al. (1983), we found that urinary cadmium was not significantly higher in smoker workers than in those who had never smoked.

In this study, in spite of a significant correlation found between urinary cadmium and blood cadmium of controls,there was no

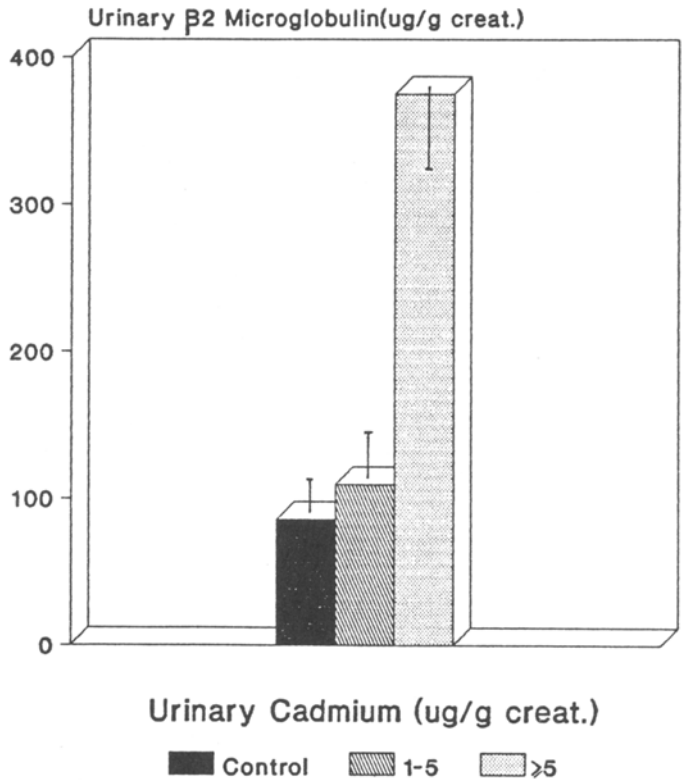

Figure 2. Urinary β2-microglobulin by urinary cadmium

significance in workers. Again, a weak correlation was found between blood cadmium and urinary β2-microglobulin of the controls. But none was found in workers. These results confirm that blood cadmium is assumed mainly to reflect recent exposure and urinary cadmium is closely related to the kidney burden of this metal before severe renal effects have occured.

We observed that increased urinary cadmium concentration accompanied rising urinary β2-microglobulin concentration in workers exposed to cadmium and excretion of β2-microglobulin was highly correlated with urinary cadmium concentration. Our results reveal that occupational exposure to cadmium may cause renal impairment and that the first sign is an increased urinary excretion of low molecular weight proteins such as β2-microglobulin. β2-microglobulin levels in urine have been determined to be useful indicator of cadmium induced renal tubular damage in exposed or previously exposed workers (Elinder et al. 1985 ; Thun and Clarkson 1986).

An urinary excretion of 5 μg/g creatinine in human corresponds to a body burden of about 140 mg and a kidney concentration of about 200 mg/kg. The level of 200 mg/kg in kidney cortex is often considered a critical level above which tubular damage occurs with a

probability of 10 to 15 % (Thun et al. 1991). These estimates agree with our observations on the relationship between urinary cadmium and urinary β_2-microglobulin excretion. In our study twenty (57.1%) of 35 workers had urinary cadmium concentration ≥ 5 µg/g creatinine. Twelve (34.3 %) of 35 workers had microproteinuria (β_2-microglobulin in urine > 300 µg/g creatinine) and 11 of these had urinary cadmium concentration ≥ 5 µg/g creatinine (mean : 7.8 µg/g creatinine). An increased prevalence (55 %) of microproteinuria has been found among workers having urinary cadmium ≥ 5 µg/g creatinine.

The World Health Organization's (WHO) recommended Health Based Biological Limit (HBBL) for cadmium in urine of occuppationally exposed workers has been set at 5 µg/g creatinine (WHO 1980). Some authors have proposed that the concentration of cadmium in urine above which the risk of occurence of microproteinuria significantly increases, is around 10 µg/g creatinine for workers occupationally exposed to cadmium (Bernard et al. 1979; Buchet et al. 1980; Lauwerys et al. 1979). Recently it was reported by Buchet et al. (1990) that tubular proteinuria in environmentally exposed persons may be seen at urinary cadmium concentration as low as 2 µg/24 h. In order to better understand the reasons for the differing threshold values of urinary cadmium, further investigation is required.

REFERENCES

Bernard A, Buchet JP, Roels H, Masson P, Lauwerys R (1979) Renal excretion of proteins and enzymes in workers exposed to cadmium. Eur J Clin Invest 9: 11-12

Buchet JP, Lauwerys R, Roels H, Bernard A, Bruaux P, Claeys F, Ducoffre G, De Plaen P, Staessen J, Amery A, Lijnen P, Thijs L, Rondia D, Sartor F, Saint Remy A, Nick L (1990) Renal effects of cadmium body burden of the general population. Lancet 336: 699-702

Buchet JP, Roels H, Bernard A, Lauwerys R (1980) Assesment of renal function of workers exposed to inorganic lead, cadmium or mercury vapor. J Occup Med 22: 741-750

Chia KS, Ong CN, Ong HY, Endo G (1989) Renal tubular function of workers exposed to low levels of cadmium. Br J Ind Med 46: 165-170 (1985a)

Elinder CG, Edling C, Lindberg E, Kagedal B, Vesterberg A (1985) β 2-microglobulinuria among workers previously exposed to cadmium: Follow up and dose-response anayses Am J Ind Med 8: 553-564

Friberg L, Kjellström T, Nordberg GF (1986) Cadmium In: Friberg L, Nordberg GF, Vouk VB (eds) Handbook of the toxicology of metals, vol II. Elsevier, Amsterdam, p 130-175

Hassler E, Lind B, Piscator M (1983) Cadmium in blood and urine related to present and past exposure. A study of workers in an alkaline battery factory. Br J Ind Med 40: 420-425

Ishizaki M, Kido T, Honda R, Tsuritani I, Yamada Y, Nakagawa H, Nogawa K (1989) Dose-response relationship between urinary cadmium and β_2-microglobulin in a Japanese environmentally cadmium exposed population. Toxicology 58: 121-131

Karakaya A, Taylor A (1989) On-line Preconcentration for the measurement of cadmium in urine by flame atomic absorption spectrometry. J Anal Atom Spec 4: 261–263
Karakaya A, Süzen S, Yücesoy B (1992) A biological monitoring method for cadmium J Anal Toxicol 16: 403
Kawada T, Koyama H, Suziki S (1989) Cadmium, NAG activity, and β2-microglobulin in the urine of cadmium pigment workers. Br J Ind Med 46: 52–55
Lauwerys R, Roels H, Regriers M, Buchet JP, Bernard A, Goret A (1979) Significance of cadmium concentration in blood and in urine in workers exposed to cadmium. Environ Res 20: 375–391
Lauwerys RR, Bernard AM (1986) Cadmium and the kidney Br J Ind Med 43: 433–435
Roels HA Lauwerys RR, Buchet JP, Bernard AM, Vos A, Oversteyns M (1989) Health significance of cadmium induced renal dysfunction: a five year follow up. Br J Ind Med 46: 755–764
Roels HA, Lauwerys RR, Bernard AM, Buchet JM, Vos A, Oversteyns M (1991) Assessment of the filtration reserve capacity of the kidney in workers exposed to cadmium. Br J Ind Med 48: 365–374
Smith TJ, Thomas LP, Reading JC, Lakshminarayan S (1976) Pulmonary effects of chronic exposure to airborne cadmium. Am Rev Respir Dis 114: 161–169
Thun MJ, Clarkson TW (1986) Spectrum of tests available to evaluate occupationally induced renal disease. J Occup Med 28: 1026–1033
Thun MJ, Elinder CG, Friberg L (1991) Scientific basis for an occupational standard for cadmium. Am J Ind Med 20: 629–642
World Health Organization (1980) Recommended health based limits in occupational exposure to heavy metals. Technical report series No.647, Geneva

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