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Effects of exposure to cadmium on calcium metabolism: a population study

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Abstract

The objective was to investigate the hypothesis that environmental exposure to cadmium may affect calcium metabolism in the population at large. The 1987 participants (965 men and 1022 women), from 20 to 80 years old, constituted a random sample of the population of four Belgian districts. The urinary excretion of cadmium, a measure of lifetime exposure, averaged 9·3 nmol/24 h in men (range 0·4–324 nmol/24 h) and 7·1 nmol/24 h (range 0·1–71 nmol/24 h) in women. Serum alkaline phosphatase activity and the urinary excretion of calcium correlated significantly and positively with urinary cadmium excretion in both men and women, and serum total calcium concentration negatively with urinary cadmium excretion in men only. The regression coefficients obtained after adjustment for significant covariates indicated that when urinary cadmium excretion increased twofold, serum alkaline phosphatase activity and urinary calcium excretion rose by 3–4% and 0·25 mmol/24 h respectively, whereas in men serum total calcium concentration fell by 6 μmol/l. After adjustment for significant covariates the relation between serum total calcium concentration and urinary cadmium excretion was not significant in women. The findings suggest that even at environmental exposure levels calcium metabolism is gradually affected, as cadmium accumulates in the body. The morbidity associated with this phenomenon in industrialised countries remains presently unknown and requires further investigation.

The exposure of human populations to cadmium via the environment is raising much concern, as cadmium is a heavy metal with high toxicity and accumulates in the body.[1]

Cadmium interferes with the metabolism of vitamin D, calcium, and collagen, and its accumulation may lead to osteomalacia and osteoporosis.[1,2] These effects are usually considered to be late manifestations of severe cadmium poisoning, and have been seen in exposed workers and in malnourished subjects.[1–4] The quantitative dose-response relation for the effects of cadmium on calcium and bone metabolism, however, remains presently unknown. The present report, part of a cross sectional study on the effects of cadmium on public health,[5–7] investigated whether environmental exposure to cadmium influences calcium metabolism in the population at large.

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Methods

SUBJECTS

As described elsewhere,[5–7] the 2327 subjects (age range from 20 to 79) constituted a random sample of the population of four Belgian districts selected to provide a wide range of environmental exposure to cadmium. Subjects were excluded from the present analysis when not all relevant measurements were available (n = 248), when 24 hour urine samples were judged under or over collected by previously published criteria (n = 44),[8] or when either occupational exposure to heavy metals (n = 41) or smoking habits (n = 7) could not be ascertained from a self administered questionnaire.

FIELD WORK

All participants were visited at home on several occasions. Body weight was determined with indoor clothing. A self administered questionnaire was used to inquire about the subjects' medical history, their current and past occupations, smoking habits, alcohol consumption, intake of medicines, and about the menstrual state of female participants. The subjects collected a 24 hour urine sample in a wide neck metal free polyethylene container. At a separate home visit, usually within two weeks of the urine collection, 20 ml of venous blood were drawn.

BIOCHEMICAL MEASUREMENTS

The biochemical techniques and procedures for quality control have been described in detail elsewhere.[5] Alkaline phosphatase activity was determined on a COBAS-BIO centrifugal analyser (Roche Diagnostics).[9] Serum and urinary calcium concentrations were measured by complexiметry,[10] and urinary cadmium by electrothermal atomic absorption spectrometry using a stabilised temperature platform furnace and Zeeman background correction.[5]

STATISTICAL ANALYSIS

For statistical analysis the SAS software package was used.[11] Where appropriate a logarithmic transformation was applied to normalise the distribution of the biochemical measurements. Statistical methods included Student's *t* test, analysis of covariance, and single and multiple linear regression.

Significant covariates were traced by stepwise regression. Age adjustments included both a linear and quadratic term of age.

Results

CHARACTERISTICS OF THE PARTICIPANTS

The present analysis included 965 men and 1022 women. Table 1 summarises their anthropometric characteristics and biochemical results.

Current smoking was reported by 471 men (median tobacco consumption equivalent to 18 cigarettes a day), and 354 women (median 20 cigarettes a day), and regular alcohol intake by 357 men (median alcohol consumption 20 g/day) and 142 women (median 16 g/day). Fifty two men and 122 women were on treatment with diuretics and 210 women took the contraceptive pill. The study population included 462 postmenopausal women.

SERUM ALKALINE PHOSPHATASE ACTIVITY

Serum alkaline phosphatase activity (SAPA) was positively associated with urinary cadmium excretion (UCd) in both sexes (figure). The single correlation coefficient was 0·10 ($p = 0·003$) in men and 0·30 ($p < 0·001$) in women.

Age and body mass index combined explained 3% ($p < 0·001$) of the variance of SAPA in men, and 21% ($p < 0·001$) in women (table 2). The SAPA was independently related to γ-glutamyltranspeptidase activity, to being a regular consumer of alcoholic beverages, and to the daily alcohol consumption (g/day) (table 2). These three covariates combined explained 5% ($p < 0·001$) of the variance of SAPA in men, and 8% of the variance ($p < 0·001$) in women.

After adjustment for significant covariates SAPA remained positively associated with UCd in men (partial $R^2 = 0·017$; $p < 0·001$) and women (partial $R^2 = 0·004$; $p = 0·02$). The slopes of these relations (table 2) indicated that a twofold increase in UCd was accompanied by a rise in SAPA by around 3–4% (95% confidence interval from 2 to 6% in men, and from 1 to 5% in women).

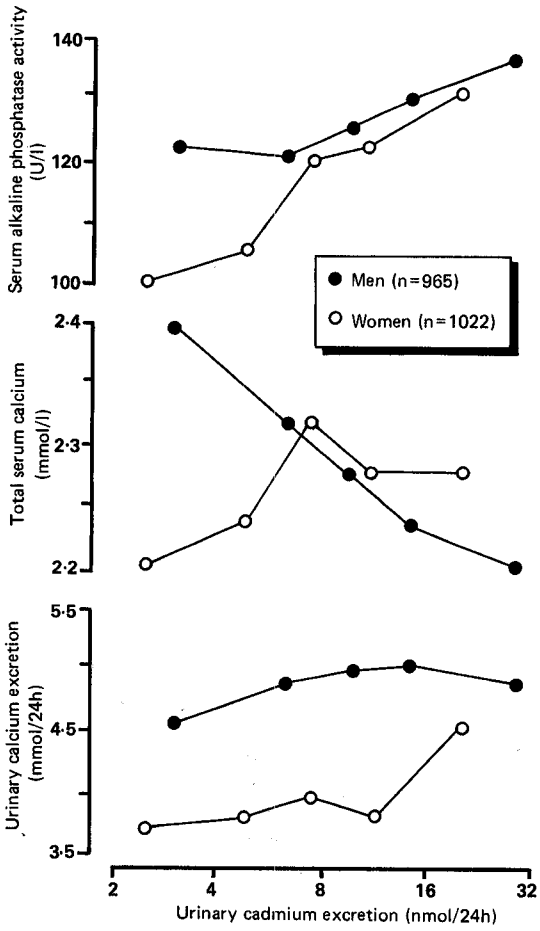
SERUM TOTAL CALCIUM CONCENTRATION

Serum total calcium concentration (STCa) was negatively associated with UCd in men (figure); the

Table 1 Characteristics of the participants

	Men (n = 965)	*Women (n = 1022)*
Clinical measurements:		
Age (y)	48·4 (15·9)	47·6 (16·4)
Body mass index (kg/m²)	25·5 (3·6)	25·3 (5·1)
Serum measurements:		
Alkaline phosphatase (U/l)†	120 (33–857)	109 (22–527)***
γ-GT (U/l)†	14 (2–252)	10 (2–335)***
Total calcium (mmol/l)	2·37 (0·10)	2·36 (0·11)
Magnesium (mmol/l)	1·01 (0·07)	1·00 (0·08)
Urinary measurements:		
Volume (l/24 h)	1·65 (0·70)	1·67 (0·74)
Cadmium (nmol/24 h)†	9·3 (0·4–324)	7·1 (0·1–70·8)***
Calcium (mmol/24 h)	4·86 (2·68)	3·95 (2·20)***
Creatinine (mmol/24 h)	15·4 (4·0)	10·5 (2·7)***

Values are means (SD). For logarithmically transformed distributions (†) the geometric mean and range are presented.
***$p < 0·001$ for difference between men and women.



Serum alkaline phosphatase activity (top panel), serum total calcium concentration (middle panel), and urinary excretion of calcium (bottom panel) in quintiles of the body burden of cadmium (estimated from the urinary excretion of cadmium). The analyses were performed in men and women separately.

correlation coefficient was $-0{\cdot}17$ ($p < 0{\cdot}001$). The single correlation coefficient between STCa and UCd in women was positive ($r = 0{\cdot}06$; $p = 0{\cdot}05$).

After adjustment for significant covariates (table 2), an independent and negative correlation was found between STCa and UCd in men (partial $R^2 = 0{\cdot}01$; $p < 0{\cdot}001$). The slope of this relation (table 2) indicated that a twofold rise in UCd was associated with a decrease in STCa of 6 μmol/l (95% confidence interval from 3 to 12 μmol/l). In women the partial correlation between STCa and UCd ($r = 0{\cdot}004$), when adjusted for significant covariates, was far from significant.

CALCIURIA

Urinary calcium excretion (UCa) tended to be positively associated with UCd in both sexes (figure). The single correlation coefficient was 0·05 ($p = 0{\cdot}1$) in men and 0·10 ($p = 0{\cdot}001$) in women.

After adjustment for significant covariates (table 2), an independent and positive correlation was found between UCa and UCd in the two sexes (partial $R^2 = 0{\cdot}01$; $p < 0{\cdot}001$ in both men and women). The slopes of these relations (table 2) indicated that a twofold rise in UCd was associated with an increase in UCa by approximately 0·25 mmol/24 h (95% confidence interval from 0·13 to 0·45 mmol/24 h in men, and from 0·10 to 0·39 mmol/24 h in women).

EXPOSURE AT WORK

Possible exposure to heavy metals at work was reported by 304 men; UCd in these subjects averaged 13·7 nmol/24 h (range: 0·7–324 nmol/24 h) and was higher ($p < 0{\cdot}001$) than in the other men (mean: 7·9 nmol/24 h; range: 0·4–34 nmol/24 h). Excluding men with exposure to cadmium at work, however, did not materially alter the size of the partial regression coefficients for UCd shown in table 2. For the relation with SAPA the partial regression coefficient was $0{\cdot}048 \pm 0{\cdot}018$ log U/l/log nmol/24 h ($p = 0{\cdot}01$); for STCa $-0{\cdot}011 \pm 0{\cdot}015$ mmol/log nmol/24 h; and for UCa $1{\cdot}313 \pm 0{\cdot}358$ mmol/nmol ($p = 0{\cdot}003$).

Discussion

In the present population study, three indices of calcium metabolism were related to the urinary excretion of cadmium, a reliable index of lifetime exposure to cadmium.[1] The direction of the correlations was positive for SAPA and for UCa in both sexes, and negative for STCa in men.

Liver and bone isoenzymes constitute the principal fractions of alkaline phosphatase activity in the serum of normal adults.[12,13] Serum alkaline phosphatase activity increases with age, mainly due to an increased release of the enzyme from the hepatocytes beyond age 50.[13,14–16] When SAPA phosphatase is high, normal serum γ-glutamyltranspeptidase activity suggests an involvement of bone tissue. In the present analysis the effects of ageing and liver dysfunction on alkaline phosphatase activity were accounted for. Adjustments for liver dysfunction were effected based on serum γ-glutamyltranspeptidase activity, reported alcohol intake, and the amount of alcohol consumed each day (g/day).

Serum total calcium concentration and the UCa decrease with advancing age.[17] Diuretics increase STCa, lower calciuria, and improve calcium balance.[18–21] Sex steroids, including oral contraceptives, stimulate bone formation and decrease SCa and UCa, whereas withdrawal of sex hormones after the menopause leads to opposite effects.[22–24] The effects of age, diuretics, the contraceptive pill, and menopause on STCa and calciuria were confirmed in the present

Table 2 Multiple regression analysis

	Men			*Women*		
	SAPA	*STCa*	*UCa*	*SAPA*	*STCa*	*UCa*
R^2	0·067	0·099	0·142	0·284	0·045	0·095
Intercept	2·164	2·411	−3·296	1·756	2·363	−3·168
			Regression coefficients			
Log urinary cadmium	0·056	−0·021	0·972	0·035	NS	0·840
Age	−78E–4	−19E–4	0·077	−13E–4	61E–5	0·076
Age^2	78E–8	94E–8	−13E–4	40E–6	−17E–6	−98E–5
Body mass index	24E–4	27E–4	0·113	29E–4	NS	NS
Log serum γ-GT	0·094	—	—	0·145	—	—
Drinking alcohol*	−0·013	—	—	−0·029	—	—
Alcohol intake (g/day)	−48E–5	—	—	−36E–5	—	—
Serum calcium	—	—	0·402	—	—	1·697
Serum magnesium	—	—	2·934	—	—	1·438
On diuretics*	NS	0·037	−1·402	NS	0·037	−1·052
On contraceptive pill*	—	—	—	NS	−0·031	−0·321
Being menopausal*	—	—	—	NS	0·046	NS

Only significant regression coefficients are presented (exponent of base 10 given, where appropriate); NS = non-significant; — = not considered for entry into the model. Bracketed covariates were tested simultaneously for entry into the model.
SAPA = Serum alkaline phosphatase activity (logarithmically transformed); STCa = serum total calcium concentration; UCa = urinary calcium excretion; GT = γ-glutamyltranspeptidase activity.
*Coded 0 or 1 for condition being present or absent.

population; they were taken into account when the relations between STCa and UCa and the body burden of cadmium were investigated (table 2). Acute hypermagnesaemia probably inhibits the secretion of parathyroid hormone[25] and magnesium ions compete with calcium for reabsorption in the loop of Henle.[26] These mechanisms[25 26] may explain why, in our study, a positive relation was found between serum magnesium concentration and UCa (table 2).

Interference with the metabolism of calcium is usually considered to be a late manifestation of severe cadmium intoxication. By contrast with this long held belief, the associations shown in the figure and the fit obtained with linear regression (table 2) suggest that no threshold exists, and that the effects on calcium metabolism develop gradually, as during life cadmium accumulates in the body. Indeed, the slopes of the independent relations reported in table 2 show that when UCd doubles SAPA and UCa rise in both sexes by 3–4% and 0·25 mmol/24 h respectively, whereas SCa in men falls by 6 μmol/l. These effects on calcium metabolism may be due to renal tubular dysfunction, or the development of vitamin D resistance, or both.[1 2]

Whether the small metabolic effects seen in the present study also lead to clinically manifest morbidity in the population at large remains to be elucidated. Among the Shipham residents[27] and among British workers[28] exposure to cadmium was not associated with excess mortality from fractures. On the other hand, bone lesions have been experimentally induced by cadmium in several species of laboratory animals, in whom the combined effects of cadmium, poor nutrition, and low vitamin D intake proved to be particularly harmful.[2] The results from these animal studies are supported by epidemiological findings. Indeed, about 50 cases of osteomalacia or osteoporosis have been seen among cadmium exposed labourers world wide,[2] and some 150 Japanese subjects have developed bone lesions as a consequence of severe exposure to cadmium via the environment.[2] The incidence of these bone effects appears to have peaked 30 to 40 years ago when dietary intake of nutrients was often deficient in countries with reported cases. In developed countries and in modern times, however, many subjects suffer from decalcification of the skeleton as a result of ageing, or hormonal or nutritional deficiencies, or both.[17] It is therefore conceivable that in these subjects, who are at higher risk of skeletal deformation, environmental exposure to cadmium through its effect on calcium metabolism may precipitate overt bone disease and contribute to osteoporosis and its consequences—for example, lower forearm fractures, compression fractures of the vertebrae, and hip fractures. As the UCas found in our present study were comparable with those of other industrialised countries,[29 30] this hypothesis is an important public health issue and requires further investigation.

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Appendix

CONVERSION OF UNITS

Cadmium:	1 nmol = 112·4 ng
Calcium:	1 mmol = 40·1 mg
Creatinine:	1 mmol = 113·1 mg
Lead:	1 μmol = 207·1 μg
Magnesium:	1 mmol = 24·3 mg

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