Review

Antioxidative Function of Zinc and Its Protection Against the Onset and Progression of Kidney Disease Due to Cadmium

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Antioxidative Function of Zinc and Its Protection Against the Onset and Progression of Kidney Disease Due to Cadmium

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Abstract: Chronic kidney disease (CKD) is now the world's top seventh cause of death from non-communicable disease, and its incidence is projected to increase further as its major risk factors, obesity, diabetes, hypertension, and non-alcoholic fatty liver disease (NAFLD) continue to rise. Current evidence has linked increased prevalence of CKD, diabetes, hypertension, and NAFLD to chronic exposure to the metal pollutant cadmium (Cd). Exposure to Cd is widespread because diet is the main exposure route for most people. Notably, however, the health risk of dietary Cd exposure is underappreciated, and the existing tolerable exposure guidelines for Cd do not afford health protection. New health-protective exposure guidelines are needed. From the diet, Cd is absorbed by the intestinal epithelium from where it passes through the liver, and accumulates within the kidney tubular epithelial cells. Here, it is bound to metallothionine (MT), and as it is gradually released, it induces tubular damage, tubulointerstitial inflammation and fibrosis, and nephron destruction. The present review provides an update knowledge on the exposure levels of Cd found to be associated with CKD, NAFLD, mortality from cardiovascular disease. It discusses the co-existence of hypertension, and CKD in people environmentally exposed to Cd. It highlights mitochondrial targeting and zinc deficiency as the universal cytotoxic mechanisms of Cd. Special emphasis is placed on novel antioxidative function of zinc involving de novo heme biosynthesis and induced expression of heme oxygenase-1 (HO-1). Other exogenous biomolecules with promising anti-Cd toxicity are highlighted.

Keywords: antioxidant defense; bilirubin; cadmium; heme oxygenase-1; hypertension; kidney disease; zinc deficiency

1. Introduction

Environmental exposure to the metal pollutant cadmium (Cd) is one of the most significant public health threats because of its ubiquitous presence in the human diet [1–3]. Polluted air and cigarette smoke are other two common environmental sources of Cd [4–6]. Cd has no nutritional value or physiological role, and it is highly toxic [7]. Because there is no physiological mechanism for its elimination. most of acquired Cd is retained within cells, tissues, and organs throughout the body, notably the kidney, which is the principal site of Cd accumulation and toxicity [7]. In the absence of an elimination mechanism, an amount of Cd accumulated in kidneys increases with age, whilst the kidney Cd burden is essentially determined by the intestinal absorption rate of Cd [7].

According to the WHO global health report (https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death) (accessed on 1 December 2024), the world's top cause of death in 2019 was ischemic heart disease, while mortality from kidney disease rose from the 13th in 2000 to the 10th in 2019. A dose–response meta-analysis of data from 26 studies observed that the risks of heart failure, coronary heart disease, and stroke were all increased with Cd exposure in a dose-dependent manner [8]. There were 2.58-fold and 2.79-fold increases in the risk of having cardiovascular disease (CVD), at Cd exposure levels, producing a blood Cd level of 1 μg/L and a

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urinary Cd excretion rate of 0.5 μg/g creatinine, respectively [8]. These exposure levels were found in a significant proportion of people exposed to Cd in a normal diet, exemplified below.

In the general U.S. population study, urinary Cd excretion rates of > 1, > 0.7, and > 0.5 μg/g creatinine were found in 2.5%, 7.1%, and 16% of non-smoking women, aged 20 years or older [9]. In a study from Thailand, 22.5% of non-smoking women, who had low body iron stores had Cd excretion rates ≥ 1 μg/g creatinine [10]. These U.S. and Thai population data indicate that the proportions of people at risk of adverse health effects of Cd are not negligible. Also, they underscore the significance of body content of metals, notably iron, and zinc as to protect against Cd absorption at high rates.

Evidence that links an enhanced risk of having chronic kidney diseases (CKD) with environmental Cd exposure is compelling [11–14]. Concerningly, the mortality among those with CKD rose with an elevated exposure to environmental Cd, reflected by Cd excretion rates ≥ 0.60 μg/g creatinine or blood Cd levels ≥ 0.70 μg/L [15]. Another public health concern is that the Cd excretion rate of 0.60 μg/g creatinine is 8.7-fold below a toxicity threshold level of 5.24 μg/g creatinine. This toxicity threshold level of Cd was derived from a risk assessment model using tubular proteinuria as an endpoint [16,17].

The present review is focused on the mechanisms of CKD onset and its progression in people environmentally exposed to Cd. Differences among people in their capacity to accumulate to absorb Cd are highlighted. A toxicological risk assessment in current practice is discussed to argue for a need to develop a new health-protective exposure limit for Cd. The universal cytotoxic mechanisms of Cd targeting the mitochondria and zinc deficiency are discussed together with the fundamental anti-Cd defenses, involving zinc, de novo heme biosynthesis, and heme oxygenase-1 (HO-1) induction. Preclinical studies on the potential use of phytochemicals to mitigate the cytotoxicity of Cd are highlighted.

2. Transport of Cadmium from the Gut to Kidneys

2.1. Multiple Metal Transport Proteins Are Involved in Cadmium Assimilation

For most people, exposure to Cd is unavoidable because of its ubiquitous presence in the human diet and polluted air (Figure 1).

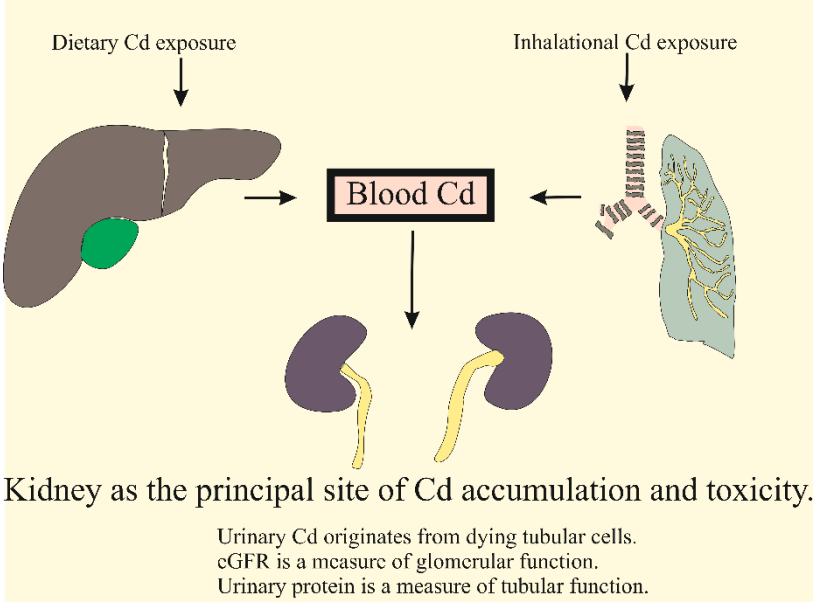

Figure 1. Exposure sources of cadmium and its pathway to kidney accumulation. From the gut, Cd ions are transported via the portal system to the liver. The Cd ions that are not taken up by hepatocytes in the first pass reach the systemic circulation, and is delivered to cells of tissues and organs throughout the body. Cd can enter

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most cells in the body through the transport proteins for metal nutrients, namely iron (Fe), calcium (Cd), zinc (Zn), copper (Co), manganese (Mn) and cobalt (Co). .

Because the body cannot synthesize nor degrade any metals, diet is an essential exogenous source of all metal nutrients the body requires such as calcium, zinc, manganese, iron, copper, and cobalt (Ca, Zn, Mn, Fe, Cu, and Co) [18–20]. These metals are assimilated from the gut through specialized transport proteins [21–25]. Unfortunately, however, these metal transporters and pathways provide also an entry route for Cd. Furthermore, Cd in food which forms complexes with the metal binding protein, metallothionine (MT) and phytochelatin (PC), denoted as CdMT and CdPC, can be absorbed through transcytosis [26], and endocytosis [27,28].

Table 1 enlists metal transport proteins responsible for Cd assimilation.

Table 1. Metal transport proteins involved in absorption of cadmium from the gut to accumulate in kidney tubular cells.

Metal transport proteins	Cell type/Localization	Physiological/Toxicological Roles
SLC39A14 (ZIP14)	Enterocyte/Basolateral membrane	Transport Fe into, and exit from enterocytes [23–25]. Transport Zn to tight junctions, especially in jejunum for maintenance of intestinal barrier function [29,30]. May mediate Cd absorption [31]
SLC11A2 (DMT1)	Enterocyte/Apical Membrane.	Transport Fe into enterocytes, has the same high affinity for Cd as it has for Fe (Km 0.5~1 μM); high abundance in duodenum [32,33]. Contribute to Cd absorption [34,35]
ATP7A	Enterocyte/Trans-Golgi network, Cytosol Basolateral membrane.	Transport Cu into portal blood, and ATP7A mutations are associated with Menkes disease [21]. May contribute to Cd absorption [36].
TRPV5, TRPV6	Enterocyte/Apical Membrane.	Transport Ca into enterocytes [37,38] and may provide Cd an entry route into enterocytes [39,40].
Calbindin-D9k	Enterocyte cytoplasm	Transport Ca to basolateral membrane and its extrusion into portal blood [38,41]. Expression in ileum is induced by 1,25-dihydroxycholecalciferol [42]. May contribute to Cd absorption [43].
The NGAL/lipocalin 2 receptor system	Enterocyte/Apical Membrane.	Assimilation of proteins, CdMT and CdPC complexes [26–28].
SLC39A8 (ZIP8)	Tubular epithelium/ Apical Membrane.	Uptake of Zn, Mn, and Cd [18,19].
The megalin/cubilin receptor system	Proximal tubule epithelium/Apical membrane	Internalization of proteins, notably albumin, β_2M and transferrin [44–48].
The NGAL/lipocalin 2 receptor system	The distal tubule and collecting duct epithelium.	Internalization of proteins which may include CdMT [49,50].

SLC, solute-linked carrier; ZIP14, Zrt- and Irt-related protein 14; ZIP8, Zrt- and Irt-related protein 8; DMT1, divalent metal transporter 1; ATP7A, copper-transporting ATPases (Cu-ATPases); NGAL, neutrophil gelatinase-associated lipocalin; TRPV5, transient receptor potential vanilloid5; TRPV6, transient receptor potential vanilloid6.

2.2. Cadmium Absorption, Renal Accumulation and Urinary Excretion

The rate of intestinal absorption of an individual metal nutrient is generally low (less than 5%) because each metal nutrient can be taken up by one or two highly specific transport proteins. This

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selectivity has been evolved to prevent toxicity from overload. In comparison, several transport proteins have been shown to mediate Cd assimilation, and consequently, Cd is absorbed at a much higher rate than each individual metal nutrient. Indeed, studies from Japan reported the absorption rates of Cd among women to be as high as 24–45% [51,52]. Concerningly, however, a conventional toxicological risk assessment assumed Cd absorption rates of 3–7%, resulting in miscalculation and underestimation of the impact of Cd on the function of kidneys [16].

Only a miniscule amount of Cd (0.001–0.005% of the total body content) is excreted each day in urine [53,54]. An extremely slow excretion rate means that most of acquired Cd is retained in the body, and hence the intestinal absorption rate essentially determines an amount of Cd accumulated in the body (termed body burden).

The absorption rate of Cd will increase, when the body content of metal nutrients is low and when the diet is deficient in these metal nutrients. Indeed, zinc and body iron status showed inverse relationships with Cd body burden [55]. Lower body iron stores are associated with higher urinary and blood Cd levels in children [56], adolescent females [57], and women of reproductive age [58,59]. Universally, women have lower body iron stores and higher blood and urinary Cd levels, compared to men of the similar age [60–63]. Habitual consumption of high-Cd-containing foods is another important determinant of the body burden of Cd [64–67].

A long half-life of Cd is another notable consequence of its extremely slow excretion rate. In Swedish workers exposed to a relatively high-dose Cd, the estimated half-life of Cd ranged from 7.4 to 16 years [68]. A half-life of Cd in non-smoking Swedish subjects, exposed to a low-dose Cd in a normal diet, was estimated to be 30 years [53,54]. Studies from Japan estimated the half-life of Cd to be 23.4 and 12.4 years in those with urinary Cd concentrations < 5 and > 5 μg/L, respectively [69,70]. These data indicate that the lower the body burden, the longer the half-life of Cd.

An estimated half-life of Cd in kidneys was 45 years in another analysis that used data on Cd levels in whole blood, plasma, kidney cortex, and urine samples from Swedish kidney transplant donors (n = 82) [71]. This kidney Cd half-life figure was obtained from a physiologically-based toxicokinetic model that incorporated the respective daily systemic Cd uptake at 0.0063 and 0.0085 μg /kg b.w. in men and women, and a daily uptake of 1.2 μg for each pack year of smoking [71].

2.3. Excretion of Cadmium Is a Manifestation of Its Cytotoxicity at the Present Time

It is important to note that most of the excreted Cd emanates from injured or dying tubular cells [72], which means that the excretion of Cd signifies tubular toxicity of Cd at the present time, not the risk of injury in the future [7,72].

For the same reason, the presence of N-acetyl-β-D-glycosaminidases (NAG) enzyme in urine is indicative of kidney tubular injury as it is released into tubular lumen following damage or death of tubular cells [73,74]. A dose–response relationship between urinary NAG and urinary Cd was reported in at least 30 publications [75].

A substantial tubular damage appeared to occur at a low Cd body burden, which produced a urinary Cd as low as 0.3 μg/g creatinine. In a study from United Kingdom (U.K.), the probability of having an elevated urinary NAG excretion rose 2.6-fold and 3.6-fold at urinary Cd excretion rates of 0.3 and 0.5 μg/g creatinine, respectively [76]. In a Thai population cohort study [77], a net loss of tubular cells per nephron was apparent as Cd exposure continued, and tubular proteinuria ensued, indicated by the β_2-microglobulin (β_2M) excretion exceeding 300 μg/g creatinine. This tubular proteinuria is a manifestation of severe pathologies, resulting in a rapid kidney functional deterioration [78–80]. Thus, it appears illogical to define a dietary exposure limit, and a toxicity threshold level of Cd based on β_2M excretion of 300 μg/g creatinine as an endpoint. A further discussion in Section 4.1.

3. Mortality Risk, Liver and Kidney Diseases in Low-Dose Exposure Scenarios

This section highlights data from U.S. population studies, known as National Health and Nutrition Examination Survey (NHANES), which provides data on exposure levels of more than 200

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environmental chemicals, Cd included, experienced by the U.S. general population, and the potential adverse health effects [82]. Here, Cd exposure levels in the U.S. associated with mortality and risks of kidney and liver diseases are listed in Table 2.

Table 2. Environmental cadmium exposure levels associated with increased mortality and disease of the liver and kidneys.

Study Design/Population	Observed Effects and Cadmium Exposure Levels	Reference
Prospective, NHANES 2005–2018, n = 8017, aged ≥ 20 years Mortality data collection as of December 31, 2019.	[a] HR (95% CI) values for all-cause mortality were 1.11 (0.85, 1.46), 1.42 (1.1, 1.84) and 1.67 (1.30, 2.13), comparing urinary Cd of 0.116 – 0.231, 0.232 – 0.455 and > 0.455 μg/L with urinary Cd <0.116 μg/L.	Zhang et al. 2024 [83]
Prospective, NHANES, 1999–2014 A cohort of 1825 adults with CKD Follow-up period, 6.8 years	HR (95% CI) values for all-cause mortality were 1.75 (1.28, 2.39) and 1.59 (1.17, 2.15) at urinary Cd levels ≥ 0.60 μg/g creatinine and blood Cd levels ≥ 0.70 μg/L, respectively.	Zhang et al. 2023 [15]
Prospective, NHANES, 2003–2012 A cohort of 24,810 adults, mean age 44.4 Median follow-up period, 11.8 years.	Respective HR (95% CI) values for all-cause mortality among CKD and non-CKD cases were 1.42 (1.07, 1.88) and 1.40 (1.24, 1.58) at blood Cd levels ≥ 0.4 μg/L.	Kuo et al. 2024 [84]
Prospective, U.S. adult participants the Multi-Ethnic Study of Atherosclerosis, n = 6599, 53% female mean age 62.1 years Followed from 2000-2001 through December 2019.	Respective HR (95% CI) values for incident CVD and all-cause mortality were 1.25 (1.03, 1.53) and 1.68 (1.43, 1.96), comparing Cd excretion rates > 0.80 with < 0.35 μg/g creatinine. A positive linear dose-response was observed between urinary Cd with both end points.	Martinez-Morata et al. 2024 [85]
Cross-sectional, NHANES, 1999 – 2020 n 55,677, 20–85 yrs, 5,175 (9.3%) had CKD	The OR values for CKD rose 2.1-fold 3.2-fold and 5.5-fold as blood Cd rose from <0.21 to 0.21–0.35, 0.36–0.60, and > 0.60 μg/L, respectively. The reported increase in the risk of CKD due to Cd exposure was adjusted for an effect of smoking.	Akinleye et al. 2024 [12].
Cross-sectional, NHANES 1988 –1994 n = 12,732, aged ≥ 20 years	OR for liver inflammation rose 1.26-fold in women with urinary Cd excretion ≥ 0.83 μg/g creatinine. Respective OR values for liver inflammation, NAFLD and NASH rose 2.21-fold,1.30-fold, and 1.95-fold in men with Cd excretion rates ≥ 0.65 μg/g creatinine.	Hyder et al. 2013 [86]
Cross-sectional, NHANES, 1999 – 2018 n = 47,422, aged ≥ 20 years	The OR for advanced liver fibrosis rose 1.81-fold among those with blood Cd in the top quartile. This risk was found across racial/ethnic groups; Hispanic black, Mexican Americans, and non-Hispanic Whites.	Ma et al. 2023 [87]

NHANES, National Health and Nutrition Examination Survey; HR, hazard ratio; CI, confidence interval; OR, odds ratio; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis. [a] HR values were adjusted for age, sex, ethnicity, marital status, education, poverty-income ratio, depression, drinking, and

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NHANES cycles. [b] Advanced liver fibrosis was defined as Fibrosis-4 ≥2.67 and/or Forns index ≥ 6.9 and abnormally high plasma level of alanine aminotransferase [86].

Low environmental Cd exposure in the U.S. contributed to mortality from CVD and all causes [83–85]. It did contribute also to the increased prevalence of CKD and NAFLD [86,87]. These adverse health effects of Cd on liver and kidneys were observed at a very low body burden, and they both are highly prevalent globally.

3.1. Diagnosis and Staging of Chronic Kidney Disease

CKD is a progressive disease, which is diagnosed when the eGFR falls below 60 mL/min/1.73 m^2 (low eGFR) or there is albuminuria which persists for at least 3 months [88–90]. CKD is now the 7th top cause of global mortality, and it will be the 5th leading cause of years of life lost by 2040 [91,92]. The incidence of kidney disease is projected to increase further as its major risk factors, obesity, diabetes type 2, hypertension, and non-alcoholic fatty liver disease continue to rise [88–92].

CKD stages 1, 2, 3, 4, and 5 correspond to eGFR of 90–119, 60–89, 30–59, 15–29, and <15 mL/min/1.73 m^2, respectively [88–90]. CKD reaches an end stage, when eGFR falls below 15 mL/min/1.73 m^2, at which time dialysis or kidney transplant is required for survival [90]. In early stages, CKD is largely asymptomatic. This makes its early detection difficult as well as the initiation of early treatment, which can significantly prevent CKD progression, limited.

3.2. CKD and Hypertension in People Chronically Exposed to Cadmium

Enhanced risks of kidney damage [93–95], albuminuria [96–98], proteinuria [98,99] and a low eGFR [11–14] have repeatedly been linked to chronic environmental Cd exposure. Proteinuria predicts continued progressive decline of eGFR [101–103].

The Fukuoka Kidney Disease Registry Study, Japan reported that advanced kidney fibrosis was found in a higher frequency among those with a higher liver Fibrosis-4 index [105]. Similarly, the Scottish prospective cohort study of 2046 persons, aged ≥ 18 years, has reported a 1.31-fold increase in risk of developing CKD among those with liver fibrosis who showed no evidence of structural, autoimmune, or malignant CKD [106].

Hypertension, defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg, is another highly prevalent ill health condition worldwide [107]. Blood Cd levels ≥ 0.80 μg/L were associated with an increased mortality from CVD in non-smokers who had hypertension, [108]. Cd-linked hypertension has consistently been noted in many general populations, including the U.S. [109–111], Canada [112], China [113–115], Korea [116,117], and Japan [118]. In a systematic review and dose-response meta-analysis, the risk of hypertension rose with levels of Cd in urine and blood samples [119].

3.3. An Inverse Relationship of Blood Pressure and eGFR

The connection between kidney damage and hypertension development can be inferred from the indispensable role of kidneys in long-term blood pressure regulation [120]. Satarug et al. (2024) investigated the relationship between blood pressure and eGFR in a Thai population cohort study [121]. They reported that there was a two-fold increase in the prevalence of hypertension at urinary Cd excretion rate of 0.98 μg/g creatinine, or blood Cd level of 0.61 μg/L, while SBP showed an inverse relationship with eGFR in both women ($\beta = -0.227$) and men ($\beta = -0.320$) who had an elevated body burden of Cd (Figure 2a). DBP showed a weak correlation with eGFR (Figure 2b).

Through mediation analysis, rising SBP and DBP were found to be due to eGFR reduction induced by Cd (Figure 3). Therefore, eGFR appeared to be a full mediator of rising SBP and DBP among subjects with an elevated body burden of Cd [121].

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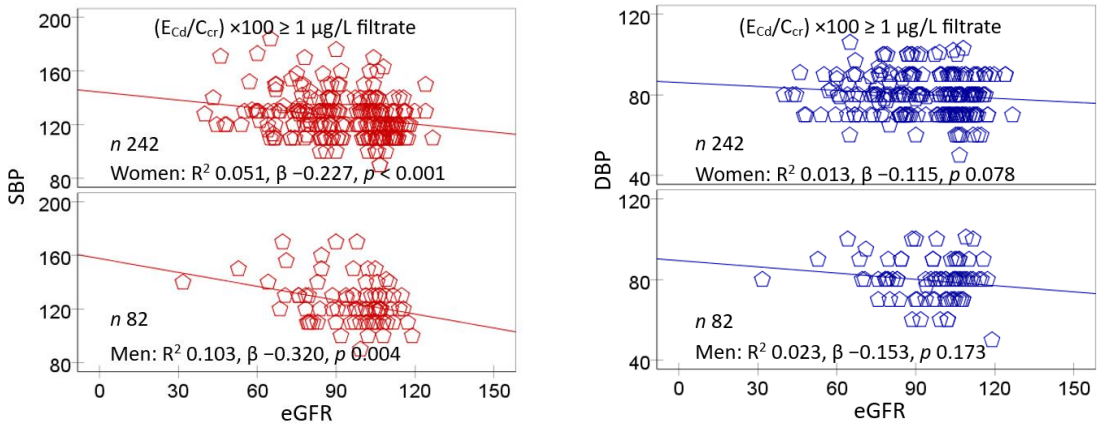
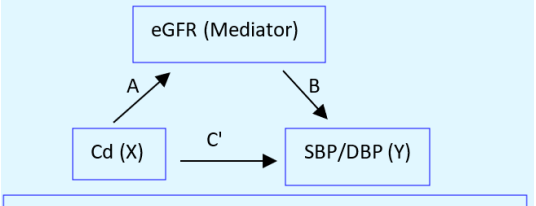


(**a**) (**b**)

Figure 2. Dose-response relationship of blood pressure and eGFR. Scatterplots relate SBP (**a**) and DBP (**b**) to eGFR in women and men. A high-Cd burden was defined as E_{Cd}/C_{cr} value ≥ 0.01 μg/L filtrate, corresponding to Cd excretion rate of μg/g creatinine.



The Sobel Test			
SBP	β (SE)	95% CI of β	*p*-value
A	−13.79 (3.628.)	−21.00, −6.148	<0.001
B	−0.249 (0.052)	−0.351, −0.156	0.001
A*B	4.433	–	0.003
C	−1.934 (2.651)	−7.119, 3.488	0.470
C'	−5.227 (2.633)	−10.62, −0.172	0.055
DBP	β (SE)	95% CI of β	*p*-value
A	−13.37 (3.640)	−21.69, −5.591	0.001
B	−0.080 (0.033)	−0.147, −0.020	0.022
A*B	1.70	–	0.044
C	−0.570 (1.675)	−3.773, 2.655	0.727
C'	−1.623 (1.734)	−5.037, 1.519	0.363

SE, standard error of mean; CI, confidence interval. β and 95% CI values were unstandardized, obtained by bootstrapping.

(**a**) (**b**)

Figure 3. An analysis for an effect of cadmium exposure on SBP and DBP. (**a**) A model depicts eGFR as a mediator of Cd effect on SBP/DBP (**b**) The Sobel test for an indirect effect of Cd on SBP/DBP.

A declining eGFR is a common sequalae of ischemic acute tubular necrosis, and acute and chronic tubulointerstitial fibrosis as they create impediments to filtration [123–125]. As the kidney function declines (indicated by a decrease in eGFR), the kidneys eliminate less water and sodium, which may increase blood pressure. Rats with Cd-induced hypertension showed increased sodium retention and reduced sodium excretion [126–128]. Thus, increased tubular avidity for filtered sodium could be the mechanism by which Cd exposure increases blood pressure and hypertension risk.

In summary, data presented in this section indicate that low environmental Cd exposure in the U.S. increased mortality from all causes and from CVD [15,83–85]. It increased also the prevalence of both liver and kidney diseases [12,87,88]. Incident CKD and NAFLD may reflect the toxic environment continues.

The benchmark dose analysis data indicate that a conventional toxicological risk assessment of dietary Cd exposure incorporated imprecisions which bias the dose-response relationship toward the null [7,122,129]. New health-protective exposure guidelines should be developed. To this end, a fall of eGFR by 5-10% can be used as a sensitive endpoint for estimating a safe dietary Cd exposure level, instead of β_2M excretion exceeding 300 μg/g creatinine. An exposure limit for dietary Cd, derived

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from eGFR reduction as an endpoint will preserve functional integrity of liver and kidneys, while minimizing risk of hypertension that is associated with GFR loss.

4. The Nephrotoxicity of Cadmium and Protective Effects of Zinc

An approximate of 8-13% of the world's population is living with CKD [91,92]. In early stages, CKD is asymptomatic, and it is diagnosed when there is a substantial loss of functioning nephrons, evident from a fall of eGFR to one third of a normal range. This diagnostic stage often co-exists with disease comorbidities such as hypertension and proteinuria [88–90,130]. As typical, reductions of eGFR are irreversible, and are likely to decline further to 15 mL/min/1.73 m^2, which marks end-stage kidney disease, a condition that requires dialysis or a kidney transplant for survival.

This section focuses on the contribution of Cd exposure to both onset and progression of CKD and protective effects of the metal nutrient zinc and antioxidants of plant origin.

4.1. Manifestation of the Nephrotoxicity of Cadmium

Kidney disease associated with chronic environmental Cd exposure is primarily due to proximal tubular cell damage and malfunction. This results in a sustained decline in eGFR, hypertension, and proteinuria. A proposed pathogenesis of Cd-induced CKD and progression to end-stage kidney disease is presented in Table 3.

Table 3. A fall of eGFR and rising blood pressure as early kidney effects of cadmium exposure.

Pathology	Consequence	Observation
Tubular cell injury.	Mild to moderate tubular dysfunction. Repair and regeneration.	Increased excretion of KIM-1, NAG, β_2M, RBP. A slight elevation in blood pressure.
Tubulointerstitial inflammation.	Nephron obstruction with cellular debris. Repair and regeneration.	eGFR falls. Blood pressure rises.
Tubulointerstitial fibrosis and tubular atrophy.	Destruction of post-glomerular peritubular capillaries. Amputation of glomeruli from tubules.	Hypertension, proteinuria, albuminuria, and a further fall of eGFR.
Net loss of tubular cells per nephron. Glomerular atrophy.	CKD onset. Severe tubular dysfunction and tubular proteinuria.	When β_2M excretion exceeding 300 μg/g creatinine, eGFR will fall at a high rate. A rapid progression to end-stage kidney disease will ensue.

eGFR, estimated glomerular filtration rate; KIM-1, kidney injury molecule-1; NAG, N-acetyl-β-D-glucosaminidase; β_2M, β_2-microglobulin; RBP, retinol binding protein.

Tubular cell injury, indicated by an increased excretion of NAG, β_2M, RBP and KIM-1, are the most frequently reported effects of chronic environmental Cd exposure [7,93–95]. A study from Taiwan suggested an increased KIM-1 excretion to be a more sensitive indicator of Cd toxicity in CKD patients than conventional markers [131].

With continuing Cd influx, tubular cell damage and cell death are intensified, and nephrons are destroyed. The tubule injury reduces reabsorption of proteins, leading to an appearance of protein in urine. A dose-response analysis informed a 5% increase in total protein excretion at urinary Cd excretion of 0.0536 μg/g creatinine [122]. Loss of functioning nephrons causes eGFR to fall further. SBP and DBP rise as eGFR falls (Figure 3), and hypertension develops. Risk of having hypertension doubled at urinary Cd excretion of 0.98 μg/g creatinine [122].

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Hypertension is one of the most widely recognized consequences of kidney damage [120,132,133]. An increased risk of hypertension was linked with tubular malfunction, reflected by urinary β_2M excretion rates ≥ 145 μg/g creatinine, compared with β_2M excretion rates ≤ 84.5 μg/g creatinine [78]. At severe tubular malfunction (β_2M excretion rates ≥ 300 μg/g creatinine), there was a 79% increase in risk of eGFR deterioration at high rates, i.e., 10 mL/min/1.73 m^2 in 5 years [79].

In summary, kidney disease associated with chronic environmental Cd exposure is primarily due to proximal tubule damage and malfunction, leading to nephron destruction, GFR decrease and hypertension [77,80,121,122].

4.2. The Kidney Tubule as the Principal Target of Cadmium Toxicity

Figure 4 depicts the kidney tubular epithelial cell, the principal Cd accumulation site and toxicity.

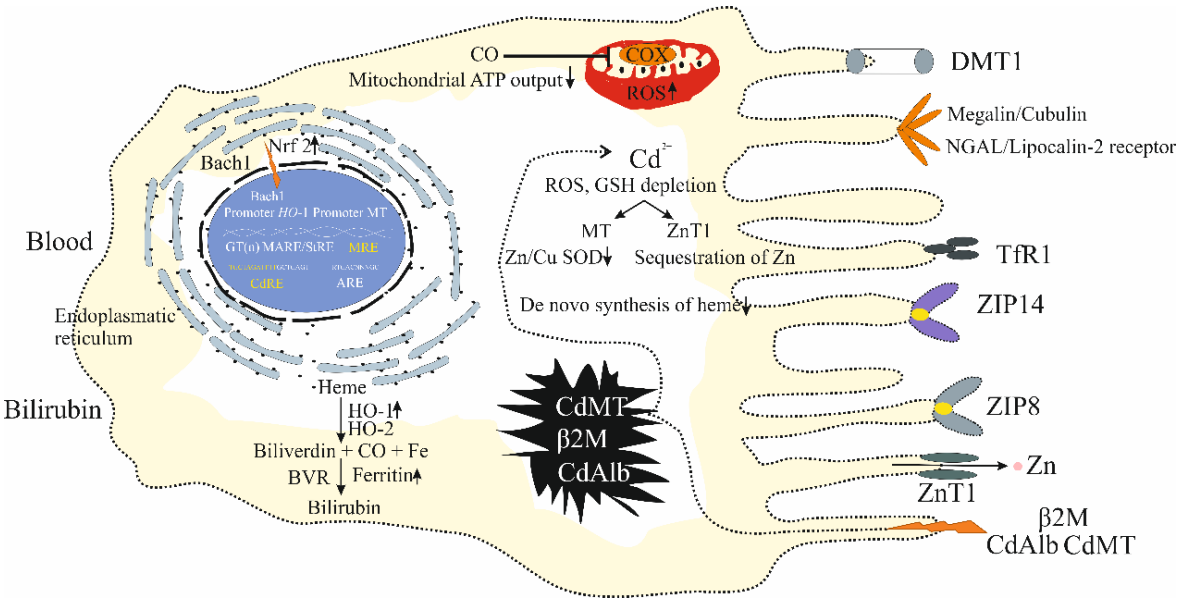

Figure 4. The kidney proximal tubular epithelial cell as the principal target of cadmium. The entry of Cd into tubular cells is through DMT1, ZIP8, ZIP10, ZIP14, and the megalin/cubilin and NGAL/lipocalin 2-mediated endocytosis. Abbreviation: DMT1, divalent metal transporter1; ZIP8, Zrt- and Irt-related protein 8; ZIP10, Zrt- and Irt-related protein 10; ZIP14, Zrt- and Irt-related protein 14; NGAL, neutrophil gelatinase-associated lipocalin.

As Figure 4 depicts, kidney tubular epithelial cells are well equipped with many metal transport proteins and receptor-mediated systems for internalization of whole proteins. These are for retrieval of all nutrients, including proteins albumin and transferrin, and essential metals Zn and Fe [48–50]. Most of these transport pathways and systems also facilitate Cd entrance. ZIP8, ZIP10, and ZIP14 mediate Cd uptake [18,134,135]. The transgenic mice with three more copies of the ZIP8 gene accumulated twice as much Cd in the kidney following oral Cd exposure, and the proximal tubular cells from these mice had elevated levels of ZIP8 on the apical membrane, which explained their high sensitivity to Cd toxicity [18]. Expression of ZIP8 protein by human proximal tubule cells have been shown [136].

4.2. The Cytotoxic Mechanisms of Cadmium

The proximal tubular epithelial cells of the kidneys are rich in mitochondria, and their homeostasis and survival depend on autophagy [137–139]. As a result, they are highly susceptible to Cd-induced apoptosis. Several mechanisms have been proposed to explain how Cd causes tubular cell injury and death.

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4.3.1. Mitochondrial Targeting

Cd reaches the inner membrane of mitochondria through MT and transport proteins for calcium and iron, metal coupling unit (MCU) and DMT1 [140]. There, Cd reduces the synthesis of adenosine triphosphate (ATP), suppresses the electron transport chain, and promotes the formation of reactive oxygen species (ROS), leading to mitochondrial injury and mitochondrial DNA (mtDNA) is released [7,140–142]. This activates the DNA-sensing mechanism (cGAS-STING) and nuclear factor-kappaB (NF-κB) signaling pathways, followed by a release of proinflammatory cytokines and cell death.

4.3.2. Endoplasmic Reticulum Targeting

Cd-induced tubular cell death through disruption of calcium homeostasis has been demonstrated [143–145]. In primary rat proximal tubular cells, Cd caused calcium release from the endoplasmic reticulum, which raised intracellular calcium concentrations and inhibited autophagy [143,144]. In mouse renal tubular cells, Cd activated at least two calcium channels, namely phospholipase C (PLC)-inositol 1, 4, 5-trisphosphate receptor (IP3R) and the sarco/endoplasmic reticulum $Ca2^{+}$-ATPase (SERCA), known to be involved in the release and reuptake of calcium by the ER [144]. Cd also suppressed SERCA expression and diminished the stability of the SERCA protein in mouse tubular epithelial cells, and the toxic effects of Cd were intensified [145].

4.3.3. Zinc Deficientcy

As Figure 4 presents, Cd interacts with the metal response element-binding transcription factor-1 (MTF-1), leading to an induction of MT and ZnT1 [146,147]. As a result of an increased MT protein expression, most Cd in the cytosol is sequestered in MT, and there is only a small fraction of Cd localized at the basolateral membrane [148,149]. There is little evidence for an exit route for Cd once it has entered tubular cells. The metal efflux transporters namely ferroportin1 (FPN1) and zinc transporter1 (ZnT1) are highly specific for Fe and Zn, respectively [150–153].

Increased expression of both MT and ZnT1 by Cd produces fatal consequences, which include zinc loss, a limited availability of zinc for de novo heme biosynthesis, decreased heme catabolism, and a reduced catalytic activity of key anti-oxidant enzymes, namely superoxide dismutase (SOD) and NADPH oxidase (Nox) [154,155]. ZnT1 is a unique efflux transporter that functions as a Zn/Ca exchanger [147,151–153], and as a mechanism to prevent toxicity from zinc overload, zinc is extruded from cells by ZnT1, and cellular zinc deficiency will follow.

As the defense mechanism against oxidative stress damage, heme is synthesized de novo in most cells for the continuous production of bilirubin, a cytoprotective biomolecule [156]. Bilirubin is a potent antioxidant and a lipid peroxidation chain breaker [157]. The discovery of HO-1 induction by zinc ensures the synthesis of bilirubin as another universal antioxidant defense mechanism [158]. Using the reporter gene assay, zinc activated the HO-1 gene expression via antioxidant response element (ARE) and the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) signaling pathway [158].

An enzyme in heme biosynthesis, named δ-aminolevulinic acid dehydratase (ALAD) requires zinc as a cofactor. Anemia due to zinc deficiency is caused by an insufficient amount of heme for hemoglobin synthesis [159]. Limited availability of zinc following MT and ZnT1 inductions by Cd causes a reduction in ALAD activity which could eventually diminish the synthesis of bilirubin.

In summary, the ability of Cd to increase the expression of both ZnT1 and MT explains the development of zinc deficiency conditions in Cd intoxicated tubular cells. The similar phenomenon in CKD and its associated disease, CVD are discussed below.

4.4. Zinc and Chronic Kidney Disease

A meta-analysis of data from 42 studies showed that CKD patients had lower serum zinc levels, compared to controls [160]. In another meta-analysis of data from 15 randomized controlled trials, zinc supplementation has been shown to reduce CVD risk in CKD patients [161,162]. Higher serum

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zinc concentrations were associated with lower risks of mortality from CVD in the Ludwigshafen Risk and Cardiovascular Health study (Germany) [163].

In NHANES 1988–1994 database, zinc intake below the RDA was associated with elevated urinary Cd excretion rates in both men and women [164]. Serum zinc levels < 74 μg/dL and blood Cd levels > 0.53 μg/L were associated with increased risk of a low eGFR in 2011-2012 NHANES cycle (n = 1545, aged ≥ 20 years) [165]. In a cohort of NHANES 2011-2018 participants, aged ≥ 18 years (n = 9557), equivalent to 236,263,413 community-dwelling U.S. adults, the top quartile of blood Cd was associated with 2.79-fold increase in risk of having CKD, compared with the bottom quartile [166]. The risk of having CKD was reduced by 90% and 89% comparing low zinc and high Cd with high zinc plus high Cd and high zinc plus low Cd, respectively.

The overall mean dietary Zn intake level among the NHANES 2003–2018 participants ((n = 37,195) was 11.85 mg/day, and a dietary zinc intake of 16.46 mg/day was associated with a reduction in prevalence of a low GFR [167]. Of note, dietary Zn levels of 15–16 mg/day are higher than RDA values, and it is important to note that dietary zinc intake levels by participants displayed a U-shaped dose–response relationship [168]. The zinc intake levels lower than 6.64 mg/day or higher than 16 mg/day was associated with a higher CKD risk. Thus, zinc intake should not be too low (deficiency) or too high (overdose).

An experimental study observed rising systemic blood pressure and declining kidney function, measured by inulin clearance, in rats fed with a diet containing 40 times higher Zn than in a normal diet for 4 weeks [169]. Thus, zinc overdose did result in an increased risk of CKD as noted in the U.S. population study above [168].

4.4. Mitigation of Cadmium Nephrotoxicity in Chronic Kidney Disease

The current population exposure to environmental Cd presents global public health significance and many challenges because Cd is found in virtually all food types [1–3]. The current environmental Cd exposure has now reached toxic levels in a significant proportion of many populations. Alarmingly, CKD is predicted to become the fifth leading cause of years of life lost by 2040 should its rising prevalence continues [91]. Developing strategies to combat CKD and its progression to kidney failure are of global importance, given an immense associated healthcare cost.

4.4.1. Population Zinc Supplementation

Zinc is a metal nutrient, required for the function of 10% of proteins in the human body [169,170]. Because storage mechanism for zinc does not exist, unlike iron, sufficient daily supply is required to prevent deficiency [169]. The recommended dietary allowance (RDA) for zinc is 8 and 11 mg/day for adult women and men, respectively [171]. Dietary intake of zinc below RDA is believed to be highly prevalent [172–174], but the health impact of marginal zinc intake is not easily recognized because no specific symptom can be attributable to zinc deficiency, and it cannot be readily measured [170,172–174].

The role for zinc in CKD has been subjected to reviewed [175–177]. Herein, findings from recent publications are summarized. Data from clinical trials have indicated efficacy of zinc supplementation in reducing risk of CKD and mortality from CVD among patients with CKD [161–163]. Population zinc supplementation, however, has many challenges; zinc and iron deficiencies co-existence and there are zinc-iron interactions if supplemented together [169,177–179]. Furthermore, there is risk of anemia due to Cu deficiency induced by a high-dose zinc (≥ 80 mg/day), and an additional 2 mg of copper is required to prevent such anemia [180].

4.4.2. Exogenous Heme Oxygenase-1 Inducers

Induction of HO-1 expression by phytochemicals can be considered as a potential mitigative strategy. In chronic environmental Cd exposure conditions, the metal binding sites of MT are saturated while other endogenous antioxidants such as glutathione, bilirubin are depleted. Many

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plant biomolecules have been found to activate HO-1 expression through the stress response transcription factor, Nrf2 and Stress Responsive Element (StRE), known also as Maf recognition Antioxidant Response Element (MARE) [181].

An induced expression of HO-1 raises intracellular concentrations of bilirubin and CO (Figure 4). Bilirubin is a potent antioxidant, while CO inhibits COX activity and restores mitochondrial ROS signaling [181–183]. HO-1 induction thus provides tubular cells the capacity to resist Cd toxicity, and ensures cell survival and normal functions are maintained. Kidney disease associated with chronic environmental Cd exposure is primarily due to oxidative damage to the tubule and zinc deficiency (Figure 4). This results in a sustained decline in eGFR, hypertension, and proteinuria (Section 3.2).

Green tea consumption increased HO-1 expression [184–186]. In a human trial that included diabetic subjects with no history of metabolic complications who did not smoker and did not take regular food supplements, consumption of green tea in normal amounts increased HO-1 expression and reduced DNA damage in lymphocytes [186]. A wide range of chemicals from plant foods, such as curcumin, catechin (in green tea), α-lipoic acid (in broccoli, and spinach), and sulforaphane (in cruciferous vegetables) are known to increase HO-1 expression [187].

4.4.3. Other Plant Biomolecules

Table 4 provide a summary of recently published preclinical studies of some plant biomolecules for alleviating the nephrotoxicity and or hepatotoxicity of Cd.

Table 4. Preclinical investigations on anti-cadmium effects of some phytochemicals.

Test Entity/Target Organ	Test Results	Reference
Hyperin/Kidney Quercetin-3-O-galactoside (flavonol glycoside)	Reduced Cd accumulation, attenuated Cd effects on mitochondria, apoptosis, and inflammation. Activated the Nrf-2/Keap-1 ARE pathway.	Lucky et al. 2024 [188]
Linalool/Kidney Monoterpene (essential oils)	Reduced histopathological lesions, inflammation, oxidative stress, and apoptosis.	Kaya and Yalçın, 2024 [189]
Pinostrobin/Kidney Flavonoid from Boesenbergia rotunda.	Reduced the mitochondrial membrane potential and ameliorated Cd effects on the TCA cycle enzymes and mitochondrial electron transport chain enzymes, such as succinate dehydrogenase, NADH dehydrogenase, cytochrome c-oxidase, and coenzyme Q-cytochrome reductase.	Ijaz et al. 2023 [190]
Physalis peruviana L. calyx extract /Kidney	Decreased TNF-α and NF-κβ levels. The molecular docking data suggest withanolides [a] may inhibit κB kinase activity.	Soliman et al. 2023 [191]
Chocolate/Liver and Kidney	Reduced DNA damage and apoptotic and necrotic cell death, restored mitochondrial membrane potential and the mitochondrial DNA copy number. Increased HO-1 and iNOS expression.	Mohamed, 2022 [192]
Helianthemum lippii extract nanoparticles/Kidney	Reduced kidney fibrosis, inflammatory cell infiltration, glomerular destruction, and tubular dilatation.	Laib et al. 2024 [193]
Diallyl disulfide/Kidney	Suppressed NF-κB, CD68 and pro-inflammatory mediators, attenuated oxidative stress, inflammation, and suppressed TGF-β1/Smad3 signaling, enhanced Nrf2/HO-1 signaling, antioxidants, and PPARγ.	Alruhaimi et al. 2024 [194]

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Diallyl disulfide/Liver	Attenuated oxidative stress, and apoptosis, suppressed TLR-4/NF-κB signaling, suppressed inflammation and oxidative stress, upregulated PPARγ.	Alruhaimi et al. 2024 [195]
Morin /Liver 3,5,7,29,49-pentahydroxyflavone	Reduced ER stress, increased SOD, GSH, Gpx, CAT, Nrf2, IL-10 and IL-4, reduced TNF-α, IL-1-β, and IL-6, retarded the apoptotic cascades and suppressed JNK and p-PERK. Modulated upstream p-GRP78/PERK/ATF6 pro-apoptotic oxidative/ER stress and downstream JNK/BAX/caspase apoptotic signaling pathways.	Sengul et al. 2024 [196]

HO-1, heme oxygenease-1; iNOS, inducible nitric oxide synthase; ER, endoplasmic reticulum; SOD, superoxide dismutase; GSH, glutathione; MDA, malondialdehyde; PPARγ, peroxisome proliferator activated receptor gamma; TNF-α, tumor necrosis factor-alpha; NF-κβ, nuclear factor kappaB. [a] β-hydroxywithanolide, physalin B and 3α,14β dihydroxywithaphysalin.

5. Conclusion and Recommendation

Cd is a toxic metal pollutant with no nutritional value or physiological role, but as it is a contaminant in nearly all food types, dietary exposure is inevitable for most people. The intestinal Cd absorption rate can be as high as 45% in those with low body iron stores. From the gut, Cd reaches the systemic circulation through specialized transport proteins, systems, and pathways for metal nutrients, like zinc and iron. The kidney proximal tubule is the principal site of Cd accumulation and toxicity because it is well equipped with metal transporters and protein internalization mechanisms that facilitate Cd uptake.

Zinc deficiency has emerged as the cytotoxic mechanism of Cd. At very low concentrations, Cd induces expression of ZnT1, a unique efflux transporter that functions as a Zn/Ca exchanger. To prevent toxicity from zinc overload, zinc is extruded from cells by ZnT1, an efflux transporter for Zn only. Zinc loss continues as Cd exposure persists. There is no equivalent exit route for Cd, and most acquired Cd is thus retained within tubular cells. Excreted Cd reflects cytotoxicity at the present time because it is released from injured or dying tubular cells.

Current evidence implicates chronic exposure to low-dose Cd does increase the worldwide prevalence of NAFLD, hypertension and CKD. Incident CKD could be viewed as the signs of toxic environment continuance. CKD and hypertension in people chronically exposed to Cd arise primarily from proximal tubule damage, inflammation, tubulointerstitial fibrosis, tubular atrophy, and irreversible nephron destruction.

As inferred by NHANES data, a significant proportion of the U.S. general population will develop CKD from exposure to Cd in a normal diet, but the existing exposure limits for Cd ranging between 0.21 and 0.83 μg/kg body weight per day do not afford health protection. New health-protective exposure guidelines should be established. By the benchmark dose response concept, a 5-10 % decrease in eGFR can be used as a sensitive endpoint for estimating a safe dietary Cd exposure level, instead of β_2M excretion exceeding 300 μg/g creatinine. A 5-10% increase in total protein excretion could also be an early warning sign of Cd nephrotoxicity suitable for estimating a dietary Cd exposure level that produces a discernable impact on kidneys.

Of concern, the current environmental Cd exposure has now reached toxic levels in a significant proportion of many populations. A permissible dietary Cd exposure level should preserve functional integrity of liver and kidneys, while minimizing risk of developing hypertension.

Public health measures should also be developed to help minimize Cd contamination of food chains. Loss of GFR in Cd-exposed people is irreversible. Furthermore, an effective chelation therapy to remove Cd from the body does not exist, and treatment options when CKD reaches its end-stage are limited. Thus, it appears pivotal to avoid foods containing high Cd and stop smoking. It is pivotal to maintain optimal body content of metal nutrients, especially Zn and iron, which reduce Cd

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absorption rate, its entrance into systemic circulation. and prevent zinc deficiency induced by the metal. Ensuring adequate intake of dietary antioxidants is a complementary preventive measure.

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