

Cadmium overload and toxicity

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Abstract

Studies suggest that cadmium is associated with several clinical complications, primarily renal dysfunction and bone disease, but also some cancers. Cadmium toxicity has been associated with clinical manifestations at exposure levels that are well below the limits set by the World Health Organization. Here I review the OSCAR study, which demonstrates an association between environmental and occupational cadmium exposure and renal tubular damage, as well as the Cadmibel study, a cross-sectional population study demonstrating an association of cadmium exposure with renal dysfunction. The paper also reviews the association of end-stage renal disease prevalence with occupational and environmental exposure to cadmium in the Swedish population of Kalmar County. Renal tubular damage was shown to develop at levels of exposure much lower than previously thought. Cadmium-induced tubular proteinuria is irreversible, and continued exposure may lead to glomerular damage with decreased glomerular filtration rate. Itai-itai disease in the Jinzu river basin is discussed, as are the implications of low-level cadmium exposure in the PheeCad project. Cadmium accumulates in bone and is associated with osteomalacia and osteoporosis. Other bone-seeking trace elements, such as chromium, lanthanum, strontium and zinc, are of concern because of low level environmental, occupational or clinical exposure. As techniques are perfected for detecting smaller amounts of trace elements in various tissues in the body, investigators are finding that the threshold for toxicity from trace elements is much lower than expected. Further research on cadmium is necessary to reveal the mechanisms of toxicity and true environmental and occupational exposure limits.

Keywords: cadmium; glomerular dysfunction; osteoporosis; tubular proteinuria

Introduction

Environmental and occupational exposure to cadmium is implicated in a number of clinical complications, primarily renal dysfunction and bone disease, but also some cancers [1]. Even at very low levels of exposure, this heavy metal can cause kidney damage [2].

Battery factories, zinc smelters, pigment plants and soldering activities cause occupational exposure to cadmium. The most significant contemporary source results from the production of nickel–cadmium batteries [2,3]. Occupational exposure occurs mainly through the respiratory route, but may also involve the gastrointestinal route to a lesser degree. Environmentally, the main source of cadmium exposure is tobacco smoke for the smoker, followed by diet for the non-smoker [1]. However, substantial environmental exposure may also result from zinc smelters, such as the Avonmouth plant near Bristol in the UK, which, according to the owners, emitted ~2000 kg cadmium/year into air and 600 kg cadmium/year into water (1996–1997) [4]. Cadmium absorption in the lungs is 10–50%, whereas gastrointestinal absorption is less than a few percent. As a result, blood cadmium concentrations of smokers (~1–4 µg/l) are ~4- to 5-fold higher than those of non-smokers. Dietary cadmium is a growing concern. Cadmium gets into soil from the use of fertilizers and as a result of zinc-mining processes, in which cadmium is a discarded impurity. For example, cadmium concentration in Swedish soil has increased continuously during the last century—at a rate of 0.2% per year in recent years—and high-fibre diets have been shown to result in increased dietary cadmium [1]. Cadmium concentrations are also high in certain species of shellfish and mushrooms. Cadmium accumulates predominantly in the kidney and liver, but is also found in other tissues including bone and placenta. In general, exposure to cadmium causes concentrations in blood, urine and kidney to be higher in women. Increasing evidence suggests that cadmium kinetics are dose-dependent [1].

The elimination half-life of cadmium is 10–30 years [1]. The cadmium concentration in urine (U-Cd) is influenced primarily by the body burden and is proportional to the concentration in the kidneys; thus, it

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is a useful estimate for long-term exposure. During occupational exposure, the concentration of cadmium in blood (B-Cd) increases fairly rapidly and mainly reflects recent exposure. However, cadmium in blood has a slow component with a very long half-life (~7–16 years) [5]. Therefore, after previous high occupational exposure, B-Cd can provide a good estimate of the body burden, provided that a few years have elapsed since the exposure [6].

Cadmium exposure is responsible for a broad spectrum of health effects that include cancer. The evidence establishing cadmium as a carcinogen in laboratory animals dates back to 1960. However, more recent studies in humans are less conclusive. Still, studies demonstrate varying degrees of association between cadmium exposure and primarily lung and prostate cancer [1].

Occupational and environmental exposure to cadmium have been implicated in renal dysfunction. Several sensitive methods exist for determining the tubular function of the kidneys. The initial cadmium-induced tubular dysfunction is manifest as tubular proteinuria, usually detected as an increased urinary excretion of low molecular weight proteins. The most common marker of tubular proteinuria is β_2 -microglobulin, although this marker has some disadvantages because it is unstable in acid urine. Tubular proteinuria is also commonly indicated by the appearance of other markers, such as *N*-acetyl- β -D-glucosaminidase (NAG) and α_1 -microglobulin (protein HC), the latter having the advantage of being both sensitive and stable [1].

Cadmium-induced tubular proteinuria is irreversible. Continued exposure to cadmium may cause tubular dysfunction to progress to glomerular damage with decreased glomerular filtration rates (GFRs). Severe cadmium-induced nephrotoxicity may manifest as renal glucosuria, aminoaciduria, hyperphosphaturia, hypercalciuria, polyuria and decreased ability to buffer acid load [1].

Prolonged exposure to cadmium may also lead to bone diseases. This was first reported in Japan, where cadmium-induced osteomalacia was found to be responsible for itai-itai (ouch-ouch) disease [7]. Cadmium exposure has also been associated with osteoporosis [8,9] and renal stones [10]. Cadmium is thought to have an indirect effect on the normal activation of vitamin D₃ [7]. However, cadmium is also known to accumulate in bone [11] and there is increasing evidence that cadmium may act independently on bone tissue [7].

Clinical implications: renal damage

Cadmium-exposed solderers

Several studies have demonstrated a decreased GFR, evidenced by changes in inulin clearance rates. Studies in cadmium-exposed solderers confirm these results. In a study of 46 workers exposed to cadmium-containing

soldering materials, kidney lesions induced by cadmium were found to be irreversible with a prevalence that appeared to be dose-dependent. Glomerular damage also correlated with loss of tubular reabsorption. There was a significant correlation between cumulative exposure and U-Cd ($r=0.54$, $P=0.0001$), and a good correlation between the exposure to cadmium and B-Cd ($r=0.44$, $P=0.002$) [12].

After an exposure period of at least 5 years (occurring between 1955 and 1978), study participants were evaluated initially in 1984, with follow-up examinations in 1989 and 1993. Cadmium-exposed solderers were examined for evidence of tubular proteinuria, blood and urine cadmium levels, and GFR. In the 1993 follow-up examination, prevalence of glomerular damage (GFR <80% of reference) was 3.4% at B-Cd concentrations below 50 nmol/l, 33% at B-Cd concentrations of 50–75 nmol/l and 100% prevalence at B-Cd concentrations exceeding 75 nmol/l. There was also a clear association between GFR and tubular proteinuria, as evidenced by relative β_2 -microglobulin clearance. Accumulation of cadmium in the kidney is likely to be the cause of tubular damage with proteinuria, enzymuria and decreased GFR [12].

The OSCAR study: osteoporosis with cadmium as a risk factor

In a study of over 1000 individuals who were environmentally or occupationally exposed to cadmium, renal tubular damage was found to develop at lower levels of cadmium body burden than previously anticipated. The results showed an increased prevalence of 10% tubular proteinuria at U-Cd concentrations of 1.0 nmol/mmol creatinine. Urinary protein HC was used to detect early renal damage. A clear dose-response relationship between cadmium and the prevalence of increased protein HC in urine was demonstrated. During the investigation, it was discovered that several environmentally exposed individuals had also worked in the battery plant, although the dose-response relationship remained even after the occupationally exposed individuals were excluded from the data. The results demonstrated an association between age and the prevalence of tubular proteinuria [2].

The study also found the odds ratio for increased urine protein HC to be >5-fold higher at urinary cadmium concentrations above 5 nmol Cd/mmol creatinine, compared with the reference category (<0.3 nmol/mmol creatinine). This is a troubling finding, given that this same cadmium concentration was recommended as a health-based limit by the World Health Organization (WHO) in the early 1990s. Several studies of both occupationally and environmental exposed populations have shown that cadmium exposure as low as 2–4 nmol/mmol creatinine is associated with the occurrence of tubular proteinuria; the findings of the OSCAR study are in agreement with these studies [2].

The Cadmibel study: environmental exposure in Belgium

Environmental cadmium exposure was shown to be associated with renal dysfunction by a cross-sectional population study. The investigation examined 1700 subjects, aged 20–80 years, randomly selected from four areas of Belgium with varying degrees of cadmium pollution. The data demonstrated a 10% probability of tubular dysfunction when cadmium excretion exceeded 2–3 µg Cd/g creatinine. Cadmium excretion reached this threshold in 10% of non-smokers. Evidence also suggested that diabetic patients were more susceptible to the toxic effect of cadmium on the renal proximal tubule [13].

Cadmium and ESRD: Kalmar County, Sweden

Occupational and environmental exposure to cadmium has been documented extensively in the Swedish population of Kalmar County, where nickel–cadmium batteries have been produced since 1910, and continues today. In a recent population cohort study of Kalmar County inhabitants, aged 20–79 years, data suggested an excess risk of end-stage renal disease (ESRD) at relatively low levels of cadmium exposure. Residency was used as a crude measure of exposure, since people living close to the cadmium-polluting plants had elevated U-Cd levels in comparison with those people living farther away from the cadmium sources (1.01 vs 0.46 nmol/mmol of creatinine), while a group in a reference area had even lower levels (0.2 nmol/mmol of creatinine) [14].

The population was divided into four categories of cadmium exposure: unexposed, low environmental exposure, moderate environmental exposure and high occupational exposure. The exposure categories were compared according to the prevalence of renal replacement therapy in each category. Results showed that renal replacement therapy was almost twice as high for men as women, and increased with age. The data also showed an exposure–response relationship between the age-standardized incidence rate ratios for renal replacement therapy and exposure to cadmium. These results were observed not only in occupationally exposed subjects, but also in environmentally contaminated regions. The main weakness of this study was the exposure assessment, since individual exposure data were not available for individuals outside of the occupationally exposed group [14].

Itai-itai disease: Kakehashi river basin, cadmium and mortality

A 15-year follow-up study of individuals living in the cadmium-polluted Kakehashi river basin in Japan suggested a dose–response relationship between U-Cd and mortality. The increased mortality in the high exposed group (20 µg Cd/g creatinine) was seen in both genders, with the cause of death reported as cardiovascular disease, nephritis and renal insufficiency.

Using the Cox proportional hazards models, there was an increased risk of death in the order of 1.4–2.0 among individuals with cadmium-induced renal damage when compared with individuals without damage [15].

Several other Japanese studies have reported increased overall mortality in persons living in cadmium-polluted areas with elevated U-Cd levels and/or tubular proteinuria [16,17]. However, these results may be explained by factors other than cadmium and lack data on the specific causes of death. Still, it is noteworthy that the prevalence of renal replacement therapy in Japan is 2–4 times higher than in Europe, perhaps due to greater degrees of cadmium pollution in Japan [18].

Clinical implications: bone disease

PheeCad: risk of forearm fractures

In a follow-up of the Public Health and Environmental Exposure to Cadmium (PheeCad) project, a prospective study demonstrated that moderate environmental exposure to cadmium, as shown by urinary excretion, was associated with an increased risk of fractures in women, and potentially related to risk of height loss in men. The relative risk of forearm fractures for individuals living in cadmium-polluted areas was 2.76 for men and 4.30 for women. The study showed that even at low levels of environmental exposure (1 µg Cd/g of creatinine), cadmium may promote skeletal demineralization, leading to increased bone fragility and risk of fractures. The study is limited, however, because it did not consider several variables, such as menopausal status, hormonal replacement or dietary calcium and vitamin D intake [19].

Itai-itai disease: Jinzu river basin

Bone disease resulting from prolonged exposure to cadmium was first reported from the Jinzu river basin in Japan where the first 150 cases of the so-called itai-itai disease were reported [20]. Itai-itai exhibits a mixed pattern of osteomalacia and osteoporosis, as well as kidney damage. Severe pain, multiple fractures and distorted long bones in the skeleton are characteristic of the disease [1]. Environmental exposure was caused by zinc mining in the nearby mountains, in which cadmium was discarded as an impurity, directly into the rivers. Cadmium eventually reached the irrigation channels used for the region's rice fields. Soil samples near the river basin had elevated cadmium concentrations, as did the rice itself. The prevalence of itai-itai disease correlated well with the geographic regions of high soil cadmium concentration and high concentrations in rice. Cadmium content in the skeleton of affected individuals was found to be several-fold higher than in non-exposed individuals (for men, 2.7 µg/g compared with 0.3 µg/g; for women, 1.8 µg/g compared with 0.6 µg/g [21]).

Conclusions

Studies suggest that cadmium is associated with several clinical manifestations at levels of exposure much lower than previously thought. Renal tubular damage due to environmental and occupational exposure to cadmium was shown to develop at lower levels of cadmium body burden. The results showed an increased prevalence of 10% tubular proteinuria in urinary cadmium concentrations of 1.0 nmol/mmol creatinine [2]. Data also demonstrate that low environmental exposure to cadmium may promote skeletal demineralization, leading to increased bone fragility and risk of fractures [19]. Furthermore, cadmium toxicity has been associated with clinical manifestations at exposure levels well below the limits set by the WHO [2].

Occupational exposure to cadmium in solderers induced irreversible glomerular lesions with a dose-related decrease in GFR, even several years after the exposure [12]. A recent study has also demonstrated increased incidence of renal replacement therapy in populations with environmental and occupational cadmium exposure [14].

Cadmium accumulates in bone and is associated with prevalence of osteomalacia and osteoporosis [1,7,11]. Several mechanisms for an indirect effect of cadmium on bone have been suggested. However, cadmium may directly affect bone by: (i) direct interference with incorporation of calcium into bone cells; (ii) direct interference with collagen production in bones; (iii) direct stimulation of bone resorption by prostaglandin production and protein synthesis; and (iv) impairment of bone formation by impeding alkaline phosphatase activity [7,22].

The finding that metals that accumulate in bone, such as cadmium, are associated with clinical manifestations, at much lower exposures than previously thought, is not an isolated finding. For instance, with aluminum accumulation, it was once thought that toxicity was predicted by exceeding threshold concentrations in total bone. However, studies have revealed that it is actually the localization of aluminum—accumulated at the mineralization front—that predicts disease [23]. In general, as techniques are being perfected to detect smaller amounts of trace elements in various tissues in the body, investigators are finding that even extremely low concentrations of metals are associated with pathology [1,13,14,19]. This raises concerns about current toxicity data for other metals that accumulate in bone; investigation of toxicity requires not only attention to acute exposure with high doses, but also investigations into long-term exposure at low doses. For instance, clinical risks of long-term exposure to the bone-seeking element, lanthanum, are currently undefined for an experimental phosphate binder, lanthanum carbonate. Only limited information has been reported on the absorption, compartmentalization and elimination of this metal, which has demonstrated cytotoxicities [24–27], warranting a thorough evaluation of long-term risks.

In conclusion, cadmium has been associated with several clinical manifestations, for which the mechanisms of toxicity are not clearly understood. Further research is necessary to reveal these processes, and to understand the true environmental and occupational exposure limits.

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