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The overlooked impact of cadmium on the progression of chronic hepatitis and the onset of renal failure in advanced cirrhosis

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ABSTRACT

The mechanism of hepatocyte destruction in chronic hepatitis is not completely understood, while renal failure in individuals with advanced cirrhosis is a significant concern. It is well known that smokers who are chronically infected with hepatitis B and C viruses (HBV, HCV) have a poor prognosis. In the present review, we propose a novel hypothesis that environmental exposure to a nephrotoxic metal pollutant, cadmium (Cd) may contribute to hepatocyte destruction and, subsequently, affect the duration of chronic hepatitis. The metal binding protein, metallothionein (MT) sequesters cadmium as CdMT complexes, and effectively neutralize its adverse effects. Cadmium can cause the damage to hepatocytes, only when it is in an unbound form. In addition to its ability to bind cadmium, MT can act as a scavenger of reactive oxygen species (ROS). However, the cellular MT levels may decrease, when ROS is excessively produced under the pathologic chronic viral hepatitis conditions, especially while the cellular levels of zinc may also be low. Zinc is an endogenous inducer of MT, and is required for maximal MT expression. High ROS levels in the hepatocytes diminishes MT binding to metals. Consequently, the proportion of unbound Cd is increased and thus there is more hepatic damage. Hepatic damage leads to a copious release of CdMT into the circulation. This significant cadmium load, which occurs after hepatic damage, and in some cases, muscle atrophy, induces kidney damage with resultant renal failure in advanced cirrhosis.

1. Introduction

1.1. Entry of environmental cadmium into the human body

The Agency for Toxic Substances and Disease Registry has listed cadmium (Cd) as one of the top ten environmental substances posing threat to human health [1]. Globally, human populations are increasingly exposed to this heavy metal through foods and polluted air [2]. Volcanic eruption on the Earth's surface is a known environmental source of Cd and the ocean floor activity is linked to elevated Cd levels in marine species [3]. Anthropogenic sources of Cd include incineration of municipal waste, mining, biomass and fossil fuel combustion [2]. The utilization of phosphorus fertilizers increases the bioavailability and bioaccumulation of Cd in the soil. Consequently, Cd is taken up by crops and deposited within their edible parts. Subsequently, Cd enters the human body directly through the consumption of plant foods and indirectly through the consumption of organ meat (offal) from animals that fed on these plants [4].

Diet is the main source of exposure among non-smokers [5], while in populations that smoke, cigarettes represent a significant source of Cd [6]. Nonetheless, occupational exposure and inhalational exposure in urban areas are rising concerns [7–9]. Essential food items such as rice, spinach, potatoes, and cereals like oats and barley, which are part of daily food consumption, significantly contribute to the body burden of Cd [10]. As a staple food, rice is a substantial source of exposure in Far East countries like Japan, Korea, and China [11,12]. In addition to

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polluted air, cigarette smoking is a significant source of Cd among smokers, who were found to have higher levels of Cd in their blood and urine, compared to non-smokers of similar age and gender [13,14].

Cd enters the body through the gut and lung, and once in circulation, including the transferrin bound form [15], is distributed to cells in tissues and organs throughout the body [16,17]. Cd is found in nearly all tissues and organs analyzed, including the liver, kidney and skeletal muscle [16,17].

Nowadays it is widely acknowledged that certain comorbidities/conditions, such as chronic obstructive pulmonary disease, anemia, iron deficiency, low dietary calcium intake, and low circulating levels of parathyroid hormone (PTH), may elevate blood Cd levels by promoting increased the intestinal absorption of Cd[18–24]. Consequently, higher levels of Cd can reach internal organs and express their toxicity. However, limited knowledge exists regarding how certain diseases could increase Cd blood levels by causing a release of Cd from its internal deposits. Therefore, the aim of this review is to summarize the potential mechanisms involved in a release of hepatic Cd and subsequent redistributing Cd to other organs, as well as to identify the pathologies to which it may be related.

2. Methods

A nonsystematic literature review was conducted using PubMed, along with other relevant sources such as the National Center for Biotechnology Information and Google Scholar. The following keywords were employed: 'cadmium hepatic toxicity,' 'cadmium renal toxicity,' 'cadmium liver fibrosis,' and 'Metallothioneins and Cd.' Etc. The search was restricted to studies published between 1980 and 2024, excluding case reports and mini-reviews. Given the narrative nature of our review and the novel hypothesis proposed, not all manuscripts identified by the search terms were included. The review focused on exploring the potential role of increased cadmium load, which is common in chronic liver disease, in the development of kidney failure

3. Chronic viral hepatitis, liver cirrhosis, and its complications

Chronic viral hepatitis remains a global health concern. In 2015 alone, nearly 1.4 million deaths were attributed to viral hepatitis, with estimates for the same year indicating that 71 million people were living with chronic hepatitis C virus (HCV) infection, and 257 million with chronic hepatitis B virus (HBV) infection [25]. Chronic viral hepatitis poses a significant challenge, and it is crucial to identify all factors influencing the duration of the disease in its chronic form. For instance, smoking, as an environmental factor, could negatively impact the course of chronic HBV and HCV infections, even though the mechanisms behind these interactions are not yet well understood.

Liver cirrhosis has traditionally been viewed as an irreversible stage of chronic liver disease. Pathological hallmarks of liver cirrhosis include the loss of normal liver microarchitecture, fibrosis, and the formation of regenerative nodules. Etiological factors contributing to liver cirrhosis encompass chronic HBV and HCV infections, chronic alcohol abuse, primary biliary cirrhosis, primary congestive conditions such as Budd-Chiari syndrome, secondary congestive conditions (e.g., heart failure), metabolic inducers (with tyrosinemia, Wilson disease, and hemochromatosis being the most frequent), and certain drugs like methotrexate, which can induce liver cirrhosis. Alternatively, the disease may be immune-mediated, as in autoimmune hepatitis. Indeed, liver cirrhosis is among the most widespread chronic diseases, imposing significant burdens in terms of both the condition itself and its associated complications. [26].

Over 450,000 deaths in the United States, between 1999 and 2016, were linked to liver cirrhosis [27]. Major complications of cirrhosis include portal hypertension, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, variceal bleeding, and hepatorenal syndrome [28]. Renal failure, in the form of hepatorenal syndrome or acute kidney injury, is common among cirrhosis patients. In a systematic review of 1827 individuals with liver cirrhosis and kidney failure, and 4142 persons with liver cirrhosis without kidney failure, Fede et al. observed a sevenfold increase in mortality from renal failure among those with cirrhosis [29].

Renal failure, as observed in hepatorenal syndrome or acute kidney injury, is a severe complication that affects patients in the advanced stages of liver cirrhosis. Renal failure is also a fatal complication of fulminant hepatitis. Liver transplantation remains the only effective therapy for resolving this critical issue [30]. The mechanisms contributing to the development of hepatorenal syndrome in cirrhosis may include alterations in splanchnic and systemic circulation, as well as the presence of inflammation [31]. Furthermore, the reasons behind poor outcomes in cirrhosis patients with severe muscle atrophy are still not entirely clear [32]. The mechanisms of renal failure in cirrhosis patients are complex and not yet fully understood.

4. Smoking's impact on chronic viral hepatitis and cadmium-induced hepatotoxicity

In a study of liver biopsies from individuals with confirmed and untreated HCV, Hézode et al. revealed a correlation between current smoking and the severity of hepatic tissue inflammation [33]. The results of meta-analyses indicate that smoking increases the risk of hepatocellular carcinoma (HCC) among HBV-positive individuals in a supra-additive manner, with an even more pronounced risk among those with HCV infection [34]. Dev et al. analyzed liver biopsies from 170 individuals with chronic hepatitis C, and they found that cigarette smoking contributes to the development of liver fibrosis [35]. In a cross-sectional study, where 310 individuals with chronic hepatitis C were included, Pessione et al. revealed a link between smoking and an increased fibrosis score after adjustment for age [36].

From the above findings, it appeared that smokers with chronic viral hepatitis had an accelerated rate of development of complications such as HCC and liver fibrosis. However, the mechanisms underlying why individuals with chronic viral hepatitis (HBV and HCV) who smoke experience poorer outcomes have yet to be fully evaluated. It's worth noting that almost 65 % of individuals living with hepatitis C infection are smokers, while only 15 % could be classified as never smokers [37] highlighting the prevalence of smoking among subjects with chronic HCV infection. Addressing the adverse effects of smoking in individuals with chronic viral hepatitis could potentially improve treatment outcomes.

Cigarettes contain numerous components that are highly toxic to humans, including heavy metals, particularly Cd [38] and the liver serves as a major repository for Cd. Moreover, increased Cd blood concentrations are observed in persons who smoke [39,40]. Additionally, Cd is potent promoter of liver fibrosis [41–43].

4.1. Human studies

Hyder et al. analyzed Cd urinary levels and parameters of liver function in 12,732 participants (20–74 years) of both sexes, and their findings revealed that high urinary levels of Cd are associated with an increased risk of non-alcoholic fatty liver disease (NAFLD) [44]. Hong et al. observe a 10-fold increment of urinary Cd was associated 1.4-fold and 1.3-fold increases in risk of elevated plasma levels of ALT and AST, respectively [45]. Hepatotoxicity of Cd was more pronounced in boys than girls [46]. Hepatic effect of Cd in adults was reproduced in Korean subjects [46].

4.2. Experimental studies

In a recent experimental study of Cd-mediated liver injury, Hu et al. used three groups of 3-week-old C57BL/6 male and female mice (control, CCl4-treated group, CCl4 + cadmium exposed group)[47]. Hu et al.

found that serum activity of alanine transaminase (ALT), aspartate transaminase (AST), and the ALT/AST ratio was elevated in the CCl4 + cadmium group compared to the CCl4-treated group after 8 weeks of the experiment. In this study [47], the authors treated mice with Cd in drinking water (100 nM).

Long-term Cd exposure has been linked to liver fibrosis by activating hepatic stellate cells to undergo myofibroblast-like differentiation [47] and Cd was associated with promoting CCl_4-mediated development of HCC, accompanied by elevated serum levels of alpha-fetoprotein.

Cd increased oxidative stress in the liver by activating phagocytic cells, leading to increased production of reactive oxygen species (ROS) [48] ultimately resulting in hepatocyte apoptosis. Renugadevi and Prabu administered an oral dose of Cd chloride at 5 mg/kg per day to Wistar albino rats for a period of 4 weeks. Their study revealed that in Cd-exposed rats, there was a significant increase in the levels of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma glutamyl transferase (GGT), and total bilirubin (TB) when compared to the control group. Furthermore, the activity of all the antioxidant enzymes examined, including glutathione peroxidase, glutathione S-transferase, and glutathione metabolizing enzymes such as glutathione reductase, as well as superoxide dismutase and catalase, was notably lower in the exposed rats compared to the controls [49]. In a study by Goodarzi et al. that investigated the hepatoprotective effects of atorvastatin, it was observed that rats exposed to Cd alone exhibited increased activity of AST, ALT, and alkaline phosphatase (ALP) in the serum. Additionally, there was a significant rise in malondialdehyde (MDA) levels in the liver tissue, while the activity of superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione (GSH) significantly decreased following Cd chloride administration[50].

5. Pathways by which Cd promotes the onset of liver fibrosis

Liver fibrosis is a substrate of advanced stage of chronic hepatitis and liver cirrhosis. Cd has pro-inflammatory effects and subsequently promotes oxidative stress by generating free oxygen radicals, i.e. Cd rises levels of TNFα, IL-1β and IL-6 [51,52]. Excess concentrations of TNFα could facilitate appearances of apoptosis in hepatocytes [53–55]. The nuclear factor-kappa B (NF-κB) is well-known transcriptional factor responsible for transcription of many inflammatory cytokines and thus enhance appreancence of inflammation [56], and Liu et al. demonstrated that mice treated with $CdCl_2$ by peritoneal injection, had higher activity of ALT and AST in the blood, had extensive necrosis of hepatocytes and upregulated NF-κB activativity[51]. Cd exposure in chickens activates the TGF-β/SMAD signaling pathway, leading to increased fibrosis markers (e.g. fibronectin) and epithelial-mesenchymal transition markers (e.g. α-SMA and vimentin) in hepatocytes, ultimately causing liver fibrosis. In this study, 7-day-old chickens were treated with Cd for 60 days to investigate these effects [57]. TGF-β which is multifunctional cytokine with immunomodulatory effects (e.g. negatively affects Th1 and Th2 cells and while promoting development into the Th17 and Th9 liens) produced by non-parenchymal liver cells such as Kupffer cells, macrophages or stellate cells, is identified as one of the key factors for the progression of liver fibrosis [58]. As we already noted, Cd exposure raises the concentrations of IL-6, while IL-6 may enhance transcription of STAT3 gene [59], and STAT3 provides substantial contribution to liver fibrosis[60].

Unambiguously, by promoting secretion of inflammatory cytokines, which in turn could promote transcription of other genes involved in liver fibrosis, such as NF-κB, TGF-β and STAT3, Cd at various levels enhance the onset of liver fibrosis and its progression.

6. Metallothioneins (MTs)

Metallothionein (MT) is a group of cysteine rich, low-molecular-weight proteins, comprising of four major isoforms; MT1, MT2, MT3, and MT4. MT1 and MT2 are commonly distributed throughout various tissues, while MT3 is primarily localized in zinc-enriched neurons found in specific regions of the brain, such as the cerebral cortex and hippocampus [61]. MT3 is expressed also in the kidney tubular cells of humans [62,63] and rats [64]. MT4 is distinctly associated with cornified and stratified squamous epithelia [61].

MT has a multifaceted role within the cell, which can be categorized into three primary functions: i) Heavy Metal Binding: MTs exhibit the capability to bind heavy metals such as Cd and lead (Pb), effectively mitigating their adverse effects on the cell; ii) Regulation of Physiological Divalent Cations: MTs also play a pivotal role in binding and regulating physiological divalent cations, including copper and zinc, crucial for cellular metabolism; iii) Protection Against Reactive Oxygen Species (ROS): MTs serve as a defense mechanism against tissue damage induced by ROS and demonstrate heightened activity during periods of inflammation.

The synthesis of MT is induced by zinc, as evidenced by a study showing that hepatic MT expression was not detectable in zinc-deficient rats [65]. In a study of men, aged 19–35 years, zinc supplements at a dose of 50 mg per day for 18 days increased MT levels in erythrocytes and monocytes [66]. Like zinc, Cd is an inducer of cellular MT synthesis [67–70]. Sequestering of Cd by MT prevent acute toxicity of the metal because Cd exerts toxicity in the unbound state, i.e., as Cd2+ ions; complexes of Cd and MT (CdMT) are often viewed as detoxified forms.

7. The interplays of zinc and cadmium

Lack of zinc may promote the hepatotoxicity of Cd in at least three different ways. Firstly, Cd and zinc compete for same metal transporters in the intestine, notably ZIP14 [71,72]. Accordingly, insufficient zinc intake or low-zinc diet may increase the intestinal absorption of Cd. Interestingly, Fujishiro et al. showed that the iron transporter, DMT-1, and calcium transporter (CaT1) may also serve as Cd transporters in high-dose exposure conditions, whereas ZIP14 may become a primary carrier for Cd in low-exposure situations [72]. Intestinal DMT-1 is overexpressed in iron deficiency due to increased HIFs accumulation [18]. Similar to DMT1 and iron deficiency, intestinal ZIP14 expression may be increased in zinc deficiency, Secondly, as discussed above zinc is required for activation of MT synthesis [65] Lack of zinc may consequently lead to cell damage due to a reduced cellular synthesis of MT and a decreased capacity to sequester a toxic metal Cd. Thirdly, zinc is integral part of superoxide dismutase 1 (SOD-1) and lack of zinc is associated with decreased antioxidant properties of the hepatocytes [73].

8. Zinc intake and cadmium toxicity

Adequate dietary Zn intake may reduce the risk of diseases associated with Cd exposure, detailed below.

In a study of U.S. population aged $\geq$ 50 years [74], elevated Cd body burden was associated with Zn intake levels below recommended dietary allowance (RDA) in both men and women. For both men and women, urinary Cd was associated with an increased mortality from cancer, but Zn intake below RDA was associated with an elevated cancer mortality risk in women only. There was a 1.55-fold increase in cancer mortality risk in women who consumed Zn below RDA, compared with women who met the RDA [74].

An effect of Zn on estimated glomerular filtration rate (eGFR) was observed in an analysis of data from 1545 participants aged $\geq$ 20 years in NHANES 2011–2012. In this cohort, 7.5 % had eGFR below 60 mL/min/1.73m^2 [75]. Blood Cd levels $>$ 0.53 μg/L were associated with a 2.04-fold increase in risk of low eGFR, compared with blood Cd levels $<$0.18 μg/L. For any given blood Cd level, serum Zn levels below 74 μg/dL were associated with a 3.38-fold increase in risk of low eGFR.

In another analysis of NHANES 1988–1994 data, environmental Cd exposure and inadequate Zn intake were associated with obstructive

lung disease independently of smoking [76]. The lowest tertile of Zn intake (<8.35 mg/day) was associated with a 1.89-fold increase in risk of obstructive lung disease, compared with the highest Zn intake tertile (>14.4 mg/day). The highest tertile of urinary Cd (>0.79 μg/g creatinine) was associated with increased risk of obstructive lung disease (OR 3.48), compared with the lowest tertile (urinary Cd <0.39 μg/g creatinine) in a model, adjusted for smoking. Thus, an approximate two-fold increase in body burden of Cd was associated with an increased risk of obstructive lung disease. Dietary Zn intake of 15 mg/day, which was higher than RDA of 11 mg/day for men and 8 mg/day for women, was required to reduce Cd absorption and limit the body burden of Cd to levels not associated with obstructive lung disease.

MT has the potential to provide protection against both acute and chronic liver injury due to Cd accumulation [77]. Klaassen and colleagues suggested that cadmium's ability to harm the cell is contingent to its free ionic state, i.e., when it is unbound or released from MT as free Cd^{2+} [77], This implies that the extent of Cd-induced hepatocyte damage is determined by the pre-existing cellular levels of MT. To detoxify Cd effectively, it is essential for cells to maintain adequate levels of MT with functional groups unoccupied by ROS. Because zinc and other physiological divalent cations are inducers of MT expression [78], the sufficient quantities of these physiologic activator of the MT gene, zinc included, ensure optimal intracellular MT levels are expressed. As shown in an early study of Sato et al. there was no detectable hepatic MT expression in rats fed with zinc-deficient diet [65].

Patients with liver cirrhosis were found to have elevated plasma levels of interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α), indicative of ongoing inflammation. During inflammatory processes, MT is upregulated to safeguard tissue from injury induced by inflammation or ROS [79–81].

Zinc and copper are essential for the normal function of the antioxidant enzyme superoxide dismutase 1 (SOD1). However, the SOD1 level in patients with chronic inflammation tended to fall due to an on-going defense against ROS.

In summary, to prevent damage from Cd accumulation, the cell must fulfill two key conditions: i) maintain the lowest possible Cd levels (which is a challenge for the liver, as it acts as a depot for Cd and continuing influx of Cd), and ii) ensure the presence of sufficient MT with functional groups unoccupied by ROS (another challenge since exogenous factors like HBV and HCV continually damage hepatocytes, and excess ROS is generated during inflammation).

Clearly, both conditions are far from what is observed in cirrhosis, leading to a state marked by high cellular Cd levels, low MT levels, and abundant ROS formation. Under such conditions, hepatocyte cell death ensues through apoptosis or necrosis [82], depending on the dose. Subsequently, Cd, once confined within hepatocytes, is released into the bloodstream (Fig. 1) and eventually reach the kidney [16]. The kidney, in particular, is the organ that accumulates most of acquired Cd [16]. As

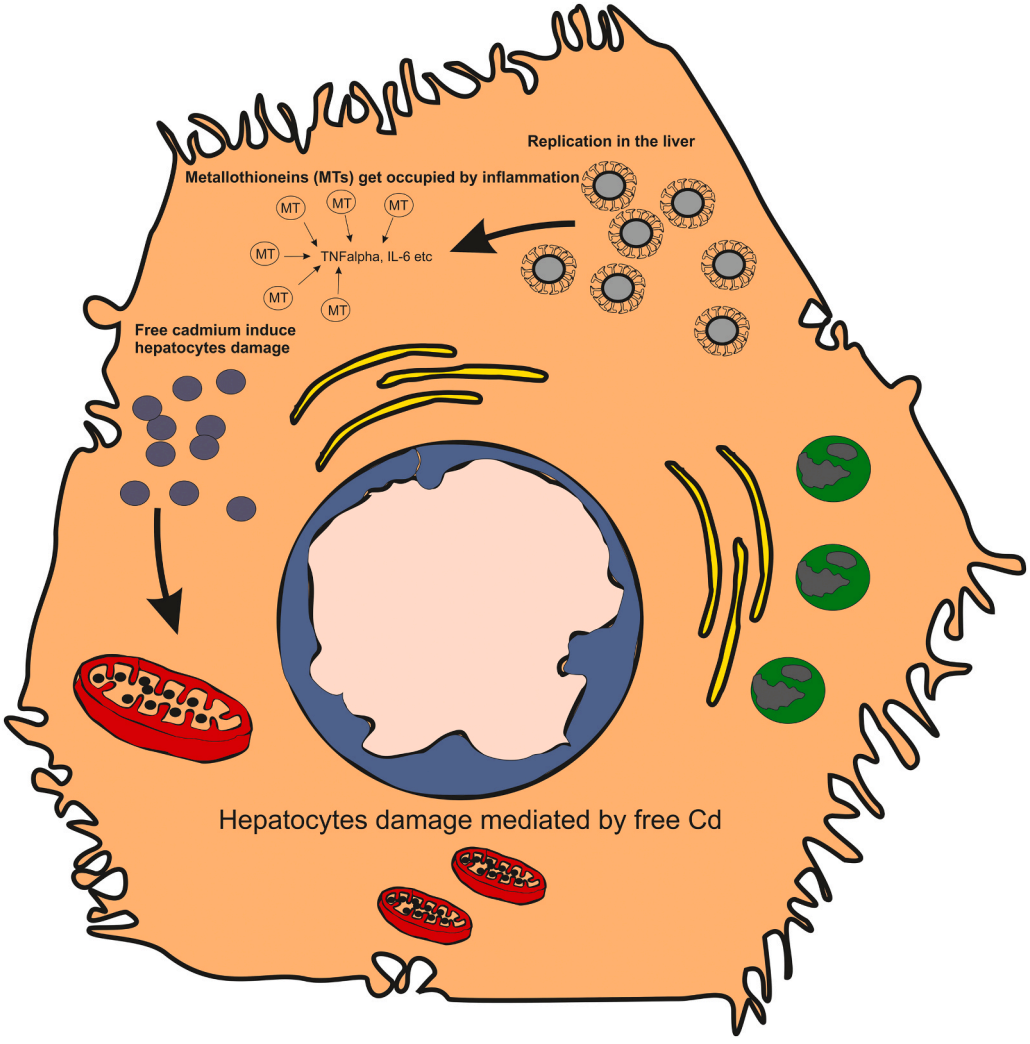

Fig. 1. Putative Mechanisms of Cadmium-Induced Hepatocyte Destruction. After hepatotropic viruses enter a hepatocyte, they promote the onset of inflammation, which 'consumes' MT molecules, leaving cadmium unbound to induce the destruction of hepatocytes.

the harmful effects of free Cd are dose-dependent[83], once the kidney accumulates a critical level of Cd, the development of hepatorenal syndrome or acute kidney injury becomes inevitable. In cases of hepatocyte destruction, the body not only loses the synthetic function of hepatocytes but also becomes intoxicated by their contents.

9. Cadmium quantities in the liver, kidney, and skeletal muscle

Baba et al. determined Cd concentration in various tissues from 80 patients with itai-itai disease (all of whom were elderly women, n = 80), and control subjects (n = 27) [84]. In the control group, the Cd concentration in the liver was 14 μg/g. When multiplied by the average liver weight of 1500 g, it was revealed that the liver contained 21,000 μg of Cd (21 mg). In advanced cirrhosis, a significant portion of the Cd once stored in the liver is released into circulation. The Cd concentration in the kidney varies between the cortex and the medulla (102 μg/g in the cortex and 44.9 μg/g in the medulla). When the average concentrations of the medulla and the cortex (73.45 μg/g) are multiplied by an average kidney weight of 120 g, the total amount of Cd in the kidney is calculated to be approximately 8.8 mg. This amount can easily increase due to the Cd release from dying hepatocytes.

It is noteworthy that even though skeletal muscle has a low average Cd concentration, as a whole, the skeletal muscle contains a substantial amount of Cd. Specifically, Baba et al. found that the Cd concentration in skeletal muscles was 1.7 μg/g. However, in men weighing 70 kg, the muscles, weighing approximately 28 kg, contain nearly 50 mg of Cd. While not all the Cd from the liver or skeletal muscles (in cases of muscle atrophy) enters the circulation, there is no doubt that the Cd burden in patients with cirrhosis is notably high.

Prystupa et al. examined the concentrations of various metals and metalloids in the serum of 62 individuals with alcoholic liver cirrhosis and 18 control subjects [85]. The authors discovered that individuals with alcoholic cirrhosis had higher serum concentrations of Cd along with lower levels of zinc[85]. When exposed to higher doses of Cd, nephrotoxic effects become more pronounced. The changes induced by Cd are irreversible, and there is no effective treatment available.

10. Transport of cadmium to renal proximal tubules and its adverse effects

Different forms of hepatocyte death are described in relation to Cd exposure, such as apoptosis [86], necrosis [87] or ferroptosis [88]. After hepatocytes membrane disintegrate, CdMT complexes enter a bloodstream and reach tubular lumen after the glomerular filtration. Previously, it was suggested that CdMT was reabsorbed by the proximal tubules via the megalin/cubulin receptor mediated endocytosis [89]. Current evidence, however, suggests that the distal and collecting ducts of kidneys reabsorbed mostly CdMT via lipocalin-2 receptor (LCN2-R; also called neutrophil gelatinase-associated lipocalin receptor or 24p3 receptor)[89,90]. LCN2-R has greater affinity for CdMT than megalin [89].

We have to keep in mind that individuals with liver cirrhosis and advanced stage of chronic hepatitis, synthetic activity of hepatocytes is low, and MTs are synthetized as in the case of healthy liver. Finally, as we discussed free Cd induces hepatocytes to undergo suicidal cell death. So free Cd may also enter a bloodstream, where 50 % of Cd is bound to transferrin, and the remainder Cd is bound to other plasma proteins including albumin and β_2-microglobulin (β_2M). In a similar way to non-transferrin bound iron, Cd can utilize zinc transporters such as ZIP8 and ZIP 4 to enter proximal tubule cells, since they both are expressed [91]. Transferrin receptor 1 is also expressed in proximal tubule cells [92]. Thus, there are multiple routes by which Cd released from liver enter proximal tubules cells. Of interest, in an *in vitro* experiment, injury to the rat proximal tubule WKPT-0293 Cl.2 cells was evident after exposure to albumin and β_2M complexed with Cd, but the injury was not found when cells were exposed to albumin or β2 M alone [93].

11. The toxicity of cadmium

Cd is a nephrotoxin that has been shown to reduce the GFR in a dose-dependent manner [94]. Chronic exposure to environmental Cd, even in low level, was associated with an increased risk of a reduced eGFR in the general U.S. population [95].

11.1. Cadmium and kidneys: human studies

In a prospective cohort study of 672 kidney transplant recipients, Sotomayor et al. found that plasma Cd concentrations are independently and consistently associated with the risk of long-term kidney graft failure [96]. Notably, the adverse effects of Cd on the kidneys are dose-dependent, meaning that higher doses are linked to more profound injury, while lower concentrations result in lesser damage.

In a case-control study of 88 subjects with diabetes and 88 age- and sex-matched controls Yimthiang et al. measured kidney function (β2-microglobulin excretion and estimated glomerular filtration rate, eGFR) and measured Cd concentrations in the blood and urine of all included subjects. They demonstrated that Cd deteriorated kidney function which was reflected in tubular proteinuria, in both individuals with and without diabetes [97]. Tsai et al. measured Cd concentrations in 200 individuals with CKD and categorized them into three groups based on Cd blood levels: low cadmium blood levels (BCL: ≤4.77 nmol/L), middle cadmium blood levels (BCL: 4.78–7.90 nmol/L), and high cadmium blood levels (BCL≥7.91 nmol/L). They found a significantly higher number of individuals in stage 5 of CKD in the group with high cadmium blood levels [98].

Satarug et al. analyzed Cd body burden and eGFR in 482 individuals (354 women and 118 men) and demonstrated that environmental exposure to Cd was closely linked to a declining GFR and albuminuria [99]. Both glomeruli and tubules are targets of Cd-induced nephrotoxicity, as evident in numerous in vivo studies and human-involved research. These results suggest that accumulated Cd impaired a single mechanism for proximal tubular reabsorption and degradation of filtered albumin and β2 M[100]. From other published information, we infer that the mechanism probably involved the availability or function of the apical receptor megalin in S1 of the proximal tubule.

11.2. Cadmium and kidneys: experimental studies

There are abundant of literature reports on Cd-induced nephrotoxicity, and some are discussed herein. Liu et al. conducted a study on 40 adult Sprague-Dawley rats divided into four groups: a control group, a low-dose Cd group (1 mg/kg of Cd-chloride), a moderate-dose Cd group (2.5 mg/kg of Cd-chloride), and a high-dose Cd group (5 mg/kg of Cd-chloride). Their findings showed that Cd exposure led to several alterations, including increased serum concentrations of blood urea, creatinine, and β2-microglobulin levels, along with a decrease in serum iron concentrations. Additionally, the Cd-treated groups exhibited higher levels of malondialdehyde (MDA) and superoxide dismutase-1 (SOD-1), while the activity of superoxide dismutase-2 (SOD-2) and catalase (CAT) was notably reduced. Unambiguously, Cd mediated renal alterations are mediated by promotion of oxidative stress (increased ROS activity) and inflammation elevated levels of inflammatory markers such as IL-18 and IL-1β)[101]. Next, an in vitro study performed by Luo et al., in which the authors utilized the NRK-52E cell line, demonstrated that an increase in Cd exposure time and dose led to a greater extent of DNA damage. Moreover, Cd exposure was associated with alterations in cell cycles, such as the appearance of arrests in the transition from the G0/G1 to the S phase[102]. Dong et al. found in their in vivo and in vitro examination that Cd, even in low doses, results in the onset and progression of premature renal senescence and the occurrence of fibrosis via the SIRT1-P53 pathway[103]. Moreover, appearance of fibrosis after Cd exposure has been demonstrated in many studies[104,105]. Exposure to Cd also induced morphological changes in mitochondria, such as

mitochondrial swelling, deformation, and vacuolar degeneration[106]. The extent of Cd-induced nephrotoxicity is directly proportional to the concentrations involved; higher Cd concentrations are associated with more pronounced deleterious effects [106,107]. Lv et al. aimed to examine the relationship between Cd-related damage to proximal tubule epithelial cells. For this purpose, they utilized Prague-Dawley rats, divided into two groups based on whether they were peritoneally treated with Cd or saline, and NRK-52E cells (for the in vitro part of the study). They demonstrated that iron accumulation and the onset of ferroptosis, mediated by heme oxygenase 1 (HO-1), played a significant role in Cd-mediated alterations in tubular epithelial cells [108].

12. Brief discussion with conclusion

In a landmark experiment, the nephrotoxicity of Cd was observed following liver transplantation from Cd-exposed rats [109]. This study provides strong evidence that the CdMT release from the "transplant" liver can be delivered to kidneys and cause toxicity.

As far as we are aware, there are no studies that have measured blood concentrations of Cd and followed renal and hepatic parameters. Additionally, no one has measured Cd levels in patients with hepatorenal syndrome. Such studies would help clarify the potential role of Cd in the pathogenesis of hepatorenal syndrome. Hara et al. correlated certain liver fibrosis parameters, such as the Fibrosis-4 (FIB-4) index and non-alcoholic fatty liver disease (NAFLD) fibrosis score (NFS), with kidney function parameters such as the eGFR and albumin-to-creatinine ratio in 3640 Japanese CKD patients [110]. They reported lower eGFR in individuals with higher FIB-4 and NAFLD fibrosis scores (Table 1). Using the same scores (FIB-4 index and NFS), Akira Mima analyzed their correlation with histopathological examination in 179 patients aged between 16 and 80 years who underwent renal biopsy. She reported an inverse correlation between eGFR measured prior to biopsy and FIB-4; urinary N-Acetyl-β-glucosaminidase (NAG) was also inversely associated with FIB-4[111]. We speculate that the results of both studies could, at least in part, be explained by increased Cd load due to the loss of hepatocytes. Hepatorenal syndrome is a complex and not entirely understood condition, and Cd load could be considered a contributing mechanism if future studies confirm our speculations.

Among other relevant factors, cigarette smoking can possibly expedite the progression of chronic HCV and HBV infections by increasing the body's Cd burden. Furthermore, given cadmium's proven carcinogenic properties, it may also contribute to the development of hepatocellular carcinoma. It is imperative that individuals with chronic viral hepatitis refrain from smoking to mitigate these risks. Additionally, the presence of zinc and selenium in adequate amounts in the human body may help mitigate the adverse effects of Cd. In cases of advanced cirrhosis, a substantial amount of Cd is released from the liver and, in some instances, from atrophied skeletal muscles. The majority of this released Cd accumulates in the kidneys, significantly contributing to the occurrence of renal failure.

Ultimately, these findings underscore the critical importance of avoiding cigarette smoking and foods that have high Cd concentrations, as well as maintaining adequate intake levels of zinc and selenium, especially for individuals with chronic viral hepatitis and advanced cirrhosis.

Ethical approval

Not applicable

Funding statement

None

Table 1
Blood and urinary cadmium levels associated with multiple adverse effects in the general population studies.

Study population	Cadmium exposure levels and observed effects	Reference
U.S. population NHANES 1988 – 1994 N = 12,732 ≥ 20 yrs	Urinary cadmium (Cd) levels ≥ 0.83 μg/g creatinine were associated with liver inflammation in women (OR 1.26), while levels ≥ 0.65 μg/g creatinine were linked to liver inflammation (OR 2.21), nonalcoholic fatty liver disease (NAFLD) (OR 1.30), and nonalcoholic steatohepatitis (NASH) (OR 1.95) in men	Hyder et al. 2013 [112]
U.S. population NHANES 1999 – 2015 N = 11, 838 ≥ 20 yrs	A tenfold increment of urinary Cd was associated with increased risk of having abnormal plasma levels of ALT (OR 1.36) and AST (OR 1.31)	Hong et al. 2021 [113]
U.S. population NHANES 1999 – 2016 N = 4411 adolescents	Urinary Cd quartile 4 was associated with abnormal plasma levels of ALT (OR 1.40) and AST (OR 1.64). The effect was larger in boys than girls	Xu et al. 2022 [114]
U.S. population, NHANES, 1999 – 2012 n 18,425 for H. pylori, n 17,389 for HBV, ≥ 3 yrs	Blood Cd levels > 0.61 μg/L were associated with increased risks of HBV infection (OR 1.72), and H. pylori infection (OR 1.5).	Krueger and Wade 2016 [115]
U.S. population, NHANES, 1999 – 2018 N = 47,422, ≥20 yrs old	Cd exposure was identified as an independent risk factor for liver fibrosis across all ethnic groups, including Hispanic Blacks, Mexican Americans, and non-Hispanic Whites. Being in the fourth quartile of blood Cd levels was associated with an increased risk of advanced liver fibrosis[a] (OR 1.81).	Ma et al. 2023 [116]
U.S. population, NHANES, 1999 – 2020 N= 55,677, 20–85 yrs, 5175 had CKD	After adjustment for blood cotinine level (smoking), risk of having CKD rose 2.1-fold 3.2-fold and 5.5-fold, comparing blood Cd levels <0.21–0.21–0.35, 0.36–0.60, and > 0.60 μg/L, respectively.	Akinleye et al. 2024 [117]
Korean population, N= 2953, ≥ 19 yrs	Urinary Cd quartile 4 (> 0.88 μg/L) was associated with higher plasma AST, compared with quartile 1. Urinary Cd quartiles 4, 3, and 2 were associated with higher plasma ALT, compared with quartile 1	Kim et al. 2021 [118]
Korean population, N = 3914, ≥ 19 yrs	Blood Cd levels ≥ 1.98 μg/L were associated with AST > 35 IU/L (OR 3.61) and ALT > 45 IU/L (OR 2.40)	Kang et al. 2013 [119]
Korean population, N = 12,099, ≥ 19 yrs	Blood Cd higher than 0.96 and 1.41 μg/L were associated with NAFLD (OR 1.91) and NASH (OR 1.41)	Park et al. 2021 [120]
The Fukuoka Kidney Disease Registry Study, Japan N = 3640 with CKD.	Higher Fibrosis−4 index was associated with lower eGFR values (β = − 0.45 for each 1-point increase in FIB−4 index) plus more advanced renal fibrosis evident from kidney biopsy data.	Hara et al. 2021 [110]
Scotland, United Kingdom N = 2046, ≥ 18 yrs, 598 had NAFLD with liver fibrosis	Risks of CKD and mortality rose, respectively 1.31-fold and 2.30-fold in those with liver fibrosis without structural, autoimmune, or malignant CKD.	Gurun et al. 2024 [121]

NHANES, National Health and Nutrition Examination Survey; n, sample size; OR, odds ratio; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase. [a] Advanced liver fibrosis was defined as Fibrosis-4 ≥2.67 and/or Forns index ≥ 6.9 and abnormal ALT [5].

CRediT authorship contribution statement

Sasa Jankovic: Writing – original draft. **Aleksandar Cirovic:** Validation, Supervision, Conceptualization. **Soisungwan Satarug:** Writing – original draft, Supervision, Conceptualization. **Jovan Jevtic:** Writing – original draft. **Ana Ivanovski:** Writing – original draft. **Orish E. Orisakwe:** Writing – original draft. **Ana Cirovic:** Writing – original draft, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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