Int Arch Occup Environ Health (1985) 55:107–111

International Archives of
Occupational
and
Environmental
Health

Problems concerning the usefulness of adjustment of urinary cadmium for creatinine and specific gravity

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Summary. A previous study concluded that there are some doubts as to the validity of creatinine as a parameter for adjusting the values of biological indicators determined on spot samples of urine, since it is subject to marked inter- and intraindividual variations. Furthermore, since there was only a moderate correlation between creatinine levels and specific density, it can be assumed that these two parameters cannot be used indifferently for adjustment. Nevertheless, it seemed advisable to verify whether correction of cadmium values determined from spot samples offers any practical advantages. For this purpose, 105 subjects with occupational exposure to cadmium were examined. They collected their 24-h urine and spot samples separately at 8.00 h. There was a close correlation between CdU/spot samples and CdU/24 h. The correlation index was very similar both for CdU/spot values expressed in μg/l and for values adjusted according to creatinine or 1024 specific gravity. These results show that no particular advantages are offered by adjusting CdU according to creatinine or specific gravity.

Key words: Biological monitoring – Urinary cadmium – Creatinine adjustment – Density adjustment

Introduction

Cadmium in urine (CdU) is the most widely used test for biological monitoring of subjects exposed to this metal. CdU in low-exposure conditions and in the absence of kidney damage reflects the body burden, while in high-exposure conditions CdU measures current exposure. Levels of cadmium in the kidney correlate well with the concentration of cadmium deposited in the renal cortex, so that this biological test can indirectly evaluate the quantity of metal deposited in this tissue, which represents the critical organ [1, 6, 10].

As with other biological indicators used in occupational medicine, for the determination of cadmium in urine it is not usually practical to obtain urine samples collected over long and fixed periods. Therefore, it is now common practice to collect spot samples of urine and to adjust the analytical values according to reference parameters, such as creatinine, specific gravity or osmolarity, mainly in order to reduce the variations due to dilution of the sample. However, there are not sufficient data available to assess whether these methods are equally valid for all biological indicators determined on urine samples.

Moreover, data obtained in a previous study raised doubts as to the reliability of creatinine as an adjustment parameter of urinary tests performed on spot samples [2]. In fact there was a wide inter- and intraindividual variation of the creatinine levels. Also, the rather poor relationship between specific gravity (S.G.) and creatinine observed in the same study seems to indicate that the two parameters cannot be used indifferently for adjustment.

The aim of the present study was to verify whether adjustment of CdU values according to urinary creatinine or specific gravity offers any particular advantage over uncorrected CdU values.

Subjects and methods

The study was carried out on 105 subjects occupationally exposed to cadmium fumes in a precious metals recovery industry (silver, copper and platinum) that also produced cadmium alloys. Details of the exposure have been presented elsewhere [7].

The mean age of the 84 male subjects was 43.5 ± 9.04 years and the mean age of the 21 female subjects was 38.9 ± 6.7 years. All subjects collected their 24-h urine and a spot sample at 8.00 h; none of the subjects suffered from renal damage and urinary B_2MG values in particular were within the range of levels found in a reference group, i.e. 260 μg/l ~ 200 μg/g creatinine [3].

The levels of cadmium in urine were determined by atomic absorption spectrophotometry [9]. Concentrations of B_2MGU were determined by radioimmunoassay using the Phadebas beta$_2$microtest kit developed by Pharmacia Diagnostics (Uppsala, Sweden).

Concentration of urinary creatinine was measured using Jaffè's method [8]. Specific gravity was measured with an AT 315 URICON diffractometer. All subjects were voluntary participants in the study and they had been informed of the aims of the research and that it was important to have properly collected samples.

Results and discussion

In the present study, CdU determined on 24-h urine (CdU μg/24 h) was considered the most reliable index of cadmium exposure. This was justified by the fact that cadmium is metabolized slowly and that CdU levels should only be slightly influenced by fluctuations in current exposure.

We therefore investigated the relationship existing between CdU μg/24 h test taken as indicative of the "true situation", and CdU on spot samples; for spot CdU we considered uncorrected values (expressed in μg/l) and values adjusted according to creatinine (μg/g creatinine) and according to 1024 specific gravity (μg/l 1024 S.G.). The correlation index between CdU μg 24-h and CdU

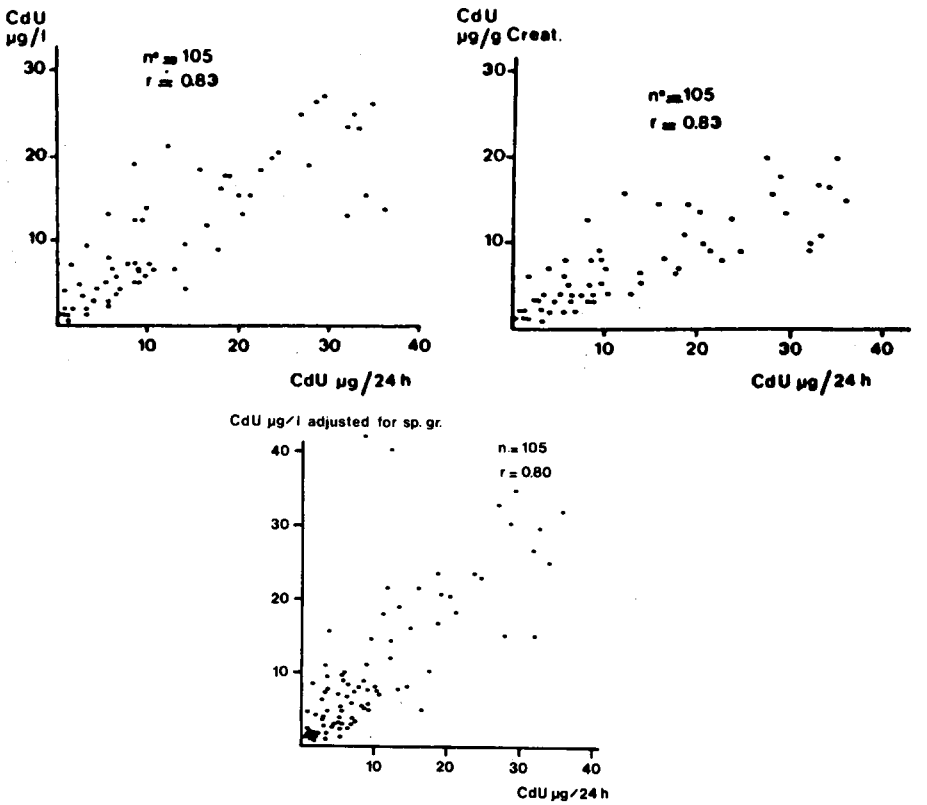

Fig. 1. Relationship between CdU µg/24 h and CdU spot (values expressed in µg/l, µg/g creatinine and in µg/l 1024 S.G.)

Table 1. Coefficient of variation (C.V.) of CdU values expressed in µg/l, µg/g creatinine and µg/l S.G. 1024 in the whole group (105 subjects) and in the male subgroup (84 subjects)

	Whole group			Males		
	Mean	SD	C.V.	Mean	SD	C.V.
CdU µg/l	9.67	7.84	81.1%	9.98	8.24	82.5%
CdU µg/g creatinine	6.24	6.71	108%	5.87	5.35	91.3%
CdU µg/l adjusted S.G. 1024	13.23	15.28	115.5%	13.13	13.23	100.7%

spot, in the whole group, was 0.83 both for uncorrected spot values and for spot values corrected according to creatinine, and 0.80 when values corrected according to specific gravity were considered (Fig. 1). Similar results were also obtained in the larger subgroup of 84 male subjects: CdU µg/24 h vs CdU spot µg/l: $r = 0.83$; CdU µg/24 h vs CdU spot µg/g creatinine: $r = 0.84$; CdU µg/24 h vs CdU µg/l S.G. 1024: $r = 0.75$.

If we examine Fig. 1, two observations can be made: (a) the correlation between CdU µg/24 h and CdU spot is very close whether the values are expressed

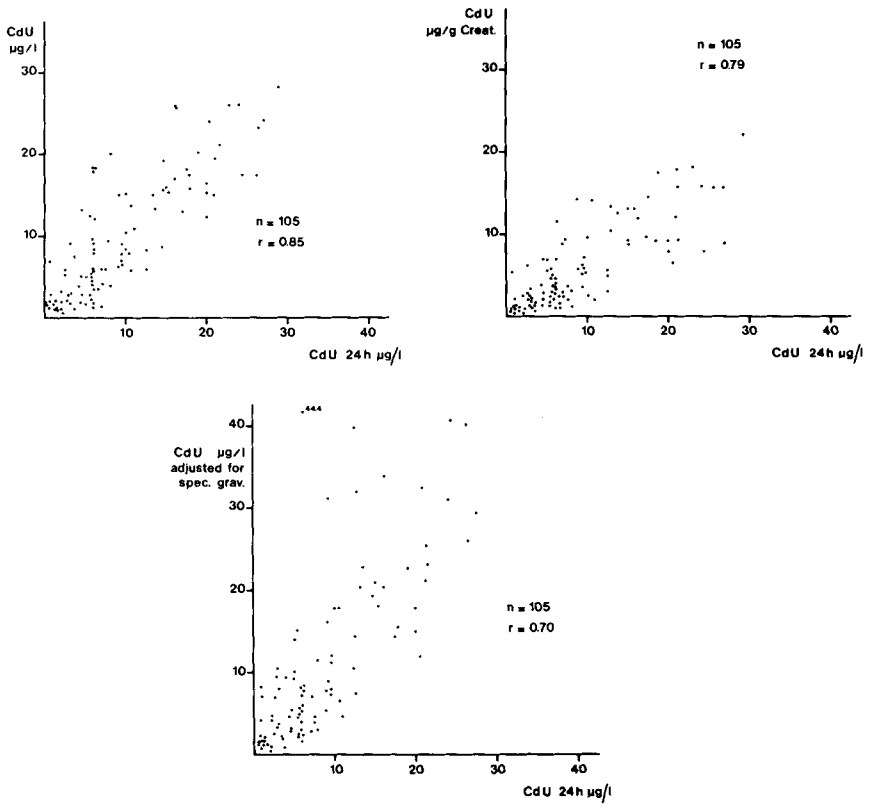

Fig. 2. Relationship between CdU µg/l (24-h urine sample) and CdU spot (values expressed in µg/l, µg/g creatinine and µg/l 1024 S.G.)

in µg/l, µg/g creatinine or in µg/l 1024 S.G.; (b) the range of values corrected for creatinine is not as wide as the range of uncorrected values. The second observation requires some comment since many, even recently published, studies have concluded the adjustment for creatinine or specific gravity is useful since it reduces the ranges of uncorrected values [4, 5, 11]. A rather critical view should be taken of this statement since it is very likely that the ranges are reduced apparently due to a mathematical artifice: when the value of a urinary indicator is adjusted for creatinine, it is usual to divide by a number greater than 1 since the creatinine values of spot samples are generally higher than 1 g/l. This interpretation is confirmed by the fact that relative variability does not improve, in fact, the correlation coefficient does not increase after adjustment and the variation coefficient is even higher for the adjusted values than for uncorrected values (Table 1).

Assuming that not all workers collected their 24-h urine samples correctly and that therefore evaluation of CdU µg/24-h might not always have been reliable, we also verified the relationship between corrected and uncorrected spot CdU and urinary cadmium expressed in µg/l and determined from 24-h urine. This seemed to be a useful approach since it is likely that, in the case of toxic substances that are slowly eliminated, the biological indicators are more reliable

when determined from a sample of urine collected over an extended period than from a spot sample, since they are less influenced by dilution. The relationship between CdU μg/l (24-h urine sample) and CdU spot (μg/l) was 0.85, the relationship with CdU spot corrected for creatinine was 0.79 and the relationship with CdU spot corrected for S.G. was 0.70 (Fig. 2).

On the whole, the data obtained in this study seem to indicate that no practical advantage is offered in adjusting the CdU values either for creatinine or for specific gravity.

In view of all the doubts that are raised, it seems advisable, at least in the case of cadmium, to use these two parameters only for the purpose of selecting over-diluted or over-concentrated samples.

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Received July 25 / Accepted December 10, 1984