MEDICAL SCIENCE

Renal effects of cadmium body burden of the general population

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In a cross-sectional population study to assess whether environmental exposure to cadmium is associated with renal dysfunction, 1699 subjects aged 20–80 years were studied as a random sample of four areas of Belgium with varying degrees of cadmium pollution. After standardisation for several possible confounding factors, five variables (urinary excretion of retinol-binding protein, N-acetyl-β-glucosaminidase, β_2-microglobulin, aminoacids, and calcium) were significantly associated with the urinary excretion of cadmium (as a marker of cadmium body burden), suggesting the presence of tubular dysfunction. There was a 10% probability of values of these variables being abnormal when cadmium excretion exceeded 2–4 μg/24 h. Excretion reached this threshold in 10% of non-smokers. There was also evidence that diabetic patients may be more susceptible to the toxic effect of cadmium on the renal proximal tubule.

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Introduction

Cadmium is an important environmental pollutant in industrialised countries. For the general population, the two main sources of exposure are the diet (from contaminated water and crops grown on polluted soil) and tobacco smoking. Cadmium is a very cumulative poison with a biological half-life in the whole body exceeding 10 years; it mainly accumulates in the kidney.[1,2] Since the beginning of this century, environmental cadmium pollution in Europe may have caused a fifty-fold rise in the concentration of the metal in the human renal cortex.[3] A role for cadmium in the pathogenesis of hypertension has also been suggested.[2] The currently accepted critical level of cadmium in the renal cortex (200 mg/kg; corresponding to urinary excretion of about 10 μg per day) is derived from studies on men occupationally exposed to the metal or its compounds.[1,4] Since such populations are usually selected because they are healthy, they may not accurately reflect the general population's susceptibility to the toxic effects of the metal. Belgium is the principal producer of cadmium in Europe and shows severe environmental contamination by the metal.[5] Preliminary studies[6-8] have suggested that the environmental contamination leads to significant uptake of cadmium by the general population and possibly to renal effects. A large-scale epidemiological study (Cadmibel) was therefore undertaken to establish whether environmental exposure to cadmium does induce renal dysfunction and to determine the critical level for the general population. The study design took advantage of the fact that biological indicators of exposure, body burden, and early nephrotoxic effects of cadmium are available which increase the likelihood of an association being detected. We also looked for an effect of cadmium exposure on blood pressure: no such effect was found (to be reported elsewhere).

Subjects and methods

The design of the Cadmibel study has been described elsewhere.[5] Briefly, the cross-sectional study was carried out from 1985 to 1989. A stratified random sample of 2327 people was obtained from two areas with low exposure and two with high exposure. For each exposure level, one district was rural and one urban. These areas were selected on the basis of available environmental data to give a

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TABLE I—MULTIPLE REGRESSION ANALYSIS

Dependent and independent variables*	Partial regression coefficient	Partial R^2	p
Retinol-binding protein excretion			
Sex	−0·14815	0·0660	0·0001
Urinary cadmium	0·14157	0·0210	0·0001
Diabetes	0·14294	0·0114	0·0001
RHE residence	0·05751	0·0114	0·0023
UHE residence	0·07839	0·0051	0·0001
Body mass index	−0·19595	0·0022	0·0448
N-acetyl-β-glucosaminidase excretion			
Urinary cadmium	0·11150	0·0684	0·0001
Sex	−0·10541	0·0452	0·0001
Diuresis	0·28963	0·0432	0·0001
Diabetes	0·16277	0·0269	0·0001
RLE residence	−0·03576	0·0150	0·0001
RHE residence	0·07300	0·0044	0·0030
Body mass index	0·27464	0·0033	0·0099
Non-smoker	−0·03906	0·0045	0·0026
UHE residence	0·03926	0·0027	0·0201
Urinary cadmium/diabetes	0·16123	0·0024	0·0259
β_2-microglobulin excretion			
Diuresis	0·39470	0·0494	0·0001
Sex	−0·11718	0·0193	0·0001
RHE residence	0·05837	0·0069	0·0005
Urinary cadmium/diabetes	0·23846	0·0051	0·0028
Body mass index	−0·33408	0·0032	0·0172
Urinary cadmium	0·08927	0·0036	0·0117
Blood lead	−0·10590	0·0027	0·0302
Urinary tract diseases	0·04258	0·0022	0·0472
Aminoacid excretion			
Sex	−0·11529	0·0758	0·0001
Diuresis	0·23069	0·0661	0·0001
Age	−0·00330	0·0600	0·0001
Urinary cadmium	0·07901	0·0160	0·0001
Blood lead	−0·10931	0·0116	0·0001
RLE residence	−0·04676	0·0128	0·0001
Body mass index	0·16782	0·0063	0·0002
Current smoker	−0·02292	0·0036	0·0052
Zinc protoporphyrins	−0·06649	0·0036	0·0054
Urinary cadmium/diuresis	−0·14111	0·0027	0·0163
Calcium excretion			
Diuresis	0·29325	0·0424	0·0001
Age	−0·00508	0·0381	0·0001
Sex	−0·07915	0·0242	0·0001
Urinary cadmium	0·25651	0·0168	0·0001
Non-smoker	0·05101	0·0086	0·0001
Zinc protoporphyrins	−0·12540	0·0045	0·0040
Urinary cadmium/non-smoker	−0·10642	0·0031	0·0170
Analgesics	−0·04631	0·0028	0·0223
Urinary tract diseases	0·03810	0·0028	0·0211
Urinary cadmium/UHE residence	−0·09229	0·0022	0·0401
RHE residence	−0·03383	0·0021	0·0461

*Log-transformed except for age. Urinary cadmium in nmol/24 h. Sex coded 0 for men, 1 for women. Non-continuous variables coded 0 when absent, 1 when present. RHE and UHE = rural and urban high exposure areas; RLE and ULE = rural and urban low exposure areas.

sufficiently large range of cadmium body burden in the study population and to match the socioeconomic environment of each polluted area with that of at least one less polluted area. The subjects were asked to fill out a detailed questionnaire, to have their blood pressure measured twice with an interval of a week, and to provide blood and urine (spot and 24-h collection) for several biological measurements.[5] We excluded from this analysis subjects who had been occupationally exposed to heavy metals (cadmium, zinc, lead, mercury), those aged under 20 or over 80 years, those who could provide no reliable information on smoking habits or occupational exposure to heavy metals, and those whose 24-h urine collections were not considered reliable on the basis of previously published criteria.[9] The final statistical analysis, by various SAS procedures,[10] was based on 1699 subjects. Except for age, the distributions of the biological measurements were normalised by logarithmic transformation. Determinants significantly affecting the renal measurements were traced by stepwise regression. To avoid collinearities, independent variables considered in the model were centred. A logistic model was used to study the relation between the frequency of abnormal values of the renal measurements and the internal dose of cadmium assessed by its urinary excretion. For the multiple regression and the logistic analyses, the urinary excretion of cadmium was expressed either as the total amount excreted in 24 h or as the concentration in the 24-h urine sample. Since the same conclusions were reached with both units, only the results obtained with the amount excreted in 24 h are presented.

Results

Indicators of heavy metal exposure (urinary cadmium excretion, blood concentrations of cadmium and lead, and erythrocyte zinc-protoporphyrins) confirmed that the body burden of cadmium and lead increases with age in both sexes and that smoking increases the concentration of both metals in blood and in urine. There was also an effect of age on erythrocyte zinc-protoporphyrins. It is interesting that in non-smokers of all age groups, men had significantly higher blood lead concentrations than women, whereas the opposite was true for blood and urine concentrations of cadmium.

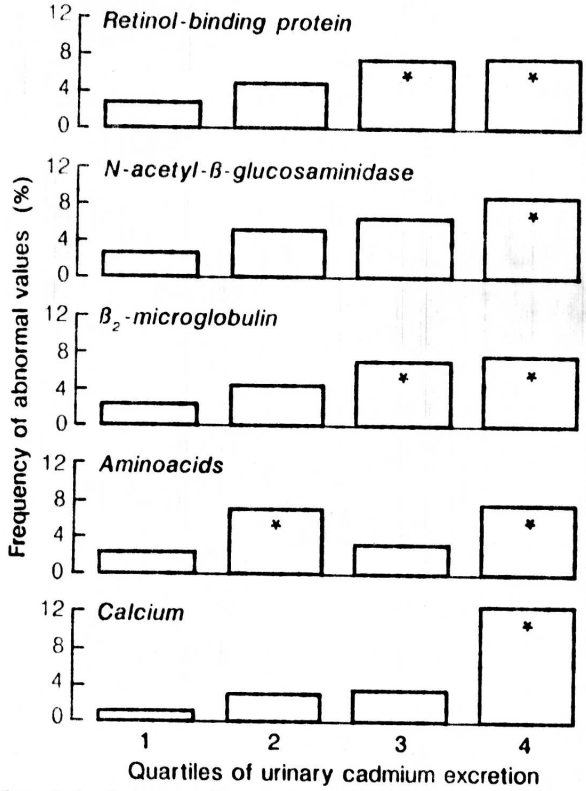
The results of renal effect measurements clearly showed the age and sex dependency of many renal variables: for example, serum creatinine and β_2-microglobulin concentrations rise with age, whereas creatinine clearance and the urinary excretion of proteins (in women) and aminoacids (in both sexes) show the opposite trend; serum creatinine, creatinine clearance, and urinary excretion of retinol-binding protein, aminoacids, and N-acetyl-β-glucosaminidase are significantly lower in women than in men. In both sexes, mean 24-h calcium excretion is lower in elderly people.

To identify the factors which affect the renal variables, multivariate correlation analysis was carried out with the following as independent variables: cadmium in urine (24-h excretion rate or concentration in the 24-h sample) or cadmium and lead in blood, zinc-protoporphyrins, age, sex, smoking habits (non-smoker, current smoker, past smoker), diuresis, the presence of diabetes or urinary tract disorders, the consumption of analgesics, the place of residence, and the first-order interaction terms between cadmium concentration in blood or urine and the other

TABLE II—ASSOCIATION BETWEEN CADMIUM EXCRETION AND MEAN VALUES OF FIVE SIGNIFICANT VARIABLES

Urinary cadmium excretion (μg/24 h)	Excretion of retinol-binding protein		Excretion of N-acetyl-β-glucosaminidase		Excretion of β_2-microglobulin		Excretion of aminoacids		Excretion of calcium	
	n	Mean*	n	Mean*	n	Mean*	n	Mean*	n	Mean*
0·00–0·51	413	119 (A)	413	1·53 (A)	402	99 (A)	402	195 (A)	403	1·54 (A)
0·52–0·89	419	132 (B)	419	1·70 (B)	407	101 (A)	408	213 (B)	410	1·90 (B)
0·90–1·40	416	145 (C)	416	1·75 (B)	401	107 (A,B)	401	211 (B)	403	2·02 (B)
1·41–8·00	421	153 (C)	420	1·89 (C)	404	117 (B)	405	229 (C)	408	2·55 (C)

*Antilog of geometric mean expressed in μg/24 h for retinol-binding protein and β_2-microglobulin, IU/24 h for N-acetyl-β-glucosaminidase, mg α-N/24 h for aminoacids, and mmol/24 h for calcium. Means with the same letter in parentheses did not differ significantly.
Since data were missing for some subjects, totals do not reach 1699.



Association between urinary cadmium excretion (quartiles: see table II) and frequency of abnormal values of five renal effect variables.

Frequencies significantly higher than that of the first class are shown by an asterisk. Abnormal values ≥ 338 µg/24 h for retinol-binding protein; 3·6 IU/24 h for N-acetyl-β-glucosaminidase; 283 µg/24 h for β_2-microglobulin; 357 mg α-N/24 h for aminoacids; and 4·9 mmol/24 h for calcium.

predictors cited above. Five variables (urinary excretion of retinol-binding protein, N-acetyl-β-glucosaminidase, β_2-microglobulin, aminoacids, and calcium) were significantly associated with 24-h urinary cadmium excretion. All the determinants statistically correlated with these five variables and their partial correlation (R^2) and regression coefficients are listed in table I. With the exception of β_2-microglobulin excretion these variables were also associated with the concentration of cadmium in the 24-h urine sample. For N-acetyl-β-glucosaminidase and β_2-microglobulin excretion there was also an interaction between the cadmium body burden (µg cadmium/24 h excreted) and the presence of diabetes. There was no indication, however, of interaction between age and sex and cadmium body burden. The renal variables listed in table I were significantly associated with urinary cadmium excretion in separate analyses of non-smokers and smokers, residents of polluted and less polluted areas, and residents of rural and urban areas. No independent association was found between these five associated variables and blood concentrations of cadmium.

The population was divided into quartiles according to the 24-h urinary excretion of cadmium and the mean values of the five associated variables standardised for the other significant determinants (table I) were compared by analysis of variance. For each variable there was a significant dose-effect relation (table II). In each quartile, the percentage of subjects with abnormal values (above 95th centile for subjects without diabetes or urinary tract diseases

TABLE III—SUBJECTS EXCRETING MORE THAN 2 µg CADMIUM / 24 h IN URINE

	No (%) of subjects			
	20–39 yr	40–59 yr	60–79 yr	Total
Men				
Never smokers	2 (2·2%)	2 (5·3%)	3 (11·5%)	7 (4·6%)
Past and current smokers	4 (2·6%)	35 (17·6%)	29 (17·6%)	68 (13·1%)
Total	6 (2·4%)	37 (15·6%)	32 (16·8%)	75 (11·1%)
Women				
Never smokers	4 (3·4%)	21 (10·1%)	33 (16·7%)	58 (11·1%)
Past and current smokers	5 (1·9%)	36 (20·3%)	10 (16·1%)	51 (10·2%)
Total	9 (2·4%)	57 (14·8%)	43 (16·5%)	109 (10·6%)
Total	15 (2·4%)	94 (15·1%)	75 (16·6%)	184 (10·8%)

and who did not regularly take analgesics) of the significantly associated variables was calculated, after standardisation for all the confounding factors (table I) except urinary cadmium excretion. This analysis also showed significant dose-response relations (see accompanying figure).

A logistic regression model was used to assess further the dose-response relations between the cadmium body burden and the renal effects. The probability that individual subjects, after adjustment for the significant covariates, would have abnormal values of the renal variables was related to the urinary cadmium excretion. It was estimated that more than 10% of values would be abnormal when the cadmium excretion rate exceeded 2·87 µg/24 h for retinol-binding protein, 2·74 µg/24 h for N-acetyl-β-glucosaminidase, 3·05 µg/24 h for β_2-microglobulin, 4·29 µg/24 h for aminoacids, and 1·92 µg/24 h for calcium. Table III shows the percentages of subjects who were excreting more than 2 µg cadmium per 24 h.

Discussion

This study shows that in people aged 20–80 years who have never been occupationally exposed to cadmium, the body burden of the metal (estimated on the basis of 24-h urinary cadmium excretion) may be associated with changes in proximal tubular function. A high cadmium burden was also associated with higher urinary excretion of calcium. It is unlikely that confounding factors, such as area of residence, smoking habits, analgesic abuse, and health status, caused these findings, since the associations were statistically significant within the various subgroups. The results were similar when 332 subjects occupationally exposed to heavy metals were included in the study population. The cadmium body burden and diabetes had a synergistic effect on two renal variables (urinary excretion of N-acetyl-β-glucosaminidase and β_2-microglobulin; table I). Although the cadmium body burden increased with age and, for the same degree of environmental exposure, was higher in female than in male non-smokers, the effect of the internal dose of cadmium on the renal variables was independent of age and sex.

The higher cadmium body burden in female than in male non-smokers may be due to higher gastrointestinal uptake of cadmium in women, since the absorption of oral cadmium rises with decreasing iron stores.[11] There was no indication that cadmium exposure had any adverse effect on glomerular function. The renal variables were not correlated with the blood level of cadmium, probably because blood levels are more affected by current exposure than are urinary cadmium concentrations.[12] Since no detailed calcium

balance study was done, the finding of an association between urinary calcium and cadmium excretion must be interpreted with caution. Human exposure to cadmium can cause higher urinary excretion of calcium.[13] Our results suggest that the cadmium body burden of this general population sample might even at a fairly low level raise renal calcium wasting. Whether this effect may be strong enough to exacerbate age-related osteoporotic changes in women with low dietary calcium intake deserves further study. This hypothesis, however, is supported by stepwise regression analysis with the same determinants as in table I which showed a synergistic effect of the cadmium body burden on the age and sex related rise in serum alkaline phosphatase (results not shown). The health significance of the renal tubular dysfunction associated with a cadmium body burden lower than that usually considered critical in adult male workers[14] is still unknown. In subjects occupationally exposed to cadmium, the presence of tubular dysfunction, more pronounced than that found in the present population, may predict the subsequent development of some degree of renal insufficiency.[15] Furthermore, no chelation treatment presently available can reduce the cadmium body burden in human beings. Therefore, it seems reasonable to propose that the exposure of the general population to cadmium should be kept at a level preventing the occurrence of tubular dysfunction.

The dose-response relations we found make it difficult to ascertain with precision the cadmium body burden that carries no renal risk for the general population. We suggest, however, that when the urinary excretion of cadmium is below 2 μg/24 h, the risk of occurrence of renal effects remains low. A similar conclusion was reached when the statistical analysis was restricted to subjects without any health disorder. The critical effect level, however, may be lower in diabetic subjects. In the study population (excluding workers occupationally exposed to heavy metals) 10·8% of subjects excreted more than 2 μg cadmium per 24 h (table III). Since cadmium is a cumulative toxin, it is not surprising that the proportions of subjects excreting more than 2 μg/24 h were greater in the older age groups.

Our conclusion from this study differs greatly from those of our previous studies on adult male workers (aged 20–55 years) in whom the level of cadmium excretion showing no detectable adverse effect was about 10 μg/g creatinine,[14] corresponding to a cadmium concentration in renal cortex of about 200 ppm.[8] This difference confirms the healthy worker effect that usually operates in industrial populations, leading to underestimates of the health risk for the general population.

The mean urinary cadmium excretion in this study (geometric mean 0·84 μg/24 h) is similar to that (0·83 μg/24 h) of adult residents of Shipham, a village in the UK where the soil was contaminated by cadmium from old mining slag heaps. No adverse health effects that could be attributed to cadmium were found in Shipham.[16] Mean β_2-microglobulin excretion, however, was greater in Shipham residents (77 μg/24 h) than in a control population (55 μg/24 h) in the neighbouring area who had lower cadmium excretion. Furthermore, the mean β_2-microglobulin excretion in our population (92 μg/24 h) was higher than that in Shipham. The Shipham study was based on volunteers, who may not be representative of the population of the exposed village as a whole, the response rate fell with age and length of residence in the contaminated area, and the control subjects were not examined during the same time period as the Shipham residents.

On the basis of current knowledge[1] on the toxicokinetics of cadmium (oral absorption rate 5%, daily excretion rate 0·005% of body burden, and a third of the latter in the kidneys), we estimate that a urinary cadmium excretion of 2 μg/24 h corresponds to a mean renal cortex concentration of about 50 ppm (wet weight). In non-smokers, this level is reached after 50 years of an oral daily intake of about 1 μg/kg body weight. Our results suggest that even for non-smokers, the current daily dietary cadmium intake by the general population in Belgium (median 0·22 μg/kg; 95th percentile 0·60 μg/kg)[17] does not offer a large safety margin. Among people aged over 60 years, about the same proportion (16%) of non-smokers and smokers excrete more than 2 μg cadmium per 24 h.

Thus, about 10% of the general population of Belgium have an internal dose of cadmium sufficient to cause slight renal dysfunction. This conclusion probably applies to the other industrialised countries with similar patterns of production and uses of this metal.

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