Biometals (2010) 23:783–792
DOI 10.1007/s10534-010-9328-y

Heavy metal poisoning: the effects of cadmium on the kidney

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Received: 7 December 2009 / Accepted: 16 March 2010 / Published online: 31 March 2010

Abstract The heavy metal cadmium (Cd) is known to be a widespread environmental contaminant and a potential toxin that may adversely affect human health. Exposure is largely via the respiratory or gastrointestinal tracts; important non-industrial sources of exposure are cigarette smoke and food (from contaminated soil and water). The kidney is the main organ affected by chronic Cd exposure and toxicity. Cd accumulates in the kidney as a result of its preferential uptake by receptor-mediated endocytosis of freely filtered and metallothionein bound Cd (Cd-MT) in the renal proximal tubule. Internalised Cd-MT is degraded in endosomes and lysosomes, releasing free Cd^{2+} into the cytosol, where it can generate reactive oxygen species (ROS) and activate cell death pathways. An early and sensitive manifestation of chronic Cd renal toxicity, which can be useful in individual and population screening, is impaired reabsorption of low molecular weight proteins (LMWP) (also a receptor-mediated process in the proximal tubule) such as retinol binding protein (RBP). This so-called 'tubular proteinuria' is a good index of proximal tubular damage, but it is not usually detected by routine clinical dipstick testing for proteinuria. Continued and heavy Cd exposure can progress to the clinical renal Fanconi syndrome, and ultimately to renal failure. Environmental Cd exposure may be a significant contributory factor to the development of chronic kidney disease, especially in the presence of other co-morbidities such as diabetes or hypertension; therefore, the sources and environmental impact of Cd, and efforts to limit Cd exposure, justify more attention.

Keywords Cadmium · Kidney · Nephrotoxicity · Low molecular weight protein · Proximal tubule · Fanconi syndrome

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Introduction

Heavy metals are a mixed group of elements with metallic properties that include those important for normal human health like iron (Fe), cobalt (Co), copper (Cu), manganese (Mn), molybdenum (Mo), and zinc (Zn), all of which are trace elements, and others that are non-essential and potentially toxic, especially if they accumulate, such as mercury (Hg), arsenic (As), lead (Pb), plutonium (Pu), vanadium (V), tungsten (W), and cadmium (Cd), which is the subject of this short review. Poisoning due to heavy metals has traditionally been thought to occur only in the setting of industrial or occupational exposure, and to present with severe and obvious clinical signs and

symptoms; however, this is now uncommon in modern industrialized economies. With the advent of more sensitive diagnostic methods and biomarkers of toxicity, it is now possible to identify tissue damage well before the onset of any significant clinical signs or symptoms, and to detect and measure much lower levels of heavy metals in blood and urine. This has made us much more aware of the consequences of chronic environmental (or non-industrial) exposure to heavy metals, and their impact on human health. In this special issue on Cd, this article will briefly review the impact of Cd exposure on human health and, primarily, its effects on the kidney. Other contributions to this special issue will describe the underlying mechanisms of Cd-induced cellular toxicity, and consequent tissue damage, in more detail.

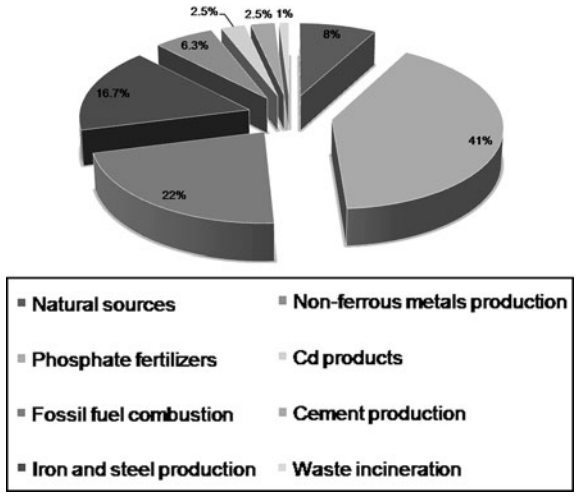

Fig. 1 A *pie chart* showing the relative contribution (in %) of the major sources of environmental Cd [Adapted from Van Assche and Ciarletta (1993)]

Cadmium toxicity

Cd toxicity was first described in the nineteenth century in those working in zinc smelters. In 1948, Friberg described emphysema and proteinuria in industrial workers exposed to CdO dust in an electric battery plant, first linking Cd to renal toxicity. Cd is a contaminant of zinc- and lead-containing ores, and chronic Cd toxicity usually occurs in industrial workers exposed to Cd or those living in heavily contaminated areas. Cd is still used in electroplating, the production of pigments (especially in plastics—using almost a quarter of world production), and in the manufacture of Li-Cd batteries (Fig. 1). Today, those involved in handling, assembling and dismantling mobile phones, computer circuit boards, and batteries ('electronic waste'), are at greatest risk; however, years of exposure are required before symptoms of chronic toxicity become evident. Moreover, heavy metal toxicity can present in different ways, depending on its route of ingestion, its chemical form, dose, tissue affinity, age and sex, as well as whether exposure is acute or chronic.

Acute toxicity

Acute Cd toxicity is now rare in Europe and North America; its symptoms depend on the route of ingestion and are listed in Table 1. Acute exposure to Cd fumes (as may occur in welders) causes a severe chemical pneumonitis with pulmonary edema and death (see Table 1) (Yates and Goldman 1990). A Parkinsonism-like neurological disorder has also been reported as a late effect of acute toxicity (Okuda et al. 1997). On the other hand Cd ingestion may be accidental, or sometimes even intentional, but can also occur from heavily contaminated dust exposure: it causes desquamation of the intestinal mucosa,

Table 1 Signs and symptoms of acute Cd toxicity (after as little as 10 mg)

Acute Cd poisoning from oral ingestion can present with
Increased salivation
Choking or vomiting
Abdominal pain
Vertigo and loss of consciousness
Painful spasm of the anal sphincter
Acute Cd poisoning from exposure by inhalation (which may cause a sweet or metallic taste) can present with
A dry throat or cough
Headache and flu-like symptoms, including fever
Choking and vomiting
Chest pains
Acute pulmonary edema (often fatal)
Asthma-like bronchospasm
Pneumonitis
Muscle weakness
Leg pains

resulting in severe and bloody diarrhea, and vomiting (Nordberg 2009). Apart from symptomatic treatment, treatment of acute toxicity consists of trying to eliminate Cd using metal chelators such as ethylenediamine tetra-acetic acid (EDTA) given by intravenous infusion to increase its urinary excretion (Dreisbach 1983), or if toxicity is so severe that renal function is impaired, i.v. EDTA during hemodialysis to remove it in the dialysate (Sheabar and Yannai 1989); oral dimercaptosuccinic acid (DMSA) can also be used (Jones et al. 1988). However, these forms of treatment are often of only limited benefit.

Chronic toxicity

The kidney, skeleton and lungs are the tissues most affected by chronic Cd toxicity. Upper respiratory tract and lung symptoms occur in those exposed to Cd fumes and heavily polluted dust (Table 1), exhibiting the clinical features of chronic bronchitis and emphysema, while those more heavily exposed to Cd developing pulmonary fibrosis (Hendrick 1996). The kidneys are particularly susceptible to Cd toxicity, and skeletal manifestations are partly a result of Cd nephrotoxicity (see later).

Chronic renal toxicity

With chronic exposure to Cd, approximately 50% of the accumulated dose is stored in the kidneys. The earliest sign of renal damage is the presence in urine of low molecular weight proteins (LMWP) such as β_2-microglobulin (β_2M) and retinol binding protein (RBP), and enzymes like *N*-acetyl-β-D-glucosaminidase (NAG). Both β_2M and RBP are freely filtered at the glomerulus, and then completely reabsorbed along the early proximal tubule by a megalin-dependent, receptor-mediated, endocytic uptake mechanism (Wolff et al. 2006) (Fig. 2). The detection of β_2M and RBP in urine is a fairly sensitive marker of impaired proximal tubular cell function. However, β_2M in urine can also be increased for non-renal reasons when its circulating levels are high, as in some forms of cancer (Manzar et al. 1992), including myeloma (Greipp et al. 1988), in amyloidosis, exposure to other toxins like nitric oxide (Halatek et al. 2005), and in autoimmune diseases like rheumatoid arthritis (Peterson et al. 1969); as well as when there is significant glomerular damage. β_2M is also less stable in an acid urine than RBP (Davey and Gosling 1982). For these reasons, RBP is considered to be a more specific marker of proximal tubular dysfunction. It is useful in screening for early tubular disease in Cd nephrotoxicity (Bernard et al. 1987) and has a urinary Cd threshold of around 10 μg/g creatinine (~10 nmol/mmol) (Bernard et al. 1995). Other urinary biomarkers claimed to be even more sensitive, and that also reflect tubular cell damage and loss, include NAG (NAG-B—'lesional enzymuria') and alanine aminopeptidase, which can be detected at urinary Cd levels below 2 μg/g creatinine (~2 nmol Cd/mmol creatinine) (Moriguchi et al. 2009; Noonan et al. 2002). Interestingly, loss of the sense of smell also occurs early in chronic Cd toxicity, which seems to correlate with the presence of tubular proteinuria; in fact, the olfactory epithelium expresses high levels of megalin (see above), which may underlie this association (Rose et al. 1992).

As tubular injury progresses, more generalized tubular dysfunction occurs with urinary losses of glucose and amino acids (not normally present in urine), bicarbonate and phosphate, all features of a renal Fanconi syndrome (Nogawa et al. 1975b) (Fig. 3). It might also be speculated that phosphate wasting and impaired vitamin D metabolism (through loss of vitamin D binding protein, a LMWP, as well as reduced conversion of 25-OH to 1,25-OH vitamin D, because of proximal tubular cell dysfunction) could indirectly contribute to renal calcium losses and bone disease (osteomalacia in adults, rickets in children), as well as to renal stone formation—prevalence rates are up to seven times higher (Jarup and Elinder 1993). However, Cd itself may directly affect bone mineralization, leading to loss of calcium from bone and increased renal excretion (see below), as well as having a direct effect on renal tubular transport of calcium. Continued Cd exposure causes glomerular damage, leading to albuminuria and a progressive decline in glomerular filtration rate (GFR), eventually causing end-stage renal failure. However, detection of early (micro-)albuminuria (Bernard et al. 1990) may be of tubular origin, rather than glomerular. It is also worth noting that tubular proteinuria is not usually detectable by clinical urine 'dipsticks' testing, and could be missed at a routine medical examination.

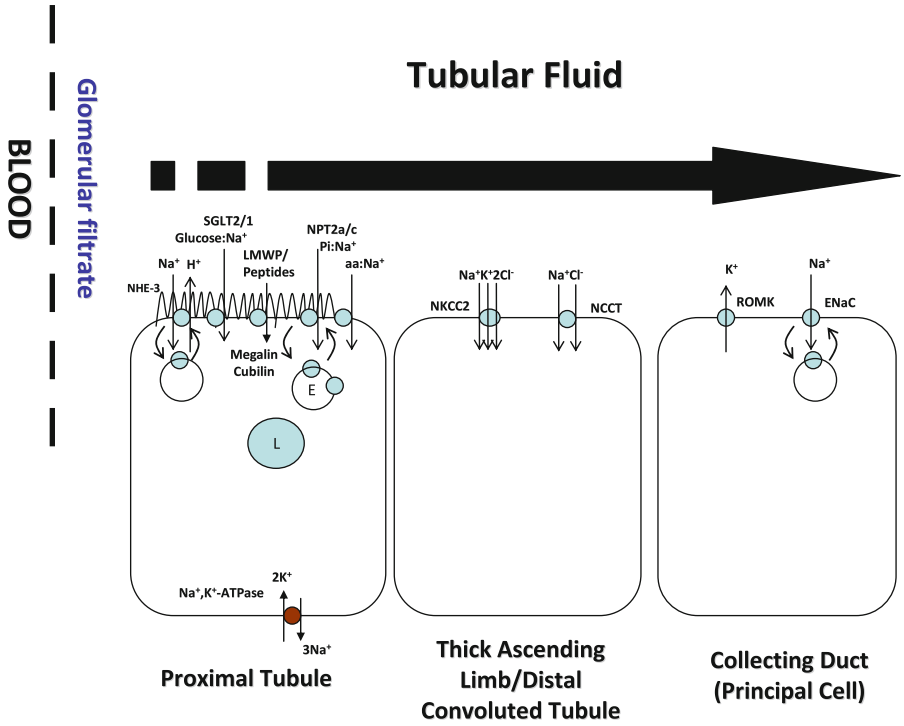

Fig. 2 Cell model of proximal and distal renal tubular cells, showing the axial distribution of some of the main solute transport pathways, including the reabsorption of LMWP in the proximal tubule (see text for details). NHE-3, isoform of Na^+–H^+ exchanger; SGLT1/2, Na^+-coupled glucose transporters; NPT2a/c, Na^+-coupled phosphate transporters; aa:Na^+, Na^+-coupled amino acid transporters; NKCC2, Na^+–K^+–Cl^- coupled transport; NCCT, Na^+–Cl^- coupled transport; ROMK, K^+ channel; ENaC, Na^+ channel. More distal nephron segments may also be affected in chronic Cd toxicity. (NAG-C is a soluble lysosomal enzyme released by exocytosis, whereas NAG-B is the membrane-bound form released when tubular cells and their lysosomes and disrupted—see text for more detail)

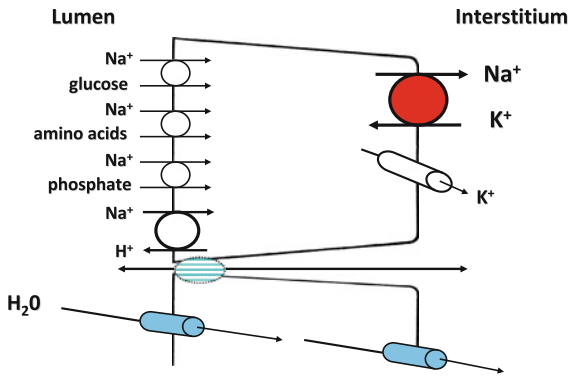

Fig. 3 Simple cell model of a proximal tubule cell present in the early part of the proximal tubule (S1), showing the main Na^+-coupled solute transporters that are affected in the renal Fanconi syndrome, including Na^+–H^+ exchange (shown) which is linked to carbonic anhydrase mediated bicarbonate reabsorption (not shown), whatever its underlying cause. Thus, increased amounts of glucose, amino acids, phosphate and bicarbonate are present in the urine, as well as LMWP (including some albumin) such as RBP (see text for details)

Chronic bone and other tissue toxicity

The relationship between Cd toxicity and osteomalacia or rickets was first described in Japan in the 1950s, when people living in the Jinzu river basin area began developing multiple bone fractures, severe bone pain, and malformations of their long bones (typical features of rickets); a syndrome that became known as Itai-Itai disease (1955) (Nogawa et al. 1975a). Cd intoxication was eventually found to be due to industrial waste discharged into the river from an upstream zinc mine (Inaba et al. 2005). Although the bone complications seen with chronic Cd poisoning were thought to be largely secondary to Cd-induced renal toxicity, and a consequence of renal Fanconi syndrome (see above), hypercalciuria and impaired vitamin D metabolism, more recent studies have found evidence for a direct effect of Cd on bone, resulting from its deposition and storage

there (Bhattacharyya et al. 1992). However, less is known about a potential association of Cd exposure with more prevalent osteopaenia and osteoporosis, which may be a more common association than with osteomalacia (Kazantzis 2004).

Besides its effect on the kidneys and bone, chronic Cd toxicity has been shown to cause infertility (Parizek and Zahor 1956) and liver damage in animals (Friberg 1952), but these effects have not been seen as significant features of Cd toxicity in humans. Cd as a carcinogen is discussed in more detail in an accompanying article in this issue. Briefly, Cd has been classified as a human carcinogen (Group 1) by the International Agency for Research on Cancer, because Cd exposure has been linked to an increased incidence of lung, prostate, renal, endometrial, breast and gastric cancers. However, it has been difficult to separate the effect of Cd exposure from the effect of other potential carcinogens, particularly in smokers, and from contamination with arsenic or nickel (Il'yasova and Schwartz 2005; Nawrot et al. 2006). More recently, Cd exposure has been considered to be yet another potential cardiovascular risk factor, linked to an increased risk of myocardial infarction (Everett and Frithsen 2008), development of hypertension (Spieker et al. 1987), and diabetes mellitus type 2 (Schwartz et al. 2003), as well as overall mortality (Nakagawa et al. 2006).

Measurement of cadmium in blood and urine

The blood level of Cd largely reflects recent Cd exposure with a half life of 75–128 days (fast component); however, it also has a slow component with a half life of 7–16 years, which correlates well with total body Cd load (Jarup et al. 1983). Normal concentrations in non-smokers are <1 μg/l, with values just under 5 μg/l in smokers; values above this concentration are probably an indication for medical surveillance in industrial workers who do not yet have proteinuria.

Environmental exposure to Cd

The incidence of chronic Cd poisoning in industrial workers declined rapidly in the second half of the last century, primarily because of increased awareness of the effects of chronic Cd exposure, stricter health and safety regulation, and more regular screening of those at risk. Until recently, concern about Cd exposure and toxicity has focused on industrial workers in those industries in which Cd is used or is a by-product. However, the decline in heavy industry and the closure of worked-out mines in many developed countries have resulted in large areas of contaminated land, which have been redeveloped subsequently for farming or domestic housing. Environmental exposure through food is increasingly recognized as an important source of heavy metal exposure in developed countries. Several heavy metals, including Cd, accumulate in plants and sea foods, and others, such as arsenic, in contaminated drinking water. Some, like lead, are still present in commercial products such as paint ('pica') and domestic water piping. Cd accumulates in adults and children by ingestion of contaminated food, inhalation of contaminated air and dust particles, and through cigarette smoke. Although there is no agreed upper limit for Cd dust exposure, the value is falling as we learn more about Cd toxicity. Studies show a sharp increase in nephrotoxicity with a cumulative exposure of >300 mg/m^3 days, which means that Cd exposure should be limited to <0.02 mg/m^3 during a typical working day over a 45 year working lifetime (Thun et al. 1989). The Occupational Safety and Health Administration (OSHA) recommends that the permissible exposure limit for Cd is 0.005 mg/m^3. The concentration of Cd in the air is generally <10 ng/m^3 (0.1–0.5 ng/m^3 in rural and 1–10 ng/m^3 in urban areas), but concentrations several fold higher, up to 1.16 μg/m^3, can be found near lead or zinc foundries (Jensen and Bro-Rasmussen 1992). It is important to recognize that Cd levels in the atmosphere are usually much higher inside than outside the home; nearby road traffic, and the use wood-burning fires or stoves, add to Cd contamination (Meyer et al. 1999).

Compared with mercury or lead, Cd passes more easily from soil to plants and can readily enter the food chain. Contamination of soil by Cd leads to its accumulation in cultivated crops and vegetables: the concentration of Cd found in cereals and tubers is estimated to be 0.025 μg/g of dry weight; the Cd concentration in meat, fish and fruit is much lower and is estimated to be between 0.005 and 0.01 μg/g of dry weight; shellfish can contain higher levels of Cd. Importantly, Cd absorption from food is increased in

the presence of iron deficiency (see later) (Flanagan et al. 1978) indeed, this may explain why young women tend to have higher Cd levels (Horiguchi et al. 2004) when compared with men who have experienced similar levels of environmental exposure. There is also evidence from rat studies that Cd toxicity suppresses erythropoietin (Horiguchi et al. 1996) and this may contribute to the development of anaemia.

Cigarette smoking is a significant source of environmental Cd exposure. Accumulation of Cd in tobacco plants can vary widely: average concentrations are 1–2 μg/g of dry weight or 0.5–1 μg per cigarette (Elinder et al. 1983). Approximately 10% of cadmium oxide (CdO) produced during cigarette smoking is absorbed into the circulation, and the concentration of Cd in smokers is 4–5 times higher in blood, and 2–3 times higher in the kidneys, when compared with non-smokers (Jarup et al. 1998). Cd is also present in several unlicensed medicinal herbal remedies used widely in parts of India and Nigeria (Arpadjan et al. 2008; Obi et al. 2006), which may still be used within immigrant communities in Europe and North America.

Since the kidneys are the 'critical organ' in Cd toxicity, urinary screening for tubular dysfunction can be carried out at individual, community, and population levels. Urinary Cd is a measure of total body Cd load, and it correlates well with the accumulation of Cd within the kidneys; however, it is not sensitive enough to predict and detect tubular injury. A bench mark dose (bMD) has been calculated for urinary Cd, according to the level at which tubular proteinuria has been detected in several epidemiological studies. Calculated bMD varies in each study, because of differences in the populations studied, the marker of proteinuria used (RBP, NAG or β_2M), and the threshold chosen for bMD: 5% or 10% above 'background' prevalence of tubular proteinuria. bMD calculated in these studies varies from 0.71 μg/g creatinine (de Burbure et al. 2006) in children to 3–4 μg/g creatinine in adults (Jin et al. 2004).

Several epidemiological studies have investigated the impact of environmental Cd exposure using urinary Cd as an index of cumulative exposure, and measurement of albumin, β_2M, RBP and NAG as markers of renal tubular dysfunction. There is a good correlation between increasing levels of urinary Cd and increased urinary excretion of RBP (Jin et al. 2004), β_2M (Hong et al. 2004), and NAG (Uno et al. 2005); serum urea or creatinine, and albuminuria, are too insensitive. The Cadmibel study in Belgium was the first to link urinary Cd with tubular proteinuria in a population study, demonstrating a dose–effect relationship between urinary Cd and tubular proteinuria. This study showed that there was a 10% chance of developing tubular dysfunction at urinary Cd levels of 2–3 μg/g creatinine (Lauwerys et al. 1991). There is still some debate as whether or not the Cd-induced tubular proteinuria is reversible (Lauwerys et al. 1994). Studies have suggested that proteinuria is reversible when β_2M levels are between 300 and 1,000 μg/g creatinine, but when levels reach >1000 μg/g creatinine, proteinuria, and hence glomerular damage, becomes more clinically evident and seemingly irreversible (Bernard 2008).

Although Cd-induced tubular proteinuria is asymptomatic, there is a clinical advantage in identifying potential Cd-induced nephrotoxicity early. Some studies suggest that affected patients may already have a reduced GFR (Akesson et al. 2005), or are prone to an accelerated decline in GFR with age (Jarup et al. 1995), and, therefore, should be targeted for more aggressive management of any associated hypertension or diabetes. Moreover, studies have found the increased risk of developing proteinuria in diabetics to be associated with higher levels of urinary Cd and tubular proteinuria (Buchet et al. 1990); a recent Australian study also found a similar correlation between urinary Cd and albuminuria in diabetics (Haswell-Elkins et al. 2008). These studies suggest that Cd exposure could have wider implications for the apparent increase in the prevalence of chronic kidney disease (Stages 2–3) in some areas. Indeed, a study in Kalamar County in Sweden showed that the renal replacement rate correlated significantly with urinary Cd levels, and a history of Cd exposure (Hellstrom et al. 2001). Finally, studies in rodents have shown that chronic Cd toxicity in pregnant females can manifest as progressive renal dysfunction in their offspring (Jacquillet et al. 2007).

Environmental co-exposure to other heavy metals

Several epidemiological studies have highlighted the fact that that environmental exposure to Cd rarely occurs in isolation. It is often associated with

exposure to other heavy metals, most commonly arsenic and lead. These metals tend to interact in a complex manner: in some tissues they may compete for common transport mechanisms, and in other tissues their toxic effects may be additive or even synergistic (Mahaffey and Fowler 1977). Studies in mice have shown that chronic combined exposure to arsenic and Cd produced greater nephrotoxicity than either metal alone (Liu et al. 2000), and a recent epidemiological study of co-exposure to Cd and lead found a higher risk of developing albuminuria and/or reduced eGFR compared with Cd exposure alone (Navas-Acien et al. 2009).

Mechanisms of cadmium toxicity

This is covered in more detail in accompanying articles in this special issue. As already mentioned, the lung and gastrointestinal tract are the two main routes of heavy metal exposure that can result in toxicity. Absorption through the skin can occur, but it is uncommon.

Cd is absorbed from the gastrointestinal tract by a transporter, DMT1 (Divalent Metal Ion Transporter 1), in the duodenum that also carries iron, and other metal ions ($Mn > Cd > Fe > Pb \sim Co \sim Ni > Zn$) (Park et al. 2002). DMT1 is upregulated in iron deficiency (Gunshin et al. 1997), which may explain why women are at greater risk of Cd accumulation and toxicity (see above). This transporter is also present in proximal tubular cells and may be responsible for the export of Cd^{2+} from the endosomes and lysosomes that have taken up the Cd-metallothionein (see later) complex reabsorbed by the proximal tubule (Rose et al. 1992). Recent studies have shown that a Zn (and Mn) transporter, ZIP8, may also be involved in Cd transport into mammalian cells (Yanagiya et al. 2000), and that extracellular Mn or Zn can reduce the cellular uptake of Cd in cells expressing this transporter (Liu et al. 2008).

Cd absorbed into the circulation is rapidly taken up by the liver, where it is bound to metallothionein (MT), which is then slowly released back into circulation. The Cd-MT complex is freely filtered at the glomerulus and reabsorbed by the proximal tubule. MT bound Cd has a very long half-life, anywhere between 10 and 30 years, and so it accumulates slowly over many years. Cd exposure up-regulates MT production in the liver and kidneys, which is a protective response to limit toxicity from free Cd (Cd^{2+}), but once the MT-producing capacity of proximal renal tubular cells is exhausted, progressive tubular cell damage occurs as the intracellular levels of Cd^{2+} increase. Cd can also induce autoantibodies to MT, which may be tubulo-toxic and interfere with Cd detoxification (Chen et al. 2006); other autoantibodies have also been implicated in Cd-related glomerular damage (Bernard and Lauwerys 1990).

While Cd has been shown in vitro to directly inhibit the ubiquitous cell 'sodium pump' (Na, K-ATPase) (Kinne-Saffran et al. 1993), mitochondria appear to be a major intracellular target for Cd toxicity. Cd^{2+} accumulates in mitochondria and inhibits the respiratory chain (and electron transfer) by acting at the level of complex III (Wang et al. 2004). This results in the generation of reactive oxygen species (ROS) (Stohs et al. 2000), and mitochondrial disruption (Tang and Shaikh 2001) with release of cytochrome c (Thevenod 2003), leading to caspase activation, causing cell death by apoptosis and necrosis (Desagher and Martinou 2000; Thevenod et al. 2000; Tzirogiannis et al. 2003). Cd can also enhance ROS accumulation by causing glutathione depletion, as well as by having direct effects on DNA structure and gene expression (Bagchi et al. 1996). In keeping with a key role for ROS in Cd-induced cellular toxicity, free radical chelators and anti-oxidants have been shown to be protective (Shaikh et al. 1999). Pre-treatment with Zn can also protect against Cd toxicity in rats (Jacquillet et al. 2006). The distribution of intercellular junction proteins (N- and E-cadherins and claudins 2 and 5) expressed in the glomerulus and proximal tubule (but not in the distal nephron) is also disturbed in Cd toxicity (Prozialeck et al. 2003), which probably contributes in as yet undefined ways to both glomerular and proximal tubular damage.

Conclusion

Recognition of the high prevalence of chronic kidney disease, detected as a result of more intensive community screening by family doctors, and the widespread use of formulae such as the MDRD to screen and estimate GFR (eGFR) (Levey et al. 2003), is prompting a search for environmental and other etiological risk factors, in addition to hypertension,

diabetes, and an aging population. It is becoming clear that environmental toxins, particularly heavy metal contamination with Cd, are potentially important contributory factors. For this reason, it is essential not only to identify sources of Cd exposure, but also to screen those at possible or particular risk, especially the young; and by improving our understanding of the cellular mechanism(s) of renal injury, to develop more specific treatments and interventions following acute and chronic Cd exposure.

Acknowledgements We thank Dr David Shirley and Dr Pedro Cutillas for their help with the figures.

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