Cadmium Nephropathy

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ABSTRACT

Cadmium, an important environmental toxic agent has the kidney as its most important target organ. It is concentrated mainly in the renal cortex. Excessive renal accumulation of cadmium causes well defined morphological and ultrastructural pathological changes in the proximal tubules. Functional changes accompanying cadmium nephropathy include proteinuria, enzymuria, aminoaciduria, glycosuria, polyuria, hypercalciuria, increased urinary uric acid, and cadmium. The observed proteinuria has two components: low molecular weight proteinuria of tubular origin (excess excretion of proteins such as β2-microglobulin) and high molecular weight proteinuria of glomerular origin, (excretion of proteins such as albumin, IgG, transferrin, etc.). The proposed mechanisms of cadmium nephropathy are reviewed. The involvement of metallothionein in cadmium nephropathy and the nephrotoxic effects of cadmium-thionein are discussed.

Introduction

Cadmium as an environmental pollutant is receiving more and more attention. With the advancement of industrialization, humans are exposed to a higher concentration of cadmium. Though cadmium has recently been shown to be essential for growth, the major concern about its biological effect is its toxicity. Cadmium is toxic to virtually every system in the human or animal body whether ingested, inhaled or injected. A wide variety of toxic manifestations are produced involving the kidneys, liver, gastrointestinal tract, heart, testes, pancreas, bones, blood vessels, etc. In addition to its high toxicological potential, several features of cadmium metabolism add to its harmful effect. There is no effective homeostatic mechanism to control excessive intake of cadmium resulting in body cadmium accumulation with advancing age. Thus, though cadmium is virtually absent from the body at birth, an average American accumulating three μg per day, will have a total body content of 30 mg of cadmium by the age of 30. The half-life of cadmium retention by the human body is estimated to be 18 to 33 years or longer. This observation enhances the toxicological potential of cadmium in man. Lastly, cadmium strongly interacts with other essential trace minerals, such as...
copper, zinc, etc., both at the absorption level and in the tissues. This results in deficiency of the essential elements as well as abnormal metal-dependent enzyme activities.\textsuperscript{22,24,54,66}

Effects of acute exposure to high concentrations of cadmium have mainly been described in animals. Besides the primary affected organ (e.g., lung in the case of inhalation of cadmium oxide fume), the rapid accumulation of cadmium by the kidney, resulting in renal damage and dysfunction, is always observed.\textsuperscript{34,65} Similar observations have been made in a few reported human cases.\textsuperscript{10,16,89} Since most of the reported renal effects of cadmium were seen in long term-exposure, only chronic renal effects will be considered in this article.

Cadmium in the Kidneys

It is well established that kidneys are the most important target organs in acute and chronic cadmium intoxication.\textsuperscript{54} Though initial uptake of administered cadmium may be high in the liver, the cation will ultimately be concentrated by the kidney.\textsuperscript{37} Cadmium follows a characteristic distribution pattern in the kidney.\textsuperscript{65} The concentration is lower in the medulla than in the cortex.\textsuperscript{33} In the renal cortex, the largest accumulation is found in the outer cortex corresponding to the proximal tubules. The glomeruli do not retain cadmium to the same degree.\textsuperscript{7} The renal cortex continues to accumulate cadmium long after other tissues reach their saturation levels.\textsuperscript{69,75} When cadmium-induced renal changes appear, cadmium accumulation in the kidney cortex starts to level off.\textsuperscript{53,54}

Renal concentration of cadmium may serve as an index for cadmium toxicity. By studying cadmium concentrations in the renal cortex of occupationally-exposed adults, Friberg et al.\textsuperscript{54} proposed that a renal cortical cadmium concentration of 200 $\mu$g per g wet weight is the critical concentration at which renal dysfunction may appear. This proposal was endorsed later by the Subcommittee on the Toxicology of Metals under the Permanent Commission and International Association of Occupational Health,\textsuperscript{54} the WHO Task Group\textsuperscript{87} and other investigators.\textsuperscript{63} However, the validity of this critical concentration of cadmium is questioned by some investigators.\textsuperscript{15,51} This objection is based on the variability of renal cortical cadmium concentrations in relationship to proteinuria and pathological changes in the renal cortex.\textsuperscript{51} Variability of the analytical results and the possible interaction between cadmium and the other trace minerals which may enhance or retard the toxic effect of cadmium\textsuperscript{15,46} further complicate this issue. Renal effects have been reported in animals at cadmium concentrations appreciably lower than 200 $\mu$g per g wet weight.\textsuperscript{10} Urine cadmium concentration is useful as an indicator of body burden.\textsuperscript{34} However, sufficient data are not available to draw any correlation between urinary cadmium level and critical renal cadmium concentration.\textsuperscript{54} Normal human blood is low and variable in cadmium content\textsuperscript{79} and is of limited value in evaluating body cadmium status.\textsuperscript{34}

Morphological and Ultrastructural Changes

Development of pathological changes in the kidney resulting from cadmium intoxication depends on the duration of exposure. Owing to the limited number of reported cases in humans (about 30),\textsuperscript{54} most of our knowledge of morphological and ultrastructural kidney changes are derived from animal studies.

Severi in 1896 reported that multiple exposure to cadmium in humans resulted in intense necrosis of the convoluted tubules, poor cell definition and irregular granulations of the cells. Urinary sediment consisted of tubular casts formed from desquamating cells together with the
formation of some calcified casts. The glomeruli showed no apparent alteration, and the collecting tubules were only slightly involved. Subsequent reports confirmed the renal tubular changes inflicted by cadmium. The involvement of the glomeruli, however, is still controversial. Animal studies of chronic cadmium intoxication demonstrate interstitial nephrosclerosis, proximal convoluted tubular degeneration, with swelling and vacuolation of epithelial cells. Though the glomeruli show some slight alterations, in most cases they are without demonstrable alterations. The collecting tubules are usually not detectably affected. Ultrastructural changes observed in cadmium intoxication include extensive loss of proximal tubular basal plasma membrane infoldings, alteration of renal vasculature, deposition of metal particles in the tubule cells, and changes in mitochondrial density. Whether or not similar ultrastructural changes are observed in human kidneys needs to be confirmed.

Functional Changes

Chronic exposure to cadmium results in characteristic changes of renal function among which the more common ones are aminoaciduria, enzymuria, and proteinuria. These symptoms have been observed in both humans and animals.

In one cadmium dosing study, glycosuria appears as the first symptom of cadmium nephropathy. This symptom was also observed in a number of cadmium exposed workers. Another frequently observed symptom is polyuria. Together with this decreased concentrating capacity, changes have been reported in the renal handling of uric acid, calcium, and phosphate. Hypercalciuria and increased urinary uric acid were reported in cadmium exposed workers. Urinary phosphate, on the other hand, has been reported to be increased by some investigators and decreased by another investigator. These proximal renal tubular abnormalities and the frequently observed distal renal tubular acidosis may be the cause for renal stone formation which is not infrequently seen in cadmium workers. Cadmiumuria is observed in some cadmium workers as well as in animal models. Since urinary excretion of cadmium is correlated with the renal cortical level, some workers suggest that cadmiumuria may be a function of the dysfunction of proximal tubules.

Aminoaciduria is a common symptom in cadmium nephropathy. Amino acids reported to be elevated in urine of cadmium intoxication patients include alanine, glycine, lysine, citrulline, arginine, proline, and hydroxyproline. Renal reabsorption of filtered amino acids is mediated by several structure-specific transport systems localized on the cell membrane facing the tubular lumen. Aminoaciduria is believed to be caused by cadmium inhibition of the carriers, thus blocking reabsorption of amino acids.

The most prominent feature of cadmium nephropathy is proteinuria. This renal damage characterized by urinary excretion of low molecular weight proteins is well documented in humans as well as in animals. Several investigators reported that the proteinuria found in cadmium-exposed workers was similar to that found in tubular dysfunction in the Fanconi syndrome. The electrophoretic pattern of the proteinuria is characterized by the presence of a relatively small albumin fraction and relatively large α, β and γ protein fractions. A post-γ-globulin is also found in some cases. Further studies in humans and in animals indicated that the proteins excreted in cadmium nephropathy were composed mainly of low molecular weight proteins.
chiefly derived from the serum. Employing techniques such as radioimmunoassay, counter immunoelectrophoresis, thin layer and gel filtration chromatography, etc., it is possible to identify some of the proteins associated with cadmium intoxication. The low molecular weight proteins identified include β₂-microglobulin, retinol-binding protein, ribonuclease, light-chain of immunoglobulin, and muramidase.

Recent investigations using agarose gel electrophoresis revealed that a large number of high molecular weight proteins are also excreted in cadmium proteinuria. The high molecular weight proteins identified include immunoglobulin G, albumin, transferrin, α₁-acidglycoprotein, α₁-B-glycoprotein, Zn-α₂-glycoprotein, α₂-HS-glycoprotein, Bence-Jones protein (types γ and κ), and orosomucoid. Quantitatively, the high molecular weight proteins are the more important component of cadmium proteinuria. The excretion of high molecular weight proteins is handled by the glomerulus. Finding of these proteins in cadmium proteinuria led the investigators to suggest that the cause of cadmium proteinuria could be proximal tubular damage as well as the glomerular lesion. Many investigators suggested that tubular proteinuria is the first event in cadmium proteinuria, and the glomerular damage may arise secondarily to the tubular damage. However, a recent study showed that cadmium proteinuria may be composed of two components, i.e., tubular proteinuria and glomerular proteinuria, and that both components can appear independently without chronological order.

Even though extensive literature has been published on proteinuria in cadmium nephropathy, the mechanism of this phenomenon has not been ascertained. The most accepted hypothesis for early proteinuria in chronic cadmium poisoning is an impairment of tubular reabsorption of the serum proteins. This hypothesis relies basically upon the fact that β₂-microglobulin passes freely through the glomerulus and is normally reabsorbed by the proximal tubules. When there is no marked reduction of glomerular filtration rate, an increased excretion of β₂-microglobulin will indicate a defect in reabsorption by the proximal tubule. The glomerular proteinuria is suggested to be caused by selective damage to the glomerulus by cadmium. The damage may either be an enlargement of the glomerular membrane pores or loss of the negative fixed charges of the glomerular capillary wall which reduce the electrostatic restriction. These result in increased permeability of the glomerulus, hence, increased excretion of high molecular weight proteins.

The reabsorption defect hypothesis is disputed by Vigliani, Vigliani and associates in 1966 showed that the light chains of γ-globulin constituted 30 to 35 percent of the excreted urinary proteins in three Swedish cadmium workers. Later, it was found that in cadmium-intoxicated rats, the leucine aminopeptidases in the epithelium of the proximal tubules was significantly depressed. These findings led them to suggest that the low molecular weight proteinuria might be caused by the depression of protein catabolism in the tubular cells instead of impaired tubular protein reabsorption. A recent report casts doubt on the protein reabsorption hypothesis. Tsuchiya et al. demonstrated that β₂-microglobulin, the major low molecular weight protein in cadmium proteinuria, is elevated in the blood of cadmium alloy workers. They suggested that the increase in urinary β₂-microglobulin in cadmium nephropathy may be the result of the increased blood level instead of renal tubular reabsorption dysfunction. More experimental evidence is required to confirm any of these hypotheses.

Enzymuria is also a frequent observation in cadmium nephropathy. Enzymes detected in increasing quantity in urine of
Cadmium exposed humans or mammals include acid phosphatase, alkaline phosphatase, glutamic oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), lactate dehydrogenase (LDH), and β-galactosidase, etc. These enzymes are normally intracellular enzymes found in the epithelium of the proximal, glomerular and distal tubules. It is suggested that the enzymuria is very likely to be caused by cellular lesions owing to cadmium intoxication. It is also suggested that enzymuria may be the most sensitive and earliest signal of renal abnormality seen in cadmium nephropathy.

Proposed Mechanisms of Cadmium Nephropathy

The nephrotoxic effects of cadmium are well described in the literature. In spite of this, the mechanism responsible for these effects still remains obscure. Several models have been put forth trying to explain the action of cadmium. The capability of cadmium to interact with the phospholipid components of membranes may explain its toxic effect on renal cells. Its ability to inhibit sulfhydryl enzymes in vitro and its interaction with nucleic acids may contribute to its effect on normal cellular metabolism.

The most accepted mechanism of cadmium nephropathy is proposed by the group of researchers in Karolinska Institute. Cadmium is transported to the proximal tubules bound to the low molecular weight protein metallothionein. Under normal conditions, this protein is completely reabsorbed in the tubules. When more cadmium accumulates in the kidney than can be bound by metallothionein, cadmium will exchange with zinc in enzymes necessary for reabsorption and catabolism of proteins. This will alter the catalytic ability of the enzymes, resulting in less protein being catabolized or reabsorbed, causing tubular proteinuria. Cadmium excretion will increase as less metallothionein will be reabsorbed. Tubular cells will be damaged by cadmium, and these desquamated tubular cells will be excreted together with cadmium resulting in a decrease in renal cadmium content. If glomerular function is impaired, there will also be less filtration of metallothionein.

The previously mentioned hypothesis is supported by some experimental observations. By following the fate in rabbits of arterially injected labeled cadmium-metallothionein, Foulkes showed that cadmium-metallothionein is freely filterable and that its reabsorption can be saturated at sufficiently high plasma concentrations. Leucine aminopeptidase, a zinc metalloprotein presumed to play an important role in renal handling of protein is significantly depressed in cadmium treated rats and rabbits. It is found that cadmium excretion is low in cadmium exposed workers who do not have proteinuria but is considerably higher in workers who had a slight proteinuria. This observation agrees with the hypothesis since cadmium is excreted when its level is high enough to affect the renal protein handling enzymes, such as leucine aminopeptidase, and also when cadmium bound metalloprotein is not completely reabsorbed. Both of these two events will give rise to proteinuria. The observation that high renal cadmium levels are usually combined with histologically normal kidneys while relatively low cadmium levels are combined with gross structural changes in chronic cadmium poisoning is explainable by the proposed mechanism. Before the cadmium level exceeds the tolerable limit, all the cadmium is reabsorbed in the form of metallothionein, resulting in a high renal cadmium level. When the cadmium level exceeds the tolerable limit, some of the cadmium is not reabsorbed resulting in damage of the tubule cells. Under this circumstance, the cadmium will be excreted together with desquamated tubular cells.
causing a decrease in renal levels of cadmium.

**Properties of Cadmium-Metallothionein**

Metallothionein, a low molecular weight, cysteine rich metalloprotein, was first isolated from equine kidney by Kagi and Vallee in 1960. Since then, metallothioneins have been isolated from various tissues (kidneys, liver, duodenum, cultured fibroblasts, cultured epithelial cells, etc.) of different species of mammals (including humans, horse, cow, monkey, pig, rabbit, rat, mouse), fish (fresh water eel, goldfish), chicken and other living organisms including mussels (*Mytilus edulis*), yeast (*Saccharomyces cerevisiae*), blue-green alga (*Synechococcus sp.*), etc. This protein has a characteristic high metal content (approximately eight g-atom per mole of protein), with the major metal constituents cadmium, followed by zinc and copper. One-third of the amino acid residues are cysteine, all of which are involved in cation binding. Tyrosine and tryptophan are absent. It is well established that metallothionein is induced in the liver and kidney of experimental animals and in cultured cells by administration of cadmium, zinc, mercury and, under some conditions, copper. The induced metallothioneins will have the induction cation as the major metal constituent. Such metallothioneins are named after the inducing metal like cadmium rich metallothionein induced by cadmium is named cadmium-thionein.

Chronic, low-level exposure to cadmium induces biosynthesis of cadmium-metallothionein (or cadmium-thionein) in experimental animals. This induction of metallothionein biosynthesis has been proposed to be a protective mechanism against cadmium intoxication. This protective role of metallothionein is supported by several animal studies in which induction of metallothionein synthesis by cadmium pretreatment enhances the tolerance threshold of the animal towards cadmium intoxication.

Cadmium and metallothionein-bound-cadmium (in form of cadmium-thionein) behave quite differently. Cadmium administered to experimental animals as the metallothionein accumulates in the kidney instead of in the liver as does the inorganic cation. Parenterally administered cadmium-thionein is more toxic than inorganic cadmium, being about seven times more toxic in the rat and five times more toxic in the mouse. The apoprotein itself, however, is not toxic. Another characteristic of the cadmium-thionein is the delayed toxic response of the experimental animal. Intravenously injected cadmium-thionein is rapidly taken up by the kidney. In the kidney, the protein is degraded with the liberation of the metal. The liberated cadmium is then quickly incorporated into nascent chains of thio­­nein. Thus, the biological half-life of hepatic and renal metallothionein is about three to four days, while the cadmium content of the organs does not change over an eight day period.

Metallothionein has been proposed to be the major carrier of cadmium for its transport from the liver to the kidney. This proposal is supported by the observed temporal redistribution of cadmium between liver and kidney, detection of cadmium-thionein in blood, and the accumulation of intravenously administered metallothionein in the kidneys of mice. However, these observations are not conclusive. The presence of cadmium-thionein in the urine, the concurrent detection of plasma cadmium-thionein, and onset of renal damage, but not normally in cadmium-pretreated animals, all argue against the transport role of metallothionein.
Cadmium-Thionein Nephropathy

The nephrotoxic nature of cadmium-thionein is well established. Administration of purified cadmium-thionein into experimental animals (rabbit, rats and mice) causes degenerative change in the kidney. The prominent observation is necrosis of proximal renal tubular lining epithelial cells. Ultrastructural changes include increased number of pinocytotic vesicles, loss of microvilli, increase in number of intracellular vacuoles, swelling of mitochondria, and increase in number of small, dense lysosomal structures.

The mechanisms of toxicity of cadmium-thionein are not clearly defined. Cherian et al suggested that the nephrotoxic effect of cadmium-thionein may be due to the liberation of cadmium. The observed greater toxicity of cadmium-thionein in comparison to inorganic cadmium may be due to the more efficient absorption of metallothionein and, thus, more rapid catabolism by the tubular cells. The affinity of metallothionein for cadmium may also contribute in concentrating and hence in enhancing the toxicity of cadmium to the kidney.

Discussion

The nephrotoxic effects of cadmium are well described in the literature. Nevertheless, there is still a big gap between the observation of the clinical manifestation of cadmium nephrotoxicity and the understanding of the mechanism of action of cadmium in the kidney. The involvement of metallothionein in cadmium metabolism is an important finding. However, the paradoxical role of metallothionein in the pathogenesis of cadmium toxicity needs to be resolved before one can assign any role for the protein in the occurrence of cadmium nephropathy. The same applies to the recent report of metallothionein in extracellular fluids as a good index of cadmium toxicity. With the development of radioimmunoassays for metallothioneins, these questions may be answered in the near future. Another important question in cadmium nephropathy is the involvement of the other trace minerals, such as zinc and copper, which interact with cadmium in in vitro and in vivo systems. These metals compete with cadmium for binding to metallothionein and other metalloproteins. Whether or not they have any protective role against cadmium toxicity needs to be investigated.

References


