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# Mechanisms and Long-Term Impact of Chronic Cadmium Exposure on Renal Function and Structural Integrity in Terrestrial Mammals: An Analysis of Nephrotoxicity, Oxidative Stress, and Species-Specific Susceptibility

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## Abstract

Cadmium (Cd), a heavy metal, is recognized for its toxicological effects on various biological systems, particularly in the kidneys of terrestrial mammals. Chronic exposure to cadmium, often through environmental contamination, occupational exposure, or dietary intake, has been associated with significant nephrotoxic effects. The kidneys, being the primary organs for filtering blood and excreting waste, are highly susceptible to cadmium accumulation. This paper examines the mechanisms by which cadmium impairs renal function, with a focus on chronic exposure outcomes. Cadmium's ability to bioaccumulate in renal tissue over time contributes to progressive renal damage, manifesting in conditions such as tubular dysfunction, glomerular injury, and reduced glomerular filtration rate (GFR). The cellular and molecular mechanisms include oxidative stress induction, interference with metal transport systems, apoptosis, and inflammatory responses. Understanding these mechanisms is essential for evaluating the long-term risks associated with cadmium exposure and developing effective preventive strategies. This study further discusses the differential impacts on renal function across various mammalian species, considering factors such as age, sex, and genetic predispositions. By elucidating cadmium's effects on the kidneys, this paper aims to provide insights that could inform public health policies, regulatory standards, and therapeutic interventions aimed at minimizing cadmium exposure risks.

**Keywords:** *Cadmium, Chronic exposure, Nephrotoxicity, Oxidative stress, Renal damage, Species differences, Toxicology*

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## 1. Background

Cadmium, a heavy metal naturally present in the Earth's crust, frequently enters the environment as a byproduct of various industrial activities, including mining, metal refining, smelting, and the manufacturing of batteries and pigments. The mobilization of cadmium from natural sources is significantly enhanced by human activities, leading to its widespread environmental dispersion. This metal tends to accumulate in soils, water bodies, and air, resulting in pervasive contamination that affects both terrestrial and aquatic ecosystems. The primary sources of cadmium exposure in the general population are through dietary intake and environmental contact. Foods such as leafy vegetables, grains, legumes, and particularly shellfish, which bioaccumulate heavy metals, are major contributors to cadmium ingestion. In areas of high environmental contamination, exposure can also occur through the inhalation of airborne cadmium particles, which may originate from industrial emissions, cigarette smoke, or the use of cadmium-containing fertilizers [1], [2].

Once cadmium enters the body, it is slowly absorbed, particularly in the gastrointestinal tract, from where it is transported to various organs. Among these, the kidneys receive substantial amounts due to their essential role in blood filtration and waste excretion. Cadmium's affinity for renal tissues makes the kidneys especially susceptible to damage, as the metal accumulates over time, leading to toxicity. This accumulation is facilitated by cadmium's binding to metallothionein, a metal-binding protein that aids in the transport of the metal through the bloodstream. Upon reaching the kidneys, cadmium is filtered by the glomeruli and subsequently reabsorbed in the proximal tubules, where it induces damage. The chronic nature of cadmium exposure implies that even at low levels, cadmium can progressively accumulate in renal tissues, resulting in nephrotoxicity that manifests after prolonged latency periods. This means that by the time significant symptoms of renal dysfunction become apparent, extensive damage may have already occurred [3], [4].

Cadmium-induced nephrotoxicity is primarily characterized by tubular dysfunction, which can progress to more severe glomerular damage. The proximal tubular cells, which play a key role in reabsorbing essential substances such as glucose, amino acids, and small proteins from the filtrate, are the main sites of cadmium accumulation. When cadmium is taken up by these cells, it disrupts cellular functions through several mechanisms. First, cadmium interferes with cellular homeostasis by displacing essential metals like zinc from metallothioneins and other metal-binding proteins, leading to impaired enzymatic activities and structural integrity. This disruption results in oxidative stress, as cadmium promotes the generation of reactive oxygen species (ROS), which can damage cellular components, including lipids, proteins, and DNA.

The oxidative stress induced by cadmium is a critical factor in its nephrotoxic effects, as it triggers a cascade of cellular events that culminate in inflammation and apoptosis. In proximal tubular cells, cadmium exposure activates stress signaling pathways, such as the mitogen-activated protein kinase (MAPK) pathways, which regulate cell survival, proliferation, and apoptosis. These pathways, once activated by oxidative stress, can lead to the expression of pro-inflammatory cytokines and chemokines, thereby exacerbating tissue injury. Moreover, cadmium has been shown to impair mitochondrial function, which not only contributes to oxidative stress but also disrupts the energy metabolism of cells, leading to reduced ATP production and further cellular dysfunction.

Another key mechanism by which cadmium exerts nephrotoxic effects is through interference with the renal transport systems. The proximal tubules contain various transporters responsible for reabsorbing essential nutrients and ions, and cadmium can disrupt these transporters either by directly inhibiting their activity or by altering their expression levels. For example, studies have demonstrated that cadmium exposure reduces the expression of aquaporin-1 (AQP1), a water channel protein in the proximal tubules, which is essential for water reabsorption. Similarly, cadmium can impair the function of sodium and phosphate transporters, resulting in imbalances in electrolyte and nutrient reabsorption that contribute to the overall dysfunction of the kidneys.

The nephrotoxic effects of cadmium are also associated with fibrotic changes within the renal tissue. Chronic cadmium exposure leads to the activation of fibrogenic signaling pathways, such as the transforming growth factor-$\beta$ (TGF-$\beta$) pathway, which promotes the accumulation of extracellular matrix components, leading to renal fibrosis. This fibrotic process further impairs renal function by disrupting the normal architecture of the kidney and reducing its ability to filter and excrete waste products. As fibrosis progresses, it can cause irreversible damage to the glomeruli and interstitial tissues, leading to chronic kidney disease (CKD).

Animal studies, particularly those involving terrestrial mammals with renal structures and functions analogous to humans, have provided valuable insights into the mechanisms underlying cadmium-induced nephrotoxicity. Rodent models, for instance, have been extensively used to study the accumulation of cadmium in the kidneys and the subsequent toxic effects. These models have shown that the progression of cadmium nephrotoxicity involves an initial phase of tubular dysfunction, characterized by proteinuria, glucosuria, and aminoaciduria, followed by a decline in glomerular filtration rate (GFR) and eventual renal failure. Furthermore, these studies have highlighted the role of metallothionein in modulating the toxicity of cadmium, as animals with higher levels of metallothionein expression tend to exhibit increased tolerance to cadmium exposure.

In human populations, chronic cadmium exposure has been linked to various kidney-related conditions, such as decreased GFR, proteinuria, and CKD. Epidemiological studies have demonstrated that individuals living in areas with high environmental cadmium contamination, such as regions near industrial plants or areas with cadmium-rich soils, have a higher prevalence of renal dysfunction compared to populations with lower exposure levels. Moreover, occupational exposure to cadmium, particularly in industries such as battery manufacturing and metalworking, has been associated with an increased risk of kidney disease. Itai-itai disease, a historical case of mass cadmium poisoning in Japan, exemplifies the severe impact of cadmium on renal health, where prolonged exposure led to significant kidney damage and skeletal abnormalities among the affected population.

In addition to direct nephrotoxic effects, cadmium exposure has been associated with the development of hypertension, which further exacerbates kidney damage. Cadmium-induced hypertension is thought to arise from several factors, including increased oxidative stress, endothelial dysfunction, and disturbances in calcium homeostasis. Hypertension, in turn, contributes to the progression of CKD by imposing additional stress on the renal vasculature and promoting glomerular sclerosis. Therefore, the relationship between cadmium exposure, hypertension, and kidney disease represents a complex interplay of factors that collectively impair renal function.

Understanding the pathways through which cadmium induces nephrotoxicity is crucial for developing effective biomarkers for early detection and strategies to mitigate its impact. Biomarkers such as urinary cadmium levels, beta-2-microglobulin, and N-acetyl-$\beta$-D-glucosaminidase (NAG) have been proposed as indicators of early renal damage due to cadmium exposure. These biomarkers reflect tubular dysfunction and can be used to monitor individuals at risk of nephrotoxic effects. However, the variability in individual susceptibility to cadmium toxicity, influenced by factors such as age, genetic polymorphisms, and pre-existing health conditions, poses challenges in establishing universal diagnostic criteria. Therefore, further research is needed to identify more sensitive and specific biomarkers that can reliably detect early renal impairment caused by cadmium.

Mitigation strategies for cadmium exposure focus on reducing environmental and occupational sources of the metal. Regulatory measures to limit cadmium emissions from industrial processes, restrict the use of cadmium-containing fertilizers, and enforce safety standards in workplaces are essential for minimizing human exposure. Additionally, public health interventions aimed at educating populations about dietary sources of cadmium and promoting dietary choices that minimize cadmium intake can further reduce the risk of nephrotoxicity. In individuals with known cadmium exposure, strategies such as chelation therapy to enhance cadmium excretion and the use of antioxidants to counteract oxidative stress may provide therapeutic benefits, although their efficacy in reversing established renal damage remains limited.

## 2. Mechanisms of Cadmium-Induced Renal Impairment

Cadmium, upon entering the body via ingestion or inhalation, undergoes a complex process of bioaccumulation and cellular uptake. When ingested, cadmium is absorbed through the gastrointestinal tract, whereas inhaled cadmium is taken up by the lungs. Once absorbed, cadmium binds to proteins such as metallothionein and albumin in the bloodstream, which facilitates its transport to various organs, especially the kidneys. Metallothionein, a low-molecular-weight, metal-binding protein, has a high affinity for cadmium and plays a significant role in buffering the metal's toxicity by sequestering it within cells. However, this sequestration is not entirely protective; rather, it enables the gradual accumulation of cadmium in tissues, particularly in the kidneys, which have a naturally high affinity for the metal. Within the renal system, cadmium accumulates predominantly in the proximal tubular cells, the nephron's primary site of reabsorption and secretion. The slow rate of cadmium excretion through urinary pathways results in prolonged retention of the metal in these cells, leading to a gradual increase in cadmium concentration over time. Chronic exposure to low levels of cadmium thus culminates in progressive accumulation within the kidneys, establishing a foundation for nephrotoxic effects [3].

The accumulation of cadmium in the renal cortex is critical because it coincides with the region most susceptible to cadmium-induced damage. The proximal tubular cells are not only responsible for reabsorbing essential nutrients and electrolytes but also for detoxifying and excreting various substances. Cadmium uptake by these cells occurs via mechanisms such as endocytosis and transport through metal ion channels. For instance, cadmium can enter cells by competing with other divalent cations, such as calcium and zinc, for transporter binding sites, thus infiltrating cellular compartments. This uptake is facilitated by cadmium's interaction with specific transport proteins, such as divalent metal transporter 1 (DMT1), which is involved in the cellular uptake of divalent metals. The binding of cadmium to metallothionein within cells further complicates its detoxification, as the cadmium-metallothionein complex can persist in the lysosomes of proximal tubular cells, potentially being released during cellular stress, thereby exacerbating cadmium toxicity.

A significant pathway through which cadmium exerts its toxic effects is via the induction of oxidative stress, a condition characterized by the imbalance between the production of reactive oxygen species (ROS) and the capacity of the cellular antioxidant system to neutralize these reactive intermediates. Although cadmium is not a redox-active metal in the same way that iron and copper are, it indirectly promotes the generation of ROS through multiple mechanisms. One way cadmium contributes to oxidative stress is by depleting intracellular levels of antioxidants such as glutathione (GSH). Glutathione, a tripeptide with a thiol group, plays a crucial role in neutralizing free radicals

**Table 1.** Pathways Involved in Cadmium-Induced Nephrotoxicity

| Pathway | Mechanism of Cadmium-Induced Disruption |
|---|---|
| Oxidative Stress | Cadmium promotes the production of reactive oxygen species (ROS), leading to damage of cellular components such as lipids, proteins, and DNA. |
| Metal Homeostasis | Cadmium displaces essential metals like zinc from metallothionein and other metal-binding proteins, disrupting enzymatic activities. |
| Mitochondrial Dysfunction | Impairs mitochondrial electron transport chain, leading to decreased ATP production and increased ROS generation. |
| Inflammatory Response | Activates pro-inflammatory pathways such as MAPK, leading to the release of cytokines and chemokines that exacerbate renal injury. |
| Fibrogenic Pathways | Stimulates pathways like TGF-$\beta$ that promote the accumulation of extracellular matrix, resulting in fibrosis. |

**Table 2.** Biomarkers of Cadmium-Induced Renal Damage

| Biomarker | Indication of Renal Dysfunction |
|---|---|
| Urinary Cadmium | Reflects chronic exposure and accumulation in the kidneys. |
| Beta-2-Microglobulin | Indicates tubular dysfunction due to impaired reabsorption. |
| N-A cetyl-$\beta$-D-Glucosaminidase (NAG) | Marker of proximal tubular damage, elevated in response to cellular injury. |
| Proteinuria | Signals glomerular and tubular damage, often observed in chronic kidney disease. |
| Glomerular Filtration Rate (GFR) | Reduced GFR suggests impaired kidney function due to nephrotoxicity. |

and detoxifying harmful substances. Cadmium exposure leads to the depletion of GSH, thus reducing the cell's ability to combat oxidative stress. Additionally, cadmium inhibits the activity of critical antioxidant enzymes, including catalase, superoxide dismutase (SOD), and glutathione peroxidase. These enzymes are involved in the breakdown of hydrogen peroxide and superoxide radicals, which, if not neutralized, can contribute to oxidative damage.

The excessive production of ROS due to cadmium exposure results in oxidative damage to various cellular components, including lipids, proteins, and DNA. Lipid peroxidation is a particularly harmful process induced by ROS, leading to the destabilization of cellular membranes, including the mitochondrial membrane, which is critical for maintaining cellular energy homeostasis. Protein oxidation, another consequence of ROS accumulation, disrupts enzyme functions and structural protein integrity, while DNA damage can trigger mutagenesis and cell death. In renal tissues, the accumulation of these molecular damages culminates in cell apoptosis or necrosis, contributing to tissue injury and loss of kidney function. The mitochondrial dysfunction associated with oxidative stress further exacerbates cadmium toxicity, as impaired mitochondrial activity leads to reduced ATP production, which is vital for the energy-dependent processes in the proximal tubular cells. Furthermore, cadmium has been shown to disrupt mitochondrial electron transport chain activity, thereby directly contributing to ROS generation within these organelles.

Disruption of metal homeostasis is another fundamental aspect of cadmium's toxicological profile, where it interferes with the biological functions of essential metals, particularly zinc, calcium, and iron. Cadmium competes with these metals for binding sites on various enzymes and transport proteins due to their similar ionic radii and charge. For instance, cadmium's competition with zinc is especially relevant because zinc plays a pivotal role in stabilizing the structure and function of numerous enzymes, including those involved in DNA repair and antioxidant defense. By displacing zinc from metallothionein and zinc-dependent enzymes, cadmium not only disrupts their function but also exacerbates oxidative stress, as the released zinc ions can no longer contribute to the antioxidant defense mechanisms [5].

Similarly, cadmium interferes with calcium signaling by disrupting calcium transport and homeostasis. Calcium is a crucial second messenger in various intracellular signaling pathways, regulating processes such as cell proliferation, apoptosis, and muscle contraction. Cadmium's interference with calcium channels, such as voltage-gated calcium channels and calcium ATPases, disrupts intracellular calcium levels, thereby impairing cellular functions dependent on precise calcium signaling. For instance, the dysregulation of calcium homeostasis can activate calpains, which are calcium-dependent proteases, leading to the cleavage of structural proteins and enzymes, further contributing to cellular injury. Moreover, cadmium-induced alterations in intracellular calcium levels have been implicated in triggering apoptosis through the activation of mitochondrial pathways, involving the release of cytochrome c and the subsequent activation of caspases.

The nephrotoxic effects of cadmium are thus multifaceted, involving a combination of oxidative stress, disruption of metal homeostasis, and interference with critical signaling pathways. The damage inflicted on the proximal tubular cells disrupts their ability to reabsorb nutrients and excrete waste products efficiently, leading to conditions such as proteinuria, glucosuria, and electrolyte imbalances. Over time, the continued accumulation of cadmium and its toxic effects can extend to the glomeruli, resulting in decreased glomerular filtration rate (GFR) and progressing towards chronic kidney disease (CKD).

In understanding the mechanisms underlying cadmium-induced nephrotoxicity, several signaling pathways emerge as key contributors to the observed cellular and tissue damage. One such pathway is the activation of mitogen-activated protein kinases (MAPKs), including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38. The activation of these kinases by cadmium-induced oxidative stress has been linked to the regulation of genes involved in cell survival, inflammation, and apoptosis. For instance, JNK activation has been associated with the promotion of apoptotic pathways in response to oxidative stress, while ERK activation can mediate inflammatory responses through the upregulation of pro-inflammatory cytokines. Additionally, cadmium exposure activates the nuclear factor-kappa B (NF-$\kappa$B) pathway, a transcription factor complex that regulates the expression of genes involved in inflammation and immune responses. The activation of NF-$\kappa$B by cadmium contributes to the inflammatory response in renal tissues, exacerbating tissue injury and fibrosis [6].

Cadmium exposure induces a pronounced inflammatory response in the kidneys, which plays a significant role in exacerbating the toxic effects of this heavy metal. The inflammation is characterized by the

**Table 3.** Mechanisms Involved in Cadmium-Induced Nephrotoxicity

| Mechanism | Description |
|---|---|
| Bioaccumulation | Cadmium accumulates primarily in the kidneys due to slow excretion rates and high affinity for renal tissues, especially proximal tubular cells. |
| Oxidative Stress | Promotes the generation of ROS, leading to lipid peroxidation, protein oxidation, and DNA damage. Inhibits antioxidant enzymes, depleting protective reserves like glutathione. |
| Metal Homeostasis Disruption | Interferes with essential metals such as zinc and calcium by displacing them from binding sites, disrupting enzyme functions and intracellular signaling pathways. |
| Mitochondrial Dysfunction | Impairs electron transport chain, leading to reduced ATP production and increased ROS generation. Triggers release of pro-apoptotic factors. |
| Inflammatory Signaling | Activates MAPK and NF-$\kappa$B pathways, leading to upregulation of pro-inflammatory cytokines and chemokines, exacerbating renal tissue injury. |

**Table 4.** Cadmium's Impact on Metal Homeostasis and Cellular Transport

| Affected Metal or Pathway | Effect of Cadmium Interference |
|---|---|
| Zinc | Cadmium competes with zinc for binding sites on metallothionein and zinc-dependent enzymes, impairing their function and exacerbating oxidative stress. |
| Calcium | Disrupts intracellular calcium levels by interfering with calcium transporters, leading to dysregulated signaling, activation of calpains, and apoptosis. |
| Iron | Alters iron metabolism by competing with iron in binding sites, contributing to oxidative stress and impairing iron-dependent enzymes. |
| Transport Proteins | Inhibits or alters the expression of transport proteins such as DMT1 and calcium channels, affecting the cellular uptake and distribution of essential ions. |
| Intracellular Signaling | Disrupts cellular signaling pathways dependent on metal ions, affecting processes such as cell proliferation, apoptosis, and response to oxidative stress. |

activation of various signaling pathways that lead to the production and release of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-$\alpha$). These cytokines serve as key mediators in the inflammatory response by recruiting immune cells, such as macrophages and neutrophils, to the site of injury. The infiltration of these immune cells into the renal interstitial tissue further contributes to inflammation through the release of additional reactive oxygen species (ROS), proteolytic enzymes, and other inflammatory mediators. This cascade of events not only perpetuates the inflammatory response but also aggravates tissue injury and fibrosis within the kidneys.

The pro-inflammatory cytokines activated by cadmium exposure play distinct roles in mediating renal inflammation. TNF-$\alpha$, for example, is known to promote the activation of nuclear factor-kappa B (NF-$\kappa$B), a transcription factor that regulates the expression of numerous genes involved in inflammation, cell proliferation, and apoptosis. The activation of NF-$\kappa$B by TNF-$\alpha$ enhances the production of additional cytokines and chemokines, thereby creating a feedback loop that amplifies the inflammatory response. Similarly, IL-6 acts as both a pro-inflammatory and anti-inflammatory cytokine, modulating immune responses and promoting the acute phase response. The persistent elevation of IL-6 in cadmium-exposed renal tissues has been associated with chronic inflammation, which contributes to the development of interstitial fibrosis. Fibrosis, a hallmark of chronic kidney disease (CKD), involves the excessive accumulation of extracellular matrix components in the renal interstitium, disrupting the normal architecture and function of the kidneys.

Moreover, the inflammatory response triggered by cadmium exposure is closely linked to the activation of cellular death pathways, including apoptosis and necrosis. Apoptosis, or programmed cell death, is a tightly regulated process that allows for the elimination of damaged or dysfunctional cells. In the context of cadmium nephrotoxicity, apoptosis is often initiated by mitochondrial dysfunction, characterized by the loss of mitochondrial membrane potential and the release of cytochrome c into the cytosol. This event triggers the activation of caspases, particularly caspase-9 and caspase-3, which execute the apoptotic process by cleaving various cellular substrates, leading to the orderly dismantling of the cell. In addition to mitochondrial pathways, cadmium-induced apoptosis can also be mediated through endoplasmic reticulum (ER) stress, which occurs when the accumulation of misfolded proteins overwhelms the protein-folding capacity of the ER. The resulting unfolded protein response (UPR) activates stress-related signaling pathways that can lead to cell death if homeostasis is not restored [7].

Necrosis, in contrast to apoptosis, is a form of uncontrolled cell death that results from acute cellular injury, leading to cell membrane rupture and the release of intracellular contents. This release triggers a robust inflammatory response, as the intracellular molecules act as damage-associated molecular patterns (DAMPs), signaling to the immune system that cell damage has occurred. Cadmium-induced necrosis in the kidneys further exacerbates inflammation and contributes to renal tissue damage. The dual occurrence of apoptosis and necrosis in cadmium-exposed renal tissues signifies a shift from a regulated response to a pathological state, where the loss of functional renal cells compromises kidney function and propagates injury.

The nephrotoxic effects of cadmium are not uniform throughout the kidney but rather exhibit variability in different segments of the nephron. The proximal tubule is particularly vulnerable to cadmium toxicity, as it is the primary site for cadmium accumulation and is involved in the reabsorption of filtered substances from the glomerular filtrate. In the proximal tubules, cadmium exposure leads to cellular dysfunction and death, resulting in impaired reabsorption of essential solutes, such as glucose, amino acids, and low-molecular-weight proteins. This dysfunction manifests clinically as tubular proteinuria and increased urinary excretion of substances that are normally reabsorbed by the renal tubular cells. The disruption of transport

**Table 5.** Cadmium-Induced Inflammatory and Cell Death Pathways in the Kidneys

| Pathway | Mechanism of Action |
|---|---|
| Inflammatory Response | Cadmium exposure leads to the release of pro-inflammatory cytokines (e.g., TNF-$\alpha$, IL-6) and chemokines, recruiting immune cells and perpetuating inflammation. NF-$\kappa$B activation enhances cytokine production. |
| Apoptosis | Triggered by mitochondrial dysfunction, caspase activation, and ER stress. Leads to the orderly elimination of damaged renal cells, contributing to tissue remodeling. |
| Necrosis | Occurs due to acute cellular injury, resulting in cell membrane rupture. Release of DAMPs activates immune response, exacerbating inflammation and tissue injury. |
| Fibrosis | Driven by the activation of TGF-$\beta$ signaling, leading to the differentiation of fibroblasts into myofibroblasts and the accumulation of extracellular matrix proteins. |
| Glomerular Injury | Impairs the filtration barrier, resulting in proteinuria and decreased GFR. Chronic exposure leads to glomerulosclerosis, reducing nephron function. |

mechanisms in the proximal tubule also leads to electrolyte imbalances, which further contribute to renal dysfunction.

Cadmium exposure also affects the glomerulus, the nephron's filtration unit, by impairing the integrity of the glomerular filtration barrier. The glomerular filtration barrier consists of endothelial cells, the glomerular basement membrane, and podocytes, which together function to selectively filter blood, allowing water and small solutes to pass while retaining larger proteins. Cadmium-induced damage to the glomerular filtration barrier can result in the leakage of proteins into the urine, a condition known as proteinuria. This proteinuria is indicative of glomerular damage and is often accompanied by a decline in the glomerular filtration rate (GFR), a measure of kidney function. The reduction in GFR reflects decreased filtration capacity due to glomerular injury and is a key feature of progressive kidney disease.

Chronic cadmium exposure has long-term consequences on renal structure and function, leading to irreversible changes such as interstitial fibrosis and glomerulosclerosis. Interstitial fibrosis involves the deposition of extracellular matrix proteins, including collagen and fibronectin, in the renal interstitium, resulting in scarring and loss of functional tissue. The fibrotic process is driven by multiple factors, including the persistent activation of fibrogenic signaling pathways, such as transforming growth factor-$\beta$ (TGF-$\beta$), which promotes the differentiation of fibroblasts into myofibroblasts. Myofibroblasts are key effectors of fibrosis, as they produce large amounts of extracellular matrix components, further contributing to tissue remodeling and stiffening of the renal parenchyma. Glomerulosclerosis, on the other hand, refers to the hardening or scarring of the glomeruli, which occurs as a result of chronic glomerular injury. The loss of functional glomeruli due to sclerosis reduces the number of nephrons capable of filtration, leading to a progressive decline in kidney function [8].

The combined effects of tubular damage, glomerular injury, inflammation, and fibrosis ultimately result in significant impairment of renal function. The kidney's ability to maintain homeostasis, filter waste products, and regulate fluid and electrolyte balance is compromised, leading to the development of chronic kidney disease. As cadmium continues to accumulate with ongoing exposure, the renal damage becomes more extensive and difficult to reverse, highlighting the importance of early detection and prevention of cadmium nephrotoxicity.

## 3. Chronic Exposure Outcomes

Chronic exposure to cadmium is associated with a progressive decline in renal function, a condition that typically develops insidiously, with affected individuals often remaining asymptomatic in the early stages of toxicity. The absence of overt symptoms during the initial phase of renal damage is due to the kidneys' considerable functional reserve, allowing them to compensate for early cellular and structural injuries. However, as exposure persists and the cumulative burden of cadmium in the renal tissues increases, the toxic effects become more pronounced, leading to the gradual loss of functional nephrons. This reduction in nephron number impairs the kidneys' ability to maintain fluid and electrolyte balance, filter waste products, and regulate acid-base homeostasis. Clinically, progressive renal dysfunction due to cadmium exposure is characterized by a decline in the glomerular filtration rate (GFR), elevated serum creatinine levels, and the appearance of proteinuria. These markers reflect the deterioration of renal function and are indicative of significant nephron loss, which, if left unaddressed, can advance to chronic kidney disease (CKD) and potentially end-stage renal disease (ESRD) [9], [10].

The reduction in GFR, a crucial indicator of renal function, occurs as the cadmium-induced damage extends beyond the tubular structures to affect the glomeruli. Cadmium exposure disrupts the integrity of the glomerular filtration barrier, leading to alterations in the selective permeability of the glomerular capillaries. As a result, larger molecules, such as albumin, which are normally retained within the bloodstream, begin to appear in the urine, manifesting as proteinuria. The decline in GFR is accompanied by an increase in serum creatinine, a waste product generated by muscle metabolism and excreted by the kidneys. Elevated serum creatinine levels reflect reduced filtration capacity and are commonly used in clinical practice to estimate the extent of renal impairment. As the nephrotoxic effects of cadmium accumulate, affected individuals may also experience uremia, a condition marked by the buildup of nitrogenous waste products in the blood, which can lead to symptoms such as fatigue, nausea, and confusion.

One of the earliest detectable manifestations of cadmium nephrotoxicity is tubular dysfunction, particularly affecting the proximal tubules, where cadmium predominantly accumulates. The proximal tubular cells are responsible for reabsorbing low-molecular-weight proteins, amino acids, glucose, and other essential solutes from the filtrate. Cadmium interferes with this reabsorptive function by damaging the tubular epithelium, leading to a decrease in the efficiency of solute transport. The impaired reabsorption results in the excretion of proteins, such as beta-2-microglobulin and retinol-binding protein, in the urine, a condition known as tubular proteinuria. Tubular proteinuria is a sensitive marker of early cadmium-induced nephrotoxicity and often precedes the decline in GFR and overt symptoms of kidney dysfunction. It reflects the direct toxic effects of cadmium on the renal tubular cells, which can lead to cell death and sloughing of tubular cells into the urine.

In addition to causing proteinuria, cadmium-induced tubular dysfunction impairs the kidneys' ability to concentrate urine. Normally, the proximal tubules play a critical role in water reabsorption, helping to concentrate the urine and conserve body fluids. Cadmium

**Table 6.** Effects of Cadmium on Different Renal Structures

| Renal Structure | Impact of Cadmium Exposure |
|---|---|
| Proximal Tubule | Cadmium accumulation leads to tubular cell dysfunction and death. Impaired reabsorption of solutes and proteins results in tubular proteinuria and electrolyte imbalances. |
| Glomerulus | Disruption of the glomerular filtration barrier causes proteinuria and reduced GFR. Long-term exposure may result in glomerulosclerosis. |
| Renal Interstitium | Persistent inflammation leads to interstitial fibrosis, characterized by the excessive accumulation of extracellular matrix and loss of normal renal architecture. |
| Mitochondria | Cadmium-induced mitochondrial dysfunction contributes to reduced ATP production, oxidative stress, and activation of apoptotic pathways. |
| Endoplasmic Reticulum | ER stress is induced by cadmium, leading to the unfolded protein response and activation of cell death pathways if cellular homeostasis is not restored. |

disrupts this process by altering the expression and function of water channel proteins, such as aquaporins, and by damaging the tubular epithelium, leading to decreased water reabsorption. This defect in tubular function manifests as polyuria, or excessive urine output, which may be accompanied by nocturia (increased urination at night). The inability to properly concentrate urine can also lead to electrolyte imbalances, as the loss of water in the urine is often accompanied by the excretion of electrolytes, such as sodium, potassium, and calcium. These electrolyte disturbances can have systemic effects, contributing to symptoms like muscle weakness, cramps, and arrhythmias [11].

The progressive accumulation of cadmium in the renal cortex exacerbates tubular dysfunction over time, eventually extending to other parts of the nephron. As tubular cells continue to suffer damage, there is a corresponding decline in the kidney's ability to maintain homeostasis, resulting in acidosis, hyperphosphatemia, and disturbances in calcium-phosphate metabolism. The disruption of calcium and phosphate balance, in particular, may contribute to secondary hyperparathyroidism and bone disorders, which are common complications of chronic kidney disease. Furthermore, the cadmium-induced damage to the tubular cells and glomeruli triggers compensatory mechanisms, such as hyperfiltration in the remaining functional nephrons, to maintain overall renal function. While these compensatory mechanisms may initially help to preserve GFR, they can ultimately accelerate the progression of nephron loss by imposing increased workload and hemodynamic stress on the surviving nephrons, leading to glomerular sclerosis and further deterioration of kidney function.

Cadmium-induced nephrotoxicity is also associated with alterations in the renal handling of essential micronutrients. For instance, cadmium exposure has been shown to interfere with the renal reabsorption of zinc and magnesium, leading to deficiencies of these trace elements. Zinc is crucial for various enzymatic processes, including those involved in antioxidant defense and DNA repair, while magnesium plays a role in neuromuscular function and bone health. The loss of these micronutrients through impaired renal reabsorption can contribute to systemic manifestations of cadmium toxicity [12], further complicating the clinical picture of renal dysfunction.

Long-term exposure to cadmium can significantly damage the glomeruli, the specialized structures within the kidneys that filter blood to produce urine. The primary effects of cadmium on the glomeruli involve structural alterations, such as thickening of the glomerular basement membrane (GBM) and mesangial expansion. The GBM is a crucial component of the filtration barrier, composed of a dense network of collagen and other extracellular matrix proteins that selectively allow water and small solutes to pass while retaining larger molecules like proteins. Cadmium exposure leads to the deposition of abnormal extracellular matrix components in the GBM, resulting in its thickening. Additionally, mesangial cells, which provide structural support to the glomerular capillaries, become activated in response to cadmium-induced oxidative stress and inflammation, causing them to proliferate and produce excess extracellular matrix material. This mesangial expansion further disrupts the normal glomerular architecture, thereby compromising the integrity and function of the filtration barrier.

The combination of GBM thickening and mesangial expansion contributes to a reduction in the filtration capacity of the kidneys, manifesting as decreased glomerular filtration rate (GFR). As the damage progresses, proteins that are normally retained in the blood, such as albumin, begin to appear in the urine, resulting in proteinuria. Persistent proteinuria not only serves as an indicator of glomerular injury but also exacerbates kidney damage by inducing a pro-inflammatory state in the renal tubules, as filtered proteins can activate tubular cells to produce cytokines and chemokines. The continued exposure to cadmium and the associated glomerular alterations may eventually lead to glomerulosclerosis, a form of scarring characterized by the accumulation of extracellular matrix material within the glomeruli. Glomerulosclerosis results in the obliteration of glomerular capillaries and a loss of functional filtration units, leading to a further decline in renal function.

Glomerulosclerosis is a pivotal pathological feature in the progression of chronic kidney disease (CKD) associated with cadmium nephrotoxicity. The process is driven by a complex interplay of factors, including persistent inflammation, oxidative stress, and hemodynamic changes within the kidneys. The scarring of the glomeruli limits the number of functional nephrons, placing a greater workload on the remaining healthy nephrons. This compensatory hyperfiltration in the surviving nephrons temporarily sustains overall kidney function but at the cost of accelerating the injury process. Over time, the increased pressure and flow through the surviving nephrons promote further damage, leading to secondary focal segmental glomerulosclerosis and progressive nephron loss.

In addition to glomerular injury, cadmium exposure induces significant changes in the renal interstitium, the connective tissue surrounding the nephron structures. The inflammatory response elicited by cadmium leads to the recruitment of immune cells, such as macrophages and lymphocytes, into the renal interstitium, where they release pro-inflammatory cytokines, growth factors, and ROS. This inflammatory milieu stimulates fibroblasts to differentiate into myofibroblasts, which are cells capable of producing large quantities of collagen and other extracellular matrix components. The accumulation of these extracellular matrix materials in the renal interstitium results in interstitial fibrosis, a process characterized by the replacement of normal kidney tissue with scar tissue.

Interstitial fibrosis is a critical factor in the progression of chronic kidney disease, as it disrupts the normal architecture and function of the kidney. The excessive deposition of collagen and extracellular matrix components around the nephrons constricts blood vessels, thereby reducing the blood flow and oxygen supply to renal tissues. This hypoxic environment exacerbates tubular and glomerular damage, creating a vicious cycle of injury, inflammation, and fibrosis.

**Table 7.** Clinical Manifestations of Progressive Renal Dysfunction Due to Cadmium Exposure

| Clinical Indicator | Description and Mechanism |
|---|---|
| Decreased GFR | Reflects reduced nephron number and filtration capacity due to glomerular and tubular damage. |
| Elevated Serum Creatinine | Indicates impaired renal excretion of creatinine, a marker of reduced GFR and renal function. |
| Proteinuria | Results from disruption of glomerular filtration barrier and proximal tubular cell damage. Presence of low-molecular-weight proteins in urine signals tubular dysfunction. |
| Polyuria | Due to impaired water reabsorption in damaged proximal tubules, resulting in excessive urine output. |
| Electrolyte Imbalances | Loss of sodium, potassium, and calcium in urine due to tubular dysfunction, leading to systemic effects such as muscle cramps and arrhythmias. |

**Table 8.** Pathophysiological Effects of Cadmium on Tubular Function

| Renal Tubular Effect | Mechanism and Consequence |
|---|---|
| Tubular Proteinuria | Cadmium-induced damage to the proximal tubular cells impairs protein reabsorption, leading to the excretion of proteins such as beta-2-microglobulin in urine. |
| Impaired Urine Concentration | Damage to aquaporins and tubular cells reduces water reabsorption, resulting in polyuria and decreased urine osmolality. |
| Electrolyte Loss | Cadmium disrupts the reabsorption of electrolytes, causing increased urinary excretion of sodium, potassium, and magnesium. |
| Acid-Base Imbalance | Reduced reabsorption of bicarbonate and other buffering substances by damaged tubular cells contributes to metabolic acidosis. |
| Altered Calcium-Phosphate Metabolism | Impaired reabsorption of calcium and phosphate disrupts bone metabolism, potentially leading to osteomalacia and secondary hyperparathyroidism. |

The fibrotic process ultimately leads to tubular atrophy, where the affected tubules shrink and lose function, further impairing the kidney's ability to filter blood and maintain homeostasis. As the extent of interstitial fibrosis increases, it becomes more challenging for the kidneys to recover from damage, making this condition a major predictor of poor prognosis in chronic kidney disease.

Cadmium-induced interstitial fibrosis is not solely a result of direct tissue injury but also involves signaling pathways that promote fibrogenesis. One key pathway implicated in this process is the transforming growth factor-$\beta$ (TGF-$\beta$) signaling pathway, which plays a central role in regulating the deposition of extracellular matrix components. Cadmium exposure upregulates the expression of TGF-$\beta$, leading to the activation of downstream signaling molecules, such as Smad proteins, which promote the transcription of genes associated with fibrosis. The upregulation of TGF-$\beta$ not only stimulates fibroblast differentiation but also inhibits the degradation of extracellular matrix by downregulating matrix metalloproteinases (MMPs), enzymes that normally break down collagen. This imbalance between matrix synthesis and degradation results in the progressive accumulation of scar tissue.

Additionally, other profibrotic factors, such as connective tissue growth factor (CTGF) and platelet-derived growth factor (PDGF), contribute to the fibrotic response by enhancing fibroblast proliferation and collagen production. The combined effect of these signaling pathways leads to a sustained fibrotic response, which becomes self-perpetuating as the kidneys continue to undergo injury and repair cycles. The severity of interstitial fibrosis often correlates with the degree of renal impairment, making it a crucial determinant of the long-term outcome of cadmium-induced nephrotoxicity.

## 4. Factors Influencing Cadmium Toxicity

The susceptibility of different terrestrial mammalian species to cadmium-induced renal damage varies significantly, reflecting species-specific differences in renal physiology, cadmium handling, and defense mechanisms against heavy metal toxicity. These variations arise from multiple factors, including the expression of cadmium-binding proteins, such as metallothionein, the capacity of antioxidant defenses, and the efficiency of renal excretion mechanisms. For example, rodents are frequently used as models to study cadmium nephrotoxicity due to their relatively rapid cadmium accumulation and clear manifestations of renal damage. However, the responses observed in rodents may not fully translate to larger mammals, such as primates or domesticated animals, due to differences in renal anatomy, metabolism, and longevity. Rodents exhibit a higher rate of metallothionein induction in response to cadmium exposure, which can provide a temporary protective effect by sequestering cadmium and mitigating its immediate toxicity. Nevertheless, the same protective mechanisms may not be as robust in larger mammals, which could explain the differences in susceptibility to cadmium nephrotoxicity observed across species.

In larger mammals, including primates, the capacity to upregulate metallothionein in response to cadmium exposure is often lower compared to rodents, potentially resulting in less efficient sequestration of cadmium within the renal tissues. This reduced metallothionein response, combined with a longer lifespan and a slower cadmium excretion rate, may lead to more pronounced accumulation of cadmium over time and a greater risk of nephrotoxicity. Additionally, species-specific differences in renal transport proteins, such as those involved in cadmium uptake and excretion, contribute to variability in cadmium handling across species. For instance, differences in the expression of divalent metal transporter 1 (DMT1) or other cadmium transporters can influence the extent to which cadmium is taken up by renal tubular cells, thereby affecting the degree of nephrotoxic damage. Understanding these interspecies differences is crucial for accurately extrapolating findings from animal models to humans and for assessing the risk of cadmium exposure in various species, including wildlife and domesticated animals.

Age is another important factor that influences the susceptibility to cadmium-induced nephrotoxicity. Older individuals are generally more prone to cadmium toxicity due to a combination of cumulative exposure over time and age-related declines in renal function. The

**Table 9.** Pathological Changes in the Kidney Due to Cadmium Exposure

| Pathological Feature | Mechanism and Consequence |
|---|---|
| Glomerular Basement Membrane Thickening | Cadmium exposure leads to abnormal deposition of extracellular matrix components, reducing the filtration capacity of the glomeruli. |
| Mesangial Expansion | Proliferation of mesangial cells and excess matrix production disrupt glomerular architecture, contributing to decreased GFR and proteinuria. |
| Glomerulosclerosis | Accumulation of scar tissue in the glomeruli results in loss of functional filtration units and further decline in renal function. |
| Interstitial Fibrosis | Inflammatory response stimulates collagen deposition and extracellular matrix accumulation, replacing normal kidney tissue with scar tissue. |
| Tubular Atrophy | Consequence of interstitial fibrosis and hypoxia, leading to shrinkage of tubular structures and loss of function. |

**Table 10.** Signaling Pathways Involved in Cadmium-Induced Fibrosis

| Pathway | Role in Fibrosis |
|---|---|
| TGF-$\beta$ Signaling | Promotes extracellular matrix deposition by activating Smad proteins and inhibiting matrix degradation. Upregulation by cadmium contributes to sustained fibrotic response. |
| Connective Tissue Growth Factor (CTGF) | Enhances fibroblast proliferation and collagen synthesis, further driving the fibrotic process. |
| Platelet-Derived Growth Factor (PDGF) | Stimulates the proliferation of mesangial cells and fibroblasts, leading to increased matrix production and fibrosis. |
| NF-$\kappa$B Pathway | Activation by inflammation increases the expression of pro-fibrotic cytokines and chemokines, exacerbating fibrosis. |
| Hypoxia-Inducible Factor (HIF) | Hypoxia in fibrotic tissue leads to upregulation of HIF, which promotes fibrogenesis by enhancing the expression of TGF-$\beta$ and other pro-fibrotic factors. |

kidneys naturally lose some of their regenerative capacity with age, resulting in a diminished ability to repair cadmium-induced cellular damage. Additionally, as the body ages, the capacity of the renal excretory system to eliminate cadmium may decrease, leading to increased retention of the metal in the kidneys. This accumulation exacerbates the toxic effects of cadmium, as the prolonged presence of the metal in renal tissues heightens the risk of oxidative stress, inflammation, and fibrosis. Furthermore, age-related reductions in the expression of protective proteins, such as metallothionein and antioxidant enzymes, contribute to the increased vulnerability of older individuals to cadmium nephrotoxicity.

Sex differences also appear to influence the extent of cadmium-induced renal damage, with some studies suggesting that males may be more susceptible than females. The higher susceptibility in males may be partly attributed to differences in renal physiology, such as variations in renal blood flow, glomerular filtration rate (GFR), and hormone regulation, which can affect the uptake and distribution of cadmium in the kidneys. Testosterone has been shown to enhance the expression of certain renal transporters involved in metal reabsorption, potentially increasing the accumulation of cadmium in the male kidney. In contrast, estrogen in females may exert a protective effect by modulating antioxidant defenses and reducing oxidative stress. Additionally, females typically have higher levels of metallothionein expression in response to cadmium exposure, which could help mitigate the metal's toxic effects. However, these protective effects may diminish with age, as the hormonal balance changes, leading to an increased risk of nephrotoxicity in postmenopausal women.

Genetic predisposition plays a critical role in determining individual and species-specific susceptibility to cadmium nephrotoxicity. Variations in genes that regulate the expression of metallothionein, antioxidant enzymes, and transport proteins can influence how an organism responds to cadmium exposure. For instance, polymorphisms in genes encoding metallothionein isoforms may result in differences in the ability to sequester cadmium and protect renal tissues from its toxic effects. Individuals with genetic variants associated with lower metallothionein expression may have a heightened risk of cadmium accumulation and subsequent kidney damage. Similarly, genetic variations in antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase, can affect the capacity to neutralize reactive oxygen species (ROS) generated during cadmium exposure. Individuals with genetic polymorphisms that result in reduced enzyme activity may experience more severe oxidative stress and cellular injury when exposed to cadmium [13].

The influence of genetic factors on cadmium susceptibility extends to differences in the regulation of transport proteins involved in metal uptake and excretion. For example, genetic variations in the gene encoding DMT1 or other metal transporters can alter the efficiency of cadmium uptake by renal tubular cells, potentially increasing the burden of cadmium in the kidneys. Moreover, genetic differences in the regulation of inflammatory pathways, such as those involving nuclear factor-kappa B (NF-$\kappa$B), may affect the extent of the inflammatory response triggered by cadmium exposure, influencing the severity of renal damage. Understanding the genetic basis of susceptibility to cadmium nephrotoxicity is important for identifying at-risk populations and for developing targeted preventive strategies that take into account individual genetic profiles [14]

## 5. Conclusion

Cadmium exposure poses a substantial threat to renal health in terrestrial mammals, with its toxic potential largely driven by the metal's tendency to bioaccumulate in the body, particularly in the kidneys. The nephrotoxicity associated with cadmium is mediated through several interconnected mechanisms, including oxidative stress, disruption of metal homeostasis, inflammatory responses, and the induction of cellular death pathways. Each of these processes contributes to the progressive deterioration of kidney function, manifesting in structural and functional damage to various nephron segments, such as the proximal tubules and glomeruli.

A key factor in cadmium-induced nephrotoxicity is its ability to generate oxidative stress, which is characterized by an imbalance between reactive oxygen species (ROS) production and the antioxidant

**Table 11.** Factors Influencing Susceptibility to Cadmium-Induced Nephrotoxicity

| Factor | Description and Impact on Susceptibility |
|---|---|
| Species Variability | Different species exhibit varying susceptibilities due to differences in cadmium handling, metallothionein expression, and antioxidant defenses. Rodents may not fully represent the nephrotoxic response seen in larger mammals. |
| Age | Older individuals are more susceptible due to cumulative exposure, reduced renal regenerative capacity, and age-related decline in metallothionein and antioxidant enzyme activity. |
| Sex Differences | Males may be more prone to cadmium nephrotoxicity due to hormonal influences on renal transporters and metal accumulation, while females may have some protection due to estrogen-mediated antioxidant effects. |
| Genetic Predisposition | Genetic polymorphisms in genes encoding metallothionein, antioxidant enzymes, and transport proteins can influence susceptibility to cadmium-induced renal damage. |
| Renal Physiology | Variations in renal blood flow, glomerular filtration rate, and transporter expression affect cadmium uptake, distribution, and excretion, influencing nephrotoxic outcomes. |

**Table 12.** Genetic Factors Affecting Cadmium Nephrotoxicity

| Genetic Factor | Role in Modulating Susceptibility |
|---|---|
| Metallothionein Gene Variants | Polymorphisms affecting metallothionein expression can alter the capacity to sequester cadmium and protect against renal damage. |
| Antioxidant Enzyme Genes | Variations in genes encoding enzymes like superoxide dismutase and glutathione peroxidase can influence the ability to neutralize ROS and mitigate oxidative stress. |
| Metal Transporter Genes | Genetic differences in transport proteins such as DMT1 affect cadmium uptake and accumulation in the kidneys, impacting nephrotoxicity risk. |
| Inflammatory Pathway Genes | Polymorphisms in genes regulating NF-$\kappa$B and other inflammatory mediators may affect the extent of the inflammatory response to cadmium exposure. |
| Hormone Receptor Genes | Genetic variations in hormone receptor expression can influence sex-specific responses to cadmium, modulating susceptibility to renal damage. |

defenses within the cells. Although cadmium itself is not redox-active, it promotes ROS generation indirectly by depleting antioxidant reserves, such as glutathione, and inhibiting critical enzymes involved in the detoxification of free radicals. The resultant oxidative stress damages lipids, proteins, and DNA, leading to cellular dysfunction and death. This damage is particularly pronounced in the proximal tubular cells, which are the primary sites for cadmium accumulation in the kidneys. Here, cadmium disrupts cellular homeostasis by interfering with mitochondrial function, exacerbating oxidative stress, and impairing ATP production, which is essential for energy-dependent processes in renal tubular cells.

In addition to oxidative stress, cadmium disrupts the transport and homeostasis of essential metals, such as zinc and calcium. This disruption occurs because cadmium competes with these metals for binding sites on various enzymes and transporters, displacing them and impairing their physiological functions. For instance, cadmium's interference with calcium transport can alter intracellular signaling pathways, triggering apoptosis or programmed cell death, which is a significant mechanism of cadmium-induced renal damage. Concurrently, cadmium's competition with zinc for binding to metallothionein and other zinc-dependent proteins disrupts enzymatic activities and further contributes to the accumulation of oxidative stress.

Inflammation plays a crucial role in the pathophysiology of cadmium nephrotoxicity. Cadmium exposure activates inflammatory pathways, including the nuclear factor-kappa B (NF-$\kappa$B) signaling cascade, which leads to the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-$\alpha$) and interleukin-6 (IL-6). These cytokines recruit immune cells to the site of injury, where they release additional ROS and proteolytic enzymes, further damaging renal tissues and perpetuating the inflammatory response. This inflammatory milieu not only aggravates tubular and glomerular injury but also stimulates fibrogenic processes, contributing to the development of interstitial fibrosis. The fibrotic process involves the excessive deposition of collagen and other extracellular matrix components in the renal interstitium, replacing functional kidney tissue with scar tissue and significantly impairing blood flow and oxygen delivery to the remaining nephrons.

Chronic cadmium exposure leads to progressive renal dysfunction, a condition that evolves insidiously over time. The kidneys initially compensate for cadmium-induced injury through mechanisms such as hyperfiltration in the remaining functional nephrons. However, as cadmium continues to accumulate, this compensatory capacity is overwhelmed, leading to a decline in glomerular filtration rate (GFR), elevated serum creatinine levels, and the onset of proteinuria. Proteinuria, particularly the excretion of low-molecular-weight proteins such as beta-2-microglobulin, is one of the earliest signs of cadmium nephrotoxicity, reflecting damage to the proximal tubular cells. As damage progresses, glomerular injury becomes more prominent, with thickening of the glomerular basement membrane and mesangial expansion contributing to reduced filtration efficiency and glomerulosclerosis.

The variability in susceptibility to cadmium-induced renal damage across different species, age groups, and genetic backgrounds highlights the complexity of assessing cadmium toxicity. Species variability is evident, as different mammals exhibit distinct responses to cadmium exposure based on differences in metallothionein expression, renal physiology, and cadmium metabolism. For instance, rodents, commonly used as models for studying cadmium nephrotoxicity, may not fully represent the nephrotoxic responses observed in larger mammals, such as primates, due to species-specific differences in renal cadmium handling and antioxidant defense mechanisms.

Age is another critical factor, with older individuals generally being more vulnerable to cadmium-induced renal damage due to cumulative exposure and age-related declines in renal function and regenerative capacity. Sex differences have also been reported, with males potentially exhibiting greater susceptibility to cadmium nephrotoxicity, possibly due to hormonal influences on cadmium metabolism and renal physiology.

Genetic factors further modulate individual susceptibility to cadmium toxicity. Variations in genes related to metallothionein expression, antioxidant enzyme activity, and inflammatory pathways can predispose certain individuals or species to more severe cadmium-induced renal damage. For example, genetic polymorphisms that result in lower metallothionein levels may reduce the capacity to sequester cadmium and mitigate its toxic effects, while variations in antioxidant enzyme genes could impair the ability to neutralize ROS, exacerbating oxidative damage. Understanding these genetic influences is essential for identifying at-risk populations and implementing targeted preventive measures.

The progression of cadmium nephrotoxicity encompasses a spectrum of renal pathologies, including tubular dysfunction, glomerular injury, and interstitial fibrosis. The early stages of exposure may present with subtle signs, such as tubular proteinuria and polyuria, which reflect impaired reabsorption of solutes in the proximal tubules. As exposure persists, more extensive structural damage develops, including thickening of the glomerular basement membrane, mesangial expansion, and the onset of glomerulosclerosis. The development of interstitial fibrosis marks an advanced stage of cadmium-induced kidney disease, where scar tissue replaces functional nephrons, leading to irreversible loss of renal function and progression to chronic kidney disease (CKD).

Given the significant public health implications of cadmium exposure, particularly in regions with high environmental contamination or occupational exposure, continued research is imperative. Studies aimed at elucidating the precise molecular pathways involved in cadmium toxicity will provide insights into the mechanisms underlying renal damage and identify potential therapeutic targets for intervention. Research efforts should also focus on the development of sensitive biomarkers for early detection of cadmium nephrotoxicity, allowing for timely intervention and prevention of irreversible kidney damage. Additionally, strategies to mitigate cadmium exposure, such as regulatory measures to limit cadmium emissions and public health initiatives to reduce dietary intake of cadmium-contaminated foods, are essential for protecting renal health in vulnerable populations.

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