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Health effects of environmental exposure to cadmium in a population study

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Summary:

The Cadmibel Study is a cross-sectional population study, which investigated the hypothesis that environmental exposure of the population to cadmium would result in health effects. The 2,327 participants constituted a random sample of the population of four Belgian districts, chosen to provide a wide range of environmental exposure to cadmium.

The urinary cadmium excretion, a measure of lifetime exposure, averaged 9.3 nmol/24h in men (range 0.4–325 nmol/24h) and 7.2 nmol (0.1–71 nmol/24h) in women. The Cadmibel Study refuted the hypothesis that exposure to cadmium would lead to an increase in BP and in the prevalence of hypertension and other cardiovascular diseases. Serum alkaline phosphatase activity and the urinary excretion of calcium correlated significantly and positively with urinary cadmium in both sexes. These findings suggest that the calcium metabolism is gradually affected, as cadmium accumulates in the body. Furthermore, several markers of renal tubular function (urinary excretion of retinol binding protein, N-acetyl-beta-glucosaminidase, beta$_2$-microglobulin and aminoacids) were significantly and positively associated with urinary cadmium. There was a 10% probability of abnormal values of these markers of tubular function when urinary cadmium exceeded ±20 nmol/24h. However, the morbidity associated with the functional changes, observed in the Cadmibel Study, remains presently unknown and requires further investigation, preferably in a longitudinal population studies.

Introduction

Cadmium is a heavy metal with high toxicity that after inhalation or gastrointestinal absorption accumulates in the human body.[1,2] The release of cadmium into the environment has considerably increased in most industrialised countries during the second part of this century. Cadmium may therefore endanger health not only in exposed workers but also in the population at large.

Belgium, one of the principal cadmium producers in Europe, has areas with a high degree of cadmium pollution mainly as a consequence of past emissions; the latter are only a short distance away from districts with lower environmental exposure levels. In view of this particular geographical situation, and because the environmental exposure of human populations to cadmium is causing much concern, a cross-sectional epidemiological study was undertaken in Belgium to elucidate the health effects of cadmium in the population at large (Cadmibel Study).[3–9] This article gives a short account of the observed effects on the cardiovascular system, on calcium and bone metabolism and on the kidney.

Design of the Cadmibel Study

As described in detail elsewhere,[3] the study was conducted from 1985 to 1989 in four Belgian districts, representing two areas with low and two with high environmental exposure to cadmium. For each exposure level a rural and urban district were selected. In each district a random sample of the households was identified with the goal to recruit an equal number of subjects in each of six subgroups by sex and age (20–39, 40–59 and ⩾60 years).

A total of 2,327 subjects took part in the study. They were visited at home on several occasions. At each of two separate home visits the BP was measured five times after one minute rest in the sitting position. The BP measurements were followed by a pulse rate count over one minute and a measurement of body weight and height. The participants were asked to complete a self-administered

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questionnaire, inquiring into their medical history, current and past occupations, smoking habits, consumption of alcohol, and intake of medications. They were also asked to collect a 24h urine sample in a wide neck metal-free polyethylene container. At a separate occasion, but usually within two weeks after the urine collection, a physician or nurse visited the households to withdraw a venous blood sample.

The cadmium measurements were performed by electrothermal atomic absorption spectrometry.[3] Two laboratories shared the burden of the biochemical determinations but for each measurement all samples were processed by the same laboratory.[3] In the two laboratories all tests were performed in duplicate and certified reference standards were run along each series of sample. In 10% of samples, the measurements of cadmium were performed in both laboratories. A series of measurements was repeated whenever the precision of the duplicate determinations or the accuracy of the measurements of the standards fell outside the published limits,[3] or whenever one sample differed more than 10% among the two laboratories.

Cardiovascular effects

The concept that exposure to cadmium may be a causal factor in human hypertension is mainly rooted in animal experiments.[10,11] Indeed, studies in exposed workers,[12] in patients with hypertension,[12] and in smaller groups of individuals with low exposure[12–15] have failed to corroborate the hypothesis. In addition, some of the positive studies relied on less accurate techniques to measure cadmium, or did not satisfactorily control for possible confounders, such as smoking.[12] Thus, more than two decades after Schroeder[10,11] published his pioneering animal studies, the hypothesis that cadmium exposure would cause hypertension, still awaited confirmation or rejection at the population level.

The hypothesis that environmental exposure to cadmium would increase both BP and the prevalence of hypertension and other cardiovascular diseases was investigated in 2,086 Cadmibel participants, in whom all relevant measurements could be obtained.[7] They were on average 48 ± 16 (SD) years old (range 20–88 years). Pulse rate averaged 75 ± 9 beats/min, urinary volume 1.66 ± 0.72 l/24h and the urinary sodium/potassium ratio 2.7 ± 1.3.

The cadmium levels in blood (8.5 vs. 11.0 nmol/1) and urine (7.2 vs. 8.7 nmol/24h) were significantly ($P < 0.001$) raised in the two high compared with the two low exposure areas ($P < 0.001$). SBP was similar in both rural areas but in the urban area with low exposure SBP was 5 mmHg ($P < 0.001$) lower than in the town with known sources of cadmium emissions. DBP was similar in the four districts. Adjustment of the SBP for blood and urinary cadmium did not remove the difference in systolic pressure between both urban areas, suggesting that it was not related to cadmium pollution of the environment. Further analyses in individual subjects showed that their BP was not positively correlated with blood and urinary cadmium. Because on average both SBP and the body burden of cadmium were lowest in the control urban area, the possibility was also investigated that a threshold cadmium concentration would exists above which BP suddenly rises. These analyses showed that there was no threshold phenomenon and that, at least for the ranges observed in the Cadmibel Study,[7] a linear model was adequate for studying the association between BP and blood and urinary cadmium.

Hypertension was defined in the Cadmibel Study as a SBP in excess of 140 mmHg, or as a DBP exceeding 90 mmHg, or as being on antihypertensive treatment regardless of the measured BP level.[7] Cardiovascular diseases (reported by a self-administered questionnaire) included ICD codes (8th revision) 390–450, and ischaemic heart disease ICD codes 410–414 and 425–429. The prevalence of hypertension and of other cardiovascular diseases was similar in the four districts and was not significantly correlated with the level of cadmium in blood and urine.

In agreement with the Cadmibel findings[7] a large Japanese cohort study[16] has demonstrated that the mortality from cerebrovascular accidents, and hypertension tended to be lower in four polluted compared with four control districts. Similarly, in a cohort of occupationally exposed workers[17] no excess mortality from hypertension was found, but rather a decreased mortality from cerebrovascular causes. By contrast, among the residents of the cadmium-polluted village of Shipham (UK), there was in comparison with a nearby control village a slight excess mortality from cardiovascular causes, and a significantly elevated mortality from cerebrovascular disease.[18] However, in the Shipham study the number of deaths was small and individual exposure measurements were not available.[18] Recently, the NHANES II Survey (Second National Health and Nutritional Examination Survey)[19] in the USA showed that the regression coefficients between BP and the urinary cadmium levels were not significant after hypertensive patients had been removed from the analysis. Many of the hypertensives included in the NHANES II Survey[19] were on diuretics, which increase the urinary cadmium output and thereby confounded the relationship between BP and urinary cadmium.

Effects on calcium metabolism

Cadmium interferes with the metabolism of vitamin D, calcium and collagen, and its accumulation may lead to osteomalacia and osteoporosis.[1,20] These effects are usually considered to be late manifestations of severe cadmium poisoning and have been observed in exposed workers and in malnourished subjects.[1,20]

Because it remained uncertain whether low-level cadmium exposure influences the homeostasis of calcium and the metabolism of bone tissue in the population at large, the quantitative dose-response

relationships with the internal cadmium dose were examined in the Cadmibel Study.[6] Three indices of calcium metabolism were found to be related to the urinary excretion of cadmium, an indirect index[1,2] of the integrated lifetime exposure to cadmium (Figure 1). These correlations were positive for serum alkaline phosphatase activity and for urinary calcium excretion in both sexes, and negative for serum total calcium in men.[6] The regression coefficients obtained after adjustment for significant covariates indicated that when urinary cadmium increased twofold, serum alkaline phosphatase and urinary calcium rose by 3–4% and 0.25 mmol/24h, respectively, while in men serum total calcium fell by 6 μmol/l.[6]

Whether the small effects on calcium metabolism observed in the Cadmibel Study also lead to clinically manifest morbidity in the population at large remains to be elucidated. Among the Shipham residents[18] and among British workers[17] cadmium exposure was not associated with an excess mortality from fractures. On the other hand, bone lesions have been experimentally induced by cadmium in several species of laboratory animals in which the combined effects of cadmium, poor nutrition and low vitamin D intake proved to be particularly harmful.[20] The results from these animal studies are supported by epidemiological findings. Indeed, about 50 cases of osteomalacia or osteoporosis have been observed among cadmium-exposed labourers worldwide,[20] and approximately 150 Japanese subjects have developed bone lesions as a consequence of severe exposure to cadmium via the environment.[20] The incidence of these bone effects appears to have peaked 30–40 years ago, when dietary intake of nutrients was often deficient in countries with reported cases. However, in developed countries and in modern times, many subjects suffer from decalcification of the skeleton as a result of ageing, and/or hormonal or nutritional deficiencies.[21] It is therefore conceivable that in the latter subjects, who are at higher risk of skeletal deformation, environmental exposure to cadmium, through its effect on the calcium metabolism, may precipate overt bone disease and contribute to osteoporosis and its consequences, e.g. forearm fractures, compression fractures of the vertebrae or hip fractures. Because the urinary cadmium levels observed in the Cadmibel Study were comparable with those of other industrialised countries, the latter hypothesis is an important public health issue and requires further investigation.

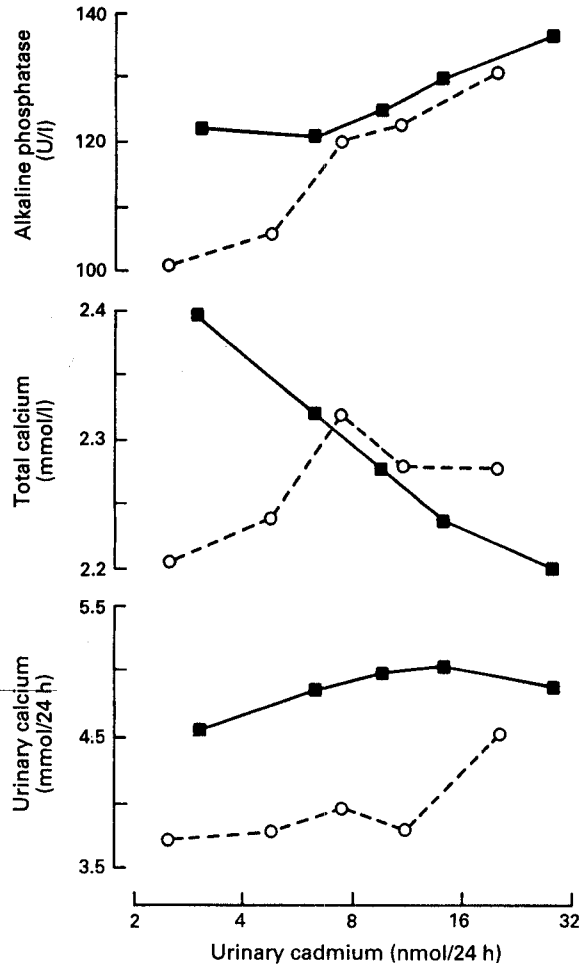

Figure 1 Serum alkaline phosphatase activity (upper), serum total calcium (middle) and the urinary excretion of calcium (lower) in quintiles of the body burden of cadmium (estimated from the urinary excretion of cadmium) in the cross-sectional Cadmibel Study. The analyses were performed in men (■), $n = 965$, and women (○), $n = 1,022$, separately. (For details see ref. 6.)

Renal effects

It is generally accepted that for the general population the kidney is the critical organ (i.e. the organ in which the first adverse effects occur) for cadmium toxicity.[1] Studies carried out in workers have previously demonstrated that one of the earliest signs of cadmium nephropathy is an increased proteinuria. The latter results from a decreased tubular reabsorption of low molecular weight proteins (e.g. $beta_2$-microglobulin, retinol binding protein), and possibly also from an increased glomerular filtration of high molecular weight proteins (e.g. albumin, transferrin).[22–25] The microproteinuria, which in workers occurs when the cadmium level in the kidney cortex exceeds 200 ppm, or in urine 10 μg per gram creatinine, is irreversible.[24]

The Cadmibel Study[4] has shown that in the population at large several markers of renal tubular dysfunction (urinary excretion of retinol binding protein, N-acetyl-beta-glucosaminidase, $beta_2$-microglobulin and aminoacids) were significantly and positively associated with urinary markers (Figure 2). There was a 10% probability of abnormal values of these renal markers when the cadmium excretion exceeded ± 20 nmol/24h.[4] A similar study in the Netherlands[26] has recently confirmed the Cadmibel findings. Furthermore, the Cadmibel Study has revealed that several of the renal markers may have already become abnormal at urinary cadmium levels found in a sizable proportion (≥10%) of the general population as a consequence of environmental exposure.[4]

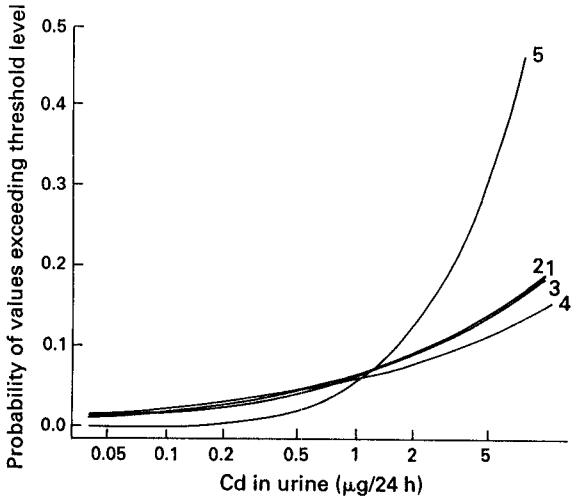

Figure 2 Probability of renal dysfunction as estimated from the urinary excretion of microproteins, aminoacids and calcium. 1 = retinol binding protein; 2 = N-acetyl-beta-glucosaminidase; 3 = beta-microglobulin; 4 = amino acids; 5 = calciuria. (For details see reference 4).

Conclusions

The Cadmibel Study showed that even low level environmental exposure to cadmium entails discernable health effects.[3–9] In industrialised countries, such as Belgium, 10% of the general population have an internal dose of cadmium sufficient to cause slight renal tubular dysfunction.[4] This percentage may even be higher in diabetic patients who are predisposed to develop renal disturbances[4] and in populations with a particularly high degree of environmental exposure, such as the inhabitants of the polluted rural areas included in the Cadmibel Study.[9]

The morbidity associated with the effects of low level environmental cadmium exposure on the kidney and on the calcium and bone metabolism remains to be clarified. This is now being done in a longitudinal follow-up of the Cadmibel participants living in a rural area. The rural areas studied in the framework of the Cadmibel Study show an important gradient in environmental cadmium pollution and are therefore particularly suited for a follow-up study (PheeCad Study, i.e. Public Health and Environmental Exposure to Cadmium Study).

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