CHAPTER

34 Nephrotoxicity Secondary to Environmental Agents, Heavy Metals, Drug Abuse, and Lithium

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Environmental kidney diseases are a consequence of occupational exposure, a particular form of environmental disease. Recognized chronic occupational renal diseases include those caused by exposure to heavy metals, organic solvents (aliphatic, aromatic, and halogenated hydrocarbons), and silica. Minamata disease from mercury and Itai-Itai disease from cadmium are two environmental diseases caused by industrial elements. Another disease is Balkan nephritis presumed to be of environmental origin and the nephropathy caused by the ingestion of germanium compounds.

Several heavy metals are generally recognized as nephrotoxic following environmental or occupational exposure, including: lead, cadmium, mercury, uranium, chromium, copper, and arsenic. However, chronic renal failure has been described only for lead, mercury, cadmium, uranium, and arsenic. Therapeutic forms of platinum, gold, lithium, and bismuth may also induce kidney damage and these aspects are explored in other chapters of this book. Other heavy metals with potentially nephrotoxic effects are barium, cobalt, manganese, nickel, silver, thallium, thorium, tin, and vanadium but there is no definitive evidence they can actually lead to renal disease.

URINARY BIOMARKERS

Urinary proteins and biochemical markers were associated with toxic renal injury. Urinary biomarkers may reflect specific sites of renal injury: (1) low molecular weight proteins and intracellular enzymes—proximal tubule damage; (2) Tamm-Horsfall glycoprotein and kallikrein—distal tubule injury; (3) high molecular weight proteins—increased glomerular permeability (if >200 mg per g creatinine); and (4) biochemical markers—eicosanoids suggesting vascular injury.

A group of urinary markers (human intestinal alkaline phosphatase [HIAP], total nonspecific alkaline phosphatase [TNAP], N-acetyl-β-D-glucosaminidase [NAG], retinol binding protein [RBP], Tamm-Horsfall glycoprotein [THG], β_2-microglobulin, microalbumin, thromboxane B_2 [TBX_2], and three prostaglandins [prostaglandin E_2, PGE_2; prostaglandin $F_{2\alpha}$, $PGF_{2\alpha}$; 6-keto-prostaglandin $F_{1\alpha}$, 6-keto-$PGF_{1\alpha}$]) are detailed to demonstrate the differentiation of the toxic nephropathies (Table 34.1).[1–5]

The excretion patterns represent occupational exposure levels indicated by the specified mean blood or urine concentrations. Mercury and cadmium exposure[3–5] is associated with the isoenzyme HIAP, a sensitive and specific indicator of injury to the S3 segment of the proximal tubule. Total nonspecific alkaline phosphatase is increased after perchloroethylene exposure[6,7] and NAG and RBP are elevated after cadmium exposure.[3,8] The urinary eicosanoids PGE_2, $PGF_{2\alpha}$, and 6-keto-$PGF_{1\alpha}$ seem to be associated to the development of hypertension and injury to the glomeruli or renal medulla. Also, low levels of urinary albumin can also express proximal tubular dysfunction and the failure to reabsorb or metabolize albumin that passes through the glomerular filter.

The ability of these urinary markers to discriminate among the diverse nephrotoxins enhances with increasing exposure levels. Urinary markers should be collected in fasting fresh voided specimens (spot urines) at 8 AM, and expressed relative to the creatinine concentration. The specificity of tubular injury decreases in the presence of renal damage.

LEAD NEPHROPATHY

The first description of lead nephrotoxicity was made by Lancereaux in 1862, who reported a patient with saturnine (lead-induced) gout with kidneys showing interstitial nephritis at postmortem examination. Nevertheless, the demonstration of lead nephrotoxicity has presented some issues. There are difficulties proving the connection between late sequelae of chronic absorption to relatively low levels of lead, and distinguishing between glomerular and extraglomerular renal disease.[9] Another difficult aspect is how to separate the transient Fanconi syndrome of acute childhood lead poisoning from the chronic interstitial nephritis characteristic of lead nephropathy in adults. Finally, one confounding aspect is the differentiation of late complications of excessive lead

34.1 Urinary Markers in Toxic Nephropathies—European Cooperative Study

	HIAP	TNAP	NAG	RBP	THG	β_2-M	mAlb	TXB_2	PG
Pb	−	−	+	−	−	−	−	++	6F−
Cd	+++	−	+++	+	−	+	++	−	6F++
Hg	+++	+	+	−	−	−	−	−	F−
					−			−	E−
PCE	−	+++	−	−	±	−	+		F−
									E–

HIAP, human intestinal alkaline phosphatase; TNAP, total nonspecific alkaline phosphatase; NAG, N-acetyl-β-D-glucosaminidase; RBP, retinol binding protein; THG, Tamm-Horsfall glycoprotein; β_2-M, β_2-microglobulin; mAlb, microalbumin; TXB_2, thromboxane B_2; PG, prostaglandin; Pb, lead; Cd, cadmium; Hg, mercury; PCE, perchloroethylene; 6F, 6-keto-$PGF_{1\alpha}$; F, $PGF2_{1\alpha}$; E, PGE_2.

absorption and gout and hypertension renal lesions, which are other important causes of renal disease.

Diagnosis

The mainstay of laboratory diagnosis is the blood lead concentration, which is usually over 60 μg per dL, although recent evidence of lead-induced organ damage occurred with blood levels over 10 μg per dL.[10] Blood lead concentrations usually decrease significantly within 4 weeks of removal from exposure making the blood lead concentration relatively insensitive to cumulative body stores acquired over years. Around 95% of the body stores of lead are accumulated in the bone with a mean residence time of approximating 20 years[11] and cumulative past lead absorption is best assessed by the calcium disodium edetate ($CaNa_2EDTA$) lead-mobilization test.[12]

The ethylenediamine tetraacetic acid (EDTA) test is performed in adults by parenteral administration of 1 to 3 g (intravenous or intramuscular) of $CaNa_2EDTA$ over 4 to 12 hours with subsequent collection of 24-hour urine samples over 1 to 4 days. The intramuscular administration of 2 g of $CaNa_2EDTA$ (1 g of EDTA mixed with local anesthetic in each of two injections, 12 hours apart) seems to be a better option of performing the chelation test because it has been well standardized in both normal subjects and patients with renal failure.[13–18] In the presence of renal damage (serum creatinine > 1.5 mg per dL), urinary excretion of lead chelate should be extended to at least 3 consecutive days and the adequacy of collection checked by simultaneous measurement of urinary creatinine excretion (1.3 g of creatinine per day is an acceptable lower limit in normal adult males). Adults without undue prior lead absorption excrete up to 650 μg of lead-chelate in the urine.

Chelatable lead correlates well with bone lead[19,20] which reflects cumulative body lead stores. Bone lead concentrations can be accurately diagnosed by a new noninvasive technique, the in vivo tibial K X-ray fluorescence.[21,22]

Acute Lead Nephropathy

In acute lead nephropathy, a proximal tubule reabsorptive defect characterized by aminoaciduria, phosphaturia, and glycosuria (Fanconi syndrome) is observed,[23] usually in the presence of blood lead levels in excess of 150 μg per dL. An increase in urinary NAG is observed, which correlates positively with the blood lead concentration.[24] Tubular dysfunction is often reversed after chelation therapy is initiated to treat the more dangerous encephalopathy. Acute lead nephropathy is associated with acid-fast intranuclear inclusions in proximal tubule epithelial cells[25] which are a lead–protein complex, also observed in the urinary sediment.[25] These inclusions can occur in other organs such as in liver, neural tissue, and osteoclasts. Morphologic and functional defects in mitochondria are also observed in acute poisoning.

Chronic Lead Nephropathy

Chronic lead nephropathy is the slowly progressive interstitial nephritis observed in adults after prolonged lead exposure. The disease is more frequently recognized in lead workers after long periods (decades) of exposure but other groups have been described such as young adults who sustained acute childhood lead poisoning,[26] illicit whiskey ("moonshine") consumers, U.S. armed service veterans suffering from renal failure attributed to gout or essential hypertension,[13,14] and sporadic case reports such as geophagia,[27] Asian folk remedies, and cosmetics.

Chronic lead nephropathy causes chronic renal damage less responsive to chelating agents. There is evidence of associated functional impairment such as inhibition of both the renin-angiotensin system and Na^+-K^+-ATPase,[17,28] and these effects may be changed by chelation therapy. This explains why some exposed individuals can restore previous reductions in glomerular filtration rate (GFR) after long-term low-dose chelation therapy (1 g of $CaNa_2EDTA$ with local anesthetic three times weekly until the chelation test returns to normal). Proteinuria and glycosuria are initially absent and an increase in TXB_2, and a decrease in PGE_2 and 6-keto-$PGF_1\alpha$, in the urine is observed.[2,24]

Renal biopsies in chronic lead nephropathy show nonspecific tubular atrophy and interstitial fibrosis with minimal inflammatory response as well as mitochondrial swelling, loss of cristae, and increased lysosomal dense bodies within proximal tubule cells (Fig. 34.1).[15,19] Arteriolar changes indistinguishable from nephrosclerosis are found, often in the absence of clinical hypertension. Intranuclear inclusion bodies are often absent when the renal disease is long-standing or following the administration of chelating agents. Clumped chromatin and nuclear invaginations of cytoplasmic contents may be found even in the absence of intranuclear inclusions. Morphologic alterations are minimal in glomeruli until the reduction in GFR is advanced. This helps explain the association between lead toxicity and hypertension.

The association between lead and gout nephropathy has long been described.[29,30] Hyperuricemia and gout are common among individuals with excessive exposure to lead, apparently the result of decreased excretion and increased production of uric acid, and half of uremic patients with lead nephropathy have clinical gout.[26] There is substantial evidence that renal failure in gout is sometimes secondary to overt or unsuspected lead poisoning. In Queensland, Australia, as many as 80% of gout patients with renal failure have elevated EDTA lead-mobilization tests.[26] In New Jersey chelatable lead was found to be significantly greater among gout patients with renal failure than among gout patients with normal renal function.[13] Therefore, unrecognized lead poisoning can be an explanation for renal failure in some gout patients with no evidence of urinary calculi or intratubular uric acid deposition disease.

The initial renal injury from lead seems to be in the microvascular endothelium.[31] Although the mechanism of injury is not completely clear, it is well known that metabolism of lead is similar to that of calcium and other cations. Also, lead interacts with vasoactive substances that may modulate blood pressure and induce endothelial injury.[32,33] These aspects help to explain the association between lead toxicity and hypertension as suggested in several reports.[34,35] Some patients presenting as "essential hypertension with nephrosclerosis" may have evidence of lead nephropathy by the EDTA lead-mobilization test.[14] Mortality from hypertensive cardiovascular disease is more frequent among lead workers than the general population.[36] In these patients, lead seems to contribute to hypertension particularly in the presence of renal dysfunction.[17]

Treatment

Lead nephropathy is one of the few renal diseases that is preventable and potentially reversible by judicious use of chelation therapy.[16,37,38] However, there is no evidence that such therapy reverses established interstitial nephritis especially if serum creatinine concentration exceeds 3 mg per dL.[39] Reports of partial remissions may be the reversal of acute poisoning superimposed on chronic lead nephropathy.

Before chelation therapy is undertaken, it may be necessary to perform the EDTA lead-mobilization test and other possible causes of renal disease should be excluded. Long-term, low-dose EDTA therapy should be undertaken until an endpoint is achieved, such as reversion of the EDTA test to normal and restoration of renal function. The cumulative nephrotoxicity of prolonged EDTA therapy in patients with advanced renal failure is unknown. Reports of deterioration of renal function after $CaNa_2EDTA$ therapy have been described and treated patients warrant careful follow-up.[40,41]

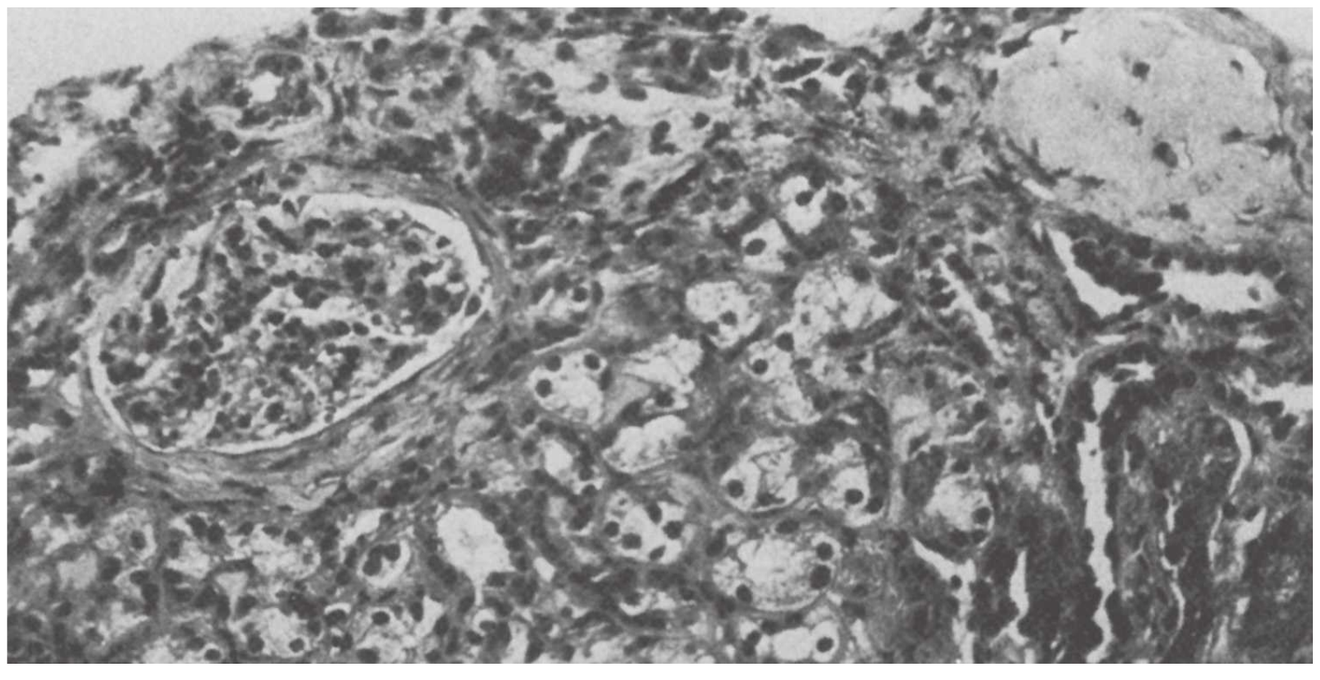

FIGURE 34.1 Renal biopsy obtained from a 28-year-old man who had prepared lead solder for 5 years. His ^{125}I-iothalamate clearance was 52 mL/min/1.73 m^2; hemoglobin, 9.6 g per dL; uric acid, 13.2 mg per dL; and blood lead, 48 μg per dL when he was initially seen. Lead-chelate excretion following 2 g of $CaNa_2EDTA$ intramuscularly was 5.2 mg for 24 hours. Light microscopy shows periglomerular fibrosis, a sclerotic glomerulus, and tubular atrophy. (Trichrome stain; magnification $\times$304.) (From Wedeen RP, Maesaka JK, Weiner B, et al. Occupational lead nephropathy. *Am J Med.* 1975;59:630, with permission.)

CADMIUM NEPHROPATHY

Several compounds containing cadmium are widely used in the manufacturing of pigments, plastics, glass, metal alloys, and electrical equipment. Acute absorption of small quantities as 10 mg of dust or fumes may cause severe gastrointestinal symptoms and fatal pulmonary edema, after a delay of 8 to 24 hours.[42] Chronic low dose exposure leads to slowly progressive emphysema, anosmia, and proximal tubular reabsorption defects characterized by low molecular weight proteinuria, enzymuria, aminoaciduria, and renal glycosuria.[43–46] Hypercalciuria (with normocalcemia), phosphaturia, and distal renal tubular acidosis result in clinically important osteomalacia, pseudofractures, and urinary tract stones.[47,48] Proximal tubular dysfunction can progress to chronic renal failure over years.[49,50]

Metabolism

Nonoccupationally exposed individuals can accumulate cadmium through food and cigarettes. The biologic half-life of cadmium in humans exceeds 15 years, and one third of the total body stores (10 to 20 mg) are accumulated in the kidneys.

Absorbed cadmium is initially sequestered in liver and kidney, where it is bound to metallothionein, a cysteine-rich apoprotein.[42,43] The cadmium–thionein complex is filtered at the glomerulus, taken up in the proximal tubule by endocytosis, and transferred to lysosomes, where it is rapidly degraded. Most of the cadmium accumulated in the proximal tubules is bound to protein and after a "critical concentration" of 200 μg per g of renal cortex is reached, renal effects become evident. Normal urinary cadmium excretion is usually under 2 μg per day and values over 10 μg per day are associated with cadmium accumulation. Urinary cadmium excretion in excess of 30 μg per day correlates with significant abnormalities of proximal tubular function.[51] Although blood cadmium concentration is less reliable as an indicator of health effects and cumulative absorption, blood levels greater than 1 μg per dL are considered evidence of excessive exposure.

β-2 microglobulin has been the most extensively examined urinary protein in cadmium nephropathy. Its excretion is an early renal effect of cadmium[42] but, considering its instability in acid urine, measurement of urinary RBP or NAG is probably more reliable.[3,8,24,51] Low level of albumin and transferrin are observed in the urine of cadmium workers with low molecular weight proteinuria and enzymuria,[3,52] but it is not clear whether this means glomerular injury or impaired tubular reabsorption. Proteinuria in cadmium workers rarely exceeds a few hundred milligrams per day and does not approach nephrotic levels.

Calcium Wasting

The leading feature of cadmium tubular dysfunction is increased calcium excretion.[53] Although osteomalacia is uncommon in cadmium workers, it can be observed, associated with diminished renal tubular reabsorption of calcium and phosphate, elevated circulating parathormone levels, and reduced hydroxylation of vitamin D metabolites.[54,55] Urinary calculi have been reported in up to 40% of those subjected to industrial exposure and ureteral colic is more likely to be the cadmium worker's chief complaint.[43,47,56]

Itai-Itai Disease

Itai-Itai disease is a painful bone condition associated with pseudofractures caused by cadmium-induced renal calcium wasting, first described in Japan. The origin is attributed to local contamination of food staples by river water polluted with industrial effluents, particularly cadmium. The syndrome afflicts postmenopausal, multiparous women presenting with reduced GFR, anemia, lymphopenia, and hypotension as well as osteomalacia. They also exhibit a waddling gait, short stature, anemia, glucosuria, and elevated serum alkaline phosphatase levels. β_2-microglobulin urinary excretion exceeds the normal maximum (1 mg per g of creatinine) by almost 100-fold, predicting the later development of renal failure. The renal damage progresses even after exposure has ceased.

Chronic Interstitial Nephritis

Although the role of cadmium in the induction of chronic interstitial nephritis has been controversial, analysis of postmortem tissue or renal biopsy specimens of exposed individuals was able to find tubulointerstitial nephritis.[57] These findings associated with recent epidemiologic studies in the United States[56] and Belgium,[58,59] and the long-term follow-up of Itai-Itai disease in Japan,[54] have consolidated cadmium as a cause of chronic interstitial nephritis. These studies presented some important evidence: there was an association between cumulative cadmium exposure and the later increase in serum creatinine after a latent period of several decades; and among exposed workers, there was an increase in serum creatinine concentrations over 5 years accompanied by an important increase in mean urinary β_2-microglobulin and loss of glomerular filtration (around 30 mL per minute, 30 times the predicted loss of kidney function for the group).

Diagnosis

Cadmium nephropathy is usually diagnosed based in a history of exposure associated with laboratory tests indicative of proximal tubule injury (e.g., increased excretion of urinary biomarkers, hypercalciuria, or renal glycosuria). Cadmium concentration over 10 μg per g of creatinine confirms the diagnosis. Assessment of renal and hepatic accumulation of cadmium by neutron-activation analysis has been explored and organ cadmium content correlates well with tissue and urinary cadmium levels and β_2-microglobulin excretion. When the hepatic cadmium level exceeds about 60 ppm, and renal cortical content exceeds 200 ppm (20 mg per kidney), tubular proteinuria is likely to occur. The diagnostic value of neutron-activation analysis of kidney is decreased in uremic patients because renal cadmium concentration tends to fall with the development of renal failure.[59]

Treatment

The chelating agent $CaNa_2EDTA$ has little effect after cadmium has been complexed with metallothionein[60] and it is not usually recommended. Progression of renal disease may occur despite removal from exposure.[54] Osteomalacia may be controlled by calcium and vitamin D replacement[51] and urinary tract stones are not a contraindication to such therapy.

MERCURY

The toxicity of mercury depends on both its chemical form and the route of absorption. Elemental mercury produces neurologic disease and even death but it does not cause nephrologic damage. However, the mercuric salt corrosive sublimate ($HgCl_2$) is the most nephrotoxic form which is accumulated in the cells of proximal tubules inducing acute tubular necrosis (ATN).[61] This mercurial compound binds avidly to sulfhydryl groups in circulating proteins and amino acids as well as intracellular glutathione, cysteine, and metallothionein. Mercury accumulates in the pars recta of proximal tubules which is accomplished by transport primarily from the luminal side of mercury bound to amino acids or proteins. Mercury-ligand complexes reach lysosomes by endocytosis[62] with subsequent release into the cytosol by intralysosomal enzymatic degradation.

Diagnosis

The diagnosis of mercury-induced renal disease is usually dependent on known exposure in the presence of renal dysfunction. Although blood mercury levels over 3 μg per dL or urine levels above 50 μg per g of creatinine are considered abnormal, the correlation of blood and urine concentrations with renal disease is poor.[63] Mercury exposure is associated with increased HIAP urinary excretion but little increase in TNAP, NAG, RBP, THG, β_2 microglobulin, or microalbuminuria (Table 34.1).[1,5] There is no evidence that enzymuria from mercury exposure predicts the development of renal failure.

Ingestion of as little as 0.5 g of $HgCl_2$ produces ATN in humans. Initially, the clinical picture is dominated by gastrointestinal symptoms including erosive gastritis with hematemesis and melena. Diuresis should be induced by hydration, mannitol, and furosemide to prevent the development of oliguric acute renal failure. Persisting oliguria in the face of adequate therapy indicates renal parenchymal damage. An elevated urinary sodium concentration (>40 mEq per L) and diminished concentrating capacity (UOsm <450 mOsm per L) in an acutely oliguric patient with adequate therapy confirms the diagnosis of ATN. Acute oliguric renal failure may rapidly lead to death unless dialysis is provided.

Histologic examination of the kidneys reveals necrosis of the proximal tubules, particularly the pars recta. Tubular necrosis extends to more proximal segments after larger doses although the extent of damage to individual nephrons is highly variable.[64]

Oliguria is replaced by polyuria, during the recovery phase, whereas the GFR is still low. Urine flow rates may double daily, achieving a maximum of 5 L per day whereas the serum creatinine continues to rise. Spontaneous regeneration of tubular epithelium occurs with subsequent recovery although dystrophic calcification of necrotic tubules may limit restoration of function, and the kidneys may show residual interstitial nephritis.[62] The process from acute oliguria through polyuria and recovery may last from a few days to many months.

Nephrotic Syndrome

Although there are some sporadic case reports of nephrotic syndrome following exposure to elemental or organic mercury since the 20th century,[65] the causal relationship of mercury exposure to proteinuria and the nephrotic syndrome has been controversial.[66] The dose-response is unpredictable and also the etiology of nephrotic syndrome unrelated to mercury is rarely known.

Renal biopsies have most often shown deposits within glomerular capillaries consistent with membranous nephropathy (Fig. 34.2),[67] but normal glomeruli and antiglomerular basement membrane (anti-GBM) antibody deposition also have been described. In most patients, proteinuria is self-limited and disappears spontaneously when the source of exposure is removed.

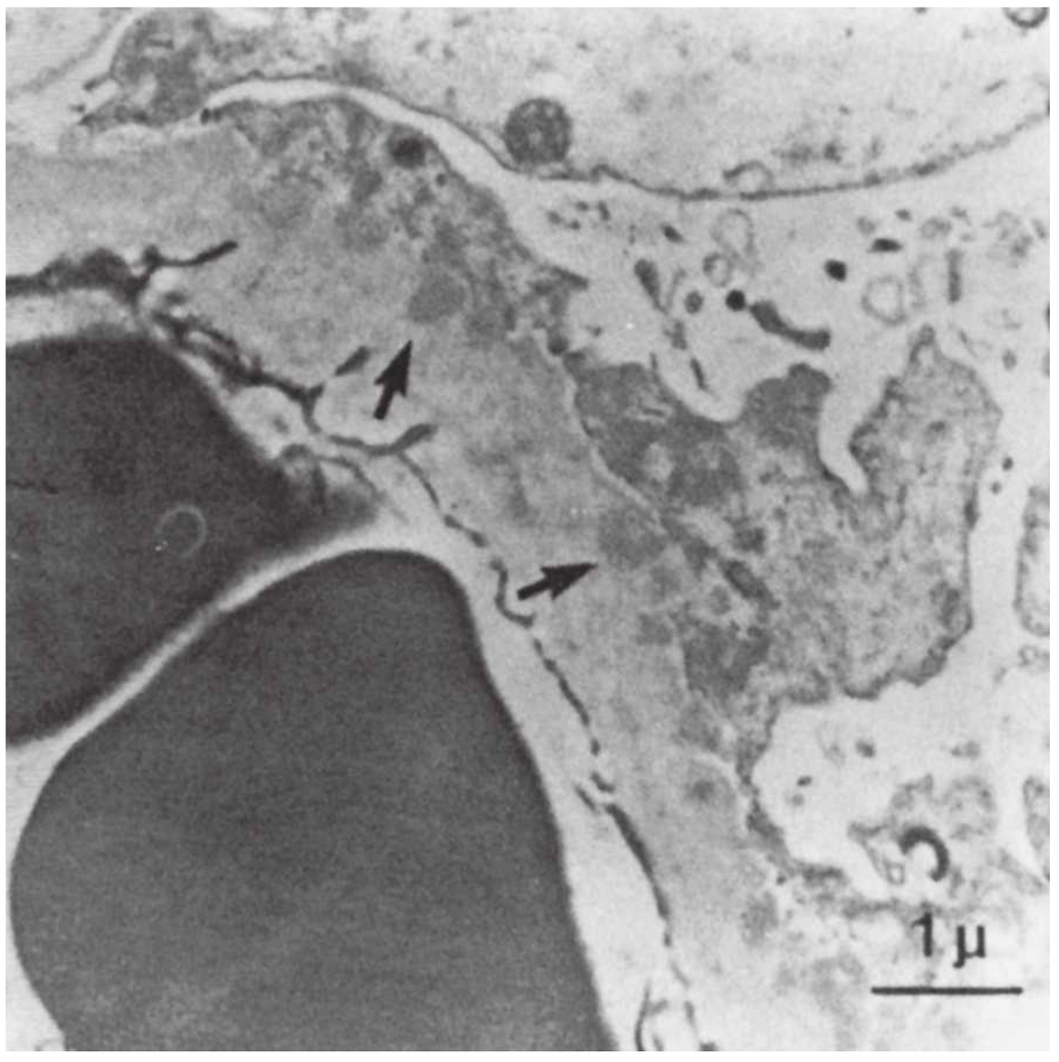

FIGURE 34.2 Electron micrograph of kidney from a 24-year-old man exposed to mercury vapor in an industrial electrolysis unit. The urinary mercury was 174 μg per 24 hours; urinary protein, 3.11 μg per 24 hours. Creatinine clearance was 116 mL/min/1.73 m^2. Subepithelial electron-dense deposits (*arrows*), presumably immune complexes, overlie the glomerular basement membrane. (Lead citrate and uranyl acetate; magnification ×11,000.) (From Tubbs RR, Gephardt GN, McMahon JT, et al. Membranous glomerulonephritis associated with industrial mercury exposure. *Am J Clin Pathol.* 1982;77:409, with permission.)

MINAMATA DISEASE

Endemic methyl mercury poisoning was recognized in Japan in the area of Minamata Bay in 1956, arising from the contamination of food by industrial effluents.[68] The mercury pollution had been going on for a decade and fish from Minamata Bay contained up to 36 mg of mercury per kg. Affected people presented neurologic defects including visual, speech, and gait disturbances. Cerebral palsy was common among the children of affected mothers. Similar clusters of cases were subsequently identified in Niigata, Japan, and in Iraq, where the disease was the result of bread prepared from grain that had been treated with methyl mercury fungicide.

Although the kidney manifestations of Minamata disease are minor, tubular proteinuria occurs[69] but clinically important albuminuria and azotemia are not common.

Treatment

Acute inorganic mercury poisoning is treated with the effective chelator British antilewisite (BAL). Recommended regimen is 5 mg per kg given by the intramuscular route, followed by 2.5 mg per kg twice daily for 10 days. In the presence of acute renal failure the mercury chelate can be removed by hemodialysis. BAL is not used in chronic poisoning, in which treatment is removal from the source of exposure. Succimer (DMSA), an oral chelating agent used for the treatment of lead poisoning in children, is not an effective chelator of mercury and its use is not recommended.[70]

OTHER HEAVY METALS

Uranium is selectively accumulated in the proximal tubule with a biologic half-life approximating 1 week for 95% of the renal stores.[71] After inhalation, the uranyl ion binds to circulating transferrin and to proteins and phospholipids in the second and third segments of the proximal tubule. ATN and increased β_2-microglobulin urinary excretion has been reported after uranium exposure, especially when urinary uranium levels were over the upper acceptable limit of 30 μg per L.[72] There is no evidence of association between uranium exposure and the development of chronic kidney disease (CKD).

Copper sulfate has been associated with ATN in young female science students attempting suicide in Delhi, India.[73]

Like other heavy metals, chromium is selectively accumulated in the proximal tubule and the hexavalent form is able to induce ATN, but there is no convincing evidence of tubular injury from usual occupational exposure.[74–78] Minimal tubular proteinuria has also been reported in chrome platers, but CKD was not documented.

Bismuth compounds prepared as therapeutic agents have produced unequivocal ATN. Lower dosages induce Fanconi syndrome with reduced glomerular filtration and bismuth-containing intranuclear inclusions in proximal tubule cells that are similar to, but distinguishable from, lead inclusions.[79–81]

Arsenic poisoning is associated with renal failure.[82,83] Usually associated with an industrial accident, arsine inhalation produces hemolysis, hematuria, and abdominal pain within a few hours, followed by acute oliguric renal failure and jaundice within 2 days.[84] Reticulocytosis, basophilic stippling, bilirubinemia, and free hemoglobin in the plasma may assist diagnosis, which is established by detecting arsenic in the urine. Patchy cortical necrosis with persistent residual renal failure has been reported.[82,85] BAL is ineffective once renal failure is present. Besides hemodialysis, exchange transfusions may be useful to eliminate hemoglobin-bound arsenic from the body.

SILICON

Silicon is a semimetal found as dioxide silica (SiO_2) in 28% of the earth's crust. Silicon is not a heavy metal because it has a specific gravity of only 2.3. It is present in the serum at concentrations of 20 to 50 μg per dL in an unbound form as silicic acid and is cleared in the urine at the rate of glomerular filtration. Silica is believed to induce renal disease by direct deposition of crystalline material in the renal parenchyma and by immunologic mechanisms acting as an adjuvant to stimulate the immune response.[86,87] Tubular proteinuria is found in workers exposed to silica dust,[88,89] and an increased risk to develop end-stage renal disease (ESRD) has been described.[90] In the accelerated form of silicosis known as silicoproteinosis, rapidly progressive, immune complex-mediated focal glomerulosclerosis, which simulates lupus erythematosus (Caplan syndrome), may appear.[89] Antineutrophil cytoplasmic antibody (c-ANCA)-positive Wegener granulomatosis has been associated with exposure to silica dust as well as to silicon containing compounds such as grain dust.[91]

GERMANIUM

Germanium has been used in the treatment of cancer, a variety of medical ailments, and in unproved remedies for conditions such as arthritis, acquired immunodeficiency syndrome (AIDS), and the chronic fatigue syndrome. Germanium-containing elixirs and health foods have been described to cause chronic tubulointerstitial nephritis first in Japan in the 1980s and more recently in Europe and the United States.[92–97] The kidney disease is different from that induced by other heavy metals in that widening of the interstitium and distal tubular atrophy has been evident after prolonged (6 to 36 months), high-dose (16 g to hundreds of grams) consumption. Electron-dense, periodic acid-Schiff (PAS) reagent-positive granules (containing germanium in the experimental rat) are found in distal tubular mitochondria.[95] The tubulointerstitial disease is slowly progressive even after exposure elimination. Fatal outcomes have been reported. The pathophysiologic mechanism of tubular damage is not defined because selective accumulation in the kidney was not found and immunologic mechanisms have not been implicated. There is no evidence of primary proximal tubular injury and proteinuria is absent.[92,94]

BALKAN NEPHROPATHY

Balkan endemic nephropathy is a slowly progressive tubulointerstitial nephritis of unknown etiology described about 40 years ago among middle-aged men and women living in farming villages along the Danube River in Croatia, Serbia (the former Yugoslavia), Romania, and Bulgaria.[98] Early clinical manifestations included clinically silent tubular dysfunction such as glucosuria and/or aminoaciduria. More advanced disease leads to decreased concentrating ability and progression to ESRD.[99] A variety of environmental factors have been suspected including lead, cadmium, and mycotoxins, but no single etiologic agent has been found. The prevalence of generally recognized kidney diseases has not been established in the Danube region, making differentiation of Balkan nephropathy from known renal diseases identified in other regions of the world problematic.

DRUG ABUSE

Substance abuse is common, involving lifetime exposure of 46% of the general population.[100] Substances with the potential to be abused include alcohol, opiates, sedatives and hypnotics, cocaine, cannabis, hallucinogens and psychedelic drugs, psychotropic, stimulant and anxiolytic medications, analgesics, and amphetamines. Such drugs have been associated with several kidney syndromes by varied mechanisms. Although some substances are directly nephrotoxic, other mechanisms are also involved, including glomerular, interstitial, and vascular diseases (Table 34.2).[101]

34.2 Renal Disease Associated with Drug Abuse

1.	Focal glomerulosclerosis in intravenous heroin users
2.	Amyloidosis in subcutaneous heroin abusers
3.	Endocarditis-associated glomerulonephritis in intravenous drug users
4.	Acute renal failure due to nontraumatic rhabdomyolysis
5	Cocaine-associated nephropathy
6.	Systemic necrotizing vasculitis
7.	Nephropathy in glue and solvent "sniffers"
8.	Hepatitis-related glomerulonephritis in drug abusers
9.	Focal glomerulosclerosis in drug abusers infected with HIV

Since the first reports in the late 1960s and early 1970s there have been numerous studies describing the clinical and pathologic features of renal diseases associated with chronic parenteral abuse of heroin, cocaine, morphine, amphetamine, and other narcotic and hallucinogenic drugs, including several adulterants. Renal disease in cocaine and heroin users is associated with the nephrotic syndrome, acute glomerulonephritis, amyloidosis, interstitial nephritis, and rhabdomyolysis.

In the past few decades an explosive growth in illicit drug use has occurred in many parts of the world. Reports indicate that in some areas of the United States the percentage of cocaine addicts among young people is as high as 20%. In a university population in the United States, 6% were found to be cocaine users as documented by hair analysis.[102] Other than the more common acute renal effects of the abuse of multiple drugs, chronic abuse may also be associated with CKD and progression to ESRD.

HEROIN

Heroin is processed from a naturally occurring substance, morphine, extracted from various poppy plants. It can be sniffed ("snorting"), eaten, smoked ("chasing the dragon"), injected subcutaneously ("skin popping"), or injected intravenously ("mainlining").[103] The purity of heroin depends on the presence of adulterants. Commonly used adulterants include sucrose, dextrose, mannitol, lactose, starches, powdered milk, quinine, caffeine, inositol, lidocaine, procaine, acetylprocaine, methapyrilene, and strychnine.[104]

Heroin is the most commonly abused opiate in the United States and has become a growing health-related problem in large metropolitan areas.[100] The term "heroin-associated nephropathy" includes different morphologic findings following chronic drug abuse.[105] Although the prevalence of heroin use in the United States has increased, the incidence of "heroin nephropathy" has declined. Socioeconomic conditions, cultural and behavioral practices, or differences in genetic susceptibilities may be more associated with the development of nephropathy in heroin users than the drug's pharmacologic properties.[103]

There are several renal complications from heroin abuse varying from hypotension to coma complicated by pressure-induced muscle damage and rhabdomyolysis. This latter event in the absence of coma, or evidence of muscle compression, could also occur as a direct toxic effect or an allergic response to heroin or the components in adulterated heroin.[106] The high rate of viral, bacterial, and fungal contamination associated with intravenous drug use increases the risk for glomerulonephritis (GN) associated with chronic infections. Local abscesses, due to Staphylococcus aureus, have been associated with GN. Bacterial and fungal endocarditis are also associated with immune-complex mediated GN. Other causes of GN in these patients are associated with hepatitis B and hepatitis C.

Secondary (AA) amyloidosis is also a cause of kidney disease in chronic drug users, particularly among those who inject drugs subcutaneously ("skin poppers").[107] In the majority of these patients, continued abuse leads to progression to end-stage renal failure and resolution of the lesions following abstinence from subcutaneous drug abuse has been reported.[108]

In the 1970s and 1980s, heroin-associated nephropathy (HAN) was described, presenting as nephrotic syndrome and progressing rapidly to end-stage renal failure. Kidney biopsy usually showed a focal segmental glomerulosclerosis.[109] Earlier studies suggested that heroin, or one of its adulterants, acted as an antigen leading to renal deposition of immune complexes in the kidney, but animal studies have shown that morphine has a direct effect on the glomerulus, causing proliferation of fibroblasts and a decrease in degradation of type IV collagen.[105,110] As heroin sold in streets became more pure a decrease in the incidence of HAN among intravenous heroin addicts was described.[111] At the same time, HIV-associated nephropathy (HIVAN) started to be diagnosed more frequently among heroin addicts with HIV infection.[112]

Recent studies suggest that morphine has direct effects on mesangial and glomerular epithelial cells (GEC), kidney fibroblasts, and the interaction of mesangial cells with circulating and resident macrophages. The classic lesion of focal segmental glomerulosclerosis (FSGS) starts with mesangial cell hyperplasia and GEC hypertrophy.[113] In the course of the FSGS, there is eventual loss of mesangial epithelial cells and GEC. The loss of GEC, or apoptosis, has been suggested as an underlying mechanism in the development of FSGS.[114] The glomerulosclerosis results from mesangial cell expansion, increased matrix deposition, and secretory factors that are modulated by macrophages. Morphine induces both inhibitory and proliferative effects on fibroblasts, mesangial cells, and macrophage activity.[115] At lower concentrations morphine predominantly stimulates mesangial cells and fibroblast proliferation, mesangial matrix deposition, and macrophage activity. At higher concentrations, morphine inhibits mesangial cells and fibroblast proliferation, mesangial matrix deposition, and macrophage activity.[115]

COCAINE-ASSOCIATED NEPHROPATHY

Cocaine (benzoyl methylecgonine) is extracted from the leaves of the South American plant Erythroxylum coca.[116] It exists in two major forms: Cocaine hydrochloride and alkaloidal freebase (crack) cocaine.[116] Cocaine abuse is epidemic in the United States, with an estimate that 34.3 million Americans have used cocaine at some time.[100]

Although the most frequent renal manifestation of cocaine abuse is acute kidney injury due to nontraumatic rhabdomyolysis, cocaine may induce nephropathy by other mechanisms.[101] The pathophysiologic basis of cocaine-related renal injury involves renal hemodynamic changes, glomerular matrix synthesis and degradation, oxidative stress, and induction of kidney atherogenesis.

Cocaine has potent vasoconstrictive effects on vascular smooth muscle.[117] It directly affects smooth muscle vascular cell calcium influx.[118–120] Endothelins (ET) have also been implicated in the vascular dysfunction that is induced by cocaine intoxication.[116] There is a high density of ET-1 receptors in the vascular smooth muscle of all renal resistance vessels.[121]

Cocaine inhibits catecholamine reuptake at the presynaptic nerve terminal, blocks norepinephrine reuptake in sympathetically innervated tissues, and releases norepinephrine and epinephrine from the adrenal medulla resulting in development of hypertension and tachycardia.[122,123]

The involvement of the renin-angiotensin-aldosterone system (RAAS) has been suggested because cocaine-induced ET release is inhibited by captopril and lisinopril in cultured human and bovine endothelial cells.[124] Activation of the RAAS and angiotensin II by cocaine may lead to renal fibrosis from stimulation of TGF-β.[116]

The resultant effect of cocaine on the kidney, through ET-1, the RAAS, and the l-arginine–NO pathway, leads to vasoconstriction of the glomerular microcirculation. Cocaine has been associated with accelerated and malignant hypertension as well as implicated in hastening the progression of hypertensive nephrosclerosis to ESRD.[125,126]

In an autopsy study 40 kidneys from patients with cocaine-related deaths were compared with kidneys from 40 accident victims.[127] The ratio of the number of sclerotic glomeruli to the total number of glomeruli was 18-fold greater in cocaine users than in controls. In that study, they also found significant differences in the degree of periglomerular fibrosis, the degree of interstitial cellular infiltrate, and hyperplastic arteriolosclerosis in cocaine users compared to controls. Medial thickening, luminal narrowing, and vessel obstruction were absent in the control group. The patients with cocaine-related deaths were found to have advanced coronary atherosclerosis, more extensive than expected in normal populations older than 60 years of age.

In a case-control study performed to examine recreational drug use as a risk factor for ESRD, cocaine use was associated with a threefold increased risk for developing ESRD.[128] In a prospective cohort including 647 patients, followed for a 15-year period, there was a threefold increased risk of kidney functional decline associated with use of cocaine or crack as compared to nonusers.[129]

Although these studies demonstrate an association of cocaine use and progression to CKD and ESRD, prospective, epidemiologic studies are needed to clarify the relationship between cocaine use and the development of CKD.

ECSTASY AND OTHER AMPHETAMINES

Ecstasy (MDMA: 3,4-methylenedioxymethamphetamine), originally used as an appetite suppressant, became a commonly used recreational drug. MDMA is rapidly absorbed, reaching plasma peak levels in approximately 2 hours.[130] It is metabolized by the liver and excreted by the kidney.

The increased physical activity, overheated environments, and dehydration associated with its use can result in hyperthermia. It has been shown that MDMA can cause fever even in the absence of strenuous exercise. Associated side effects can be mild—nausea, vomiting, headaches, cramps—or serious—convulsions, hyperpyrexia, hepatic dysfunction, rhabdomyolysis, disseminated intravascular coagulation, and acute kidney injury.[131]

There is an increased risk of hyponatremia associated with ingestion of large quantities of water to prevent dehydration and inappropriate antidiuretic hormone secretion.[132] As a consequence, cases of cerebral edema have occurred after ecstasy abuse. Ecstasy has marked sympathomimetic effects and has been associated with cases of accelerated hypertension and acute kidney injury.

SOLVENTS

Fumes of toluene or toluene-containing compounds (spray paint, household and model glue, lacquer, and paint thinners) contain a number of volatile substances including n-hexane, methyl ketones, chlorohydrocarbons, and benzene. The deliberate inhalation of volatile solvents ("glue sniffing") first emerged as a form of substance abuse in the early 1960s. Solvents can rapidly cause hallucinations of short duration (15 to 30 minutes), and are associated with a variety of electrolyte and acid–base disturbances. In addition, serious cardiac, pulmonary, hepatic, neurologic, and renal complications may develop, as well as sudden death.

The nephrotoxic insult of volatile glues appears to be due principally to toluene. Various renal lesions have been associated with its abuse: microhematuria, pyuria and proteinuria, distal renal tubular acidosis and Fanconi syndrome, urinary calculi, glomerulonephritis, Goodpasture syndrome, ATN, hepatorenal syndrome, and acute and chronic interstitial nephritis.[101] Taher and coworkers first recognized non-anion gap hyperchloremic metabolic acidosis in association with toluene "sniffing" in two patients.[133] The tubular defect was documented by the presence of metabolic acidosis (pH, 7.2 to 7.3) with a normal anion gap, hyperchloremia (level of 118 to 120 mEq per L), and an inappropriately high urinary pH (>6.0). Numerous other cases of hyperchloremic metabolic acidosis, due to toluene inhalation, have subsequently been reported. In addition, transient congenital renal tubular dysfunction with hyperchloremic metabolic acidosis due to maternal toluene abuse have been described.[134]

Toluene, a hydrophobic compound, accumulates in lipoidal structures. After sniffing stops, this volatile chemical is excreted via the lungs. The conversion of toluene to organic acids occurs in the liver where toluene is metabolized by the cytochrome P-450 system. There is a spectrum of disorders that are responsible for the metabolic acidosis associated with toluene abuse, caused primarily by the conversion of toluene to hippuric acid, with the subsequent rapid excretion of hippurate in the urine.[135] Patients with a fast metabolism of toluene by the cytochrome P-450 system have a high rate of production of organic, hippuric, and benzoic acids. With a normal kidney function these patients will usually present a hyperchloremic acidosis and a wide anion gap, if the production exceeds the excretion of the anions. In the presence of impairment in the rate of excretion of ammonium, demonstrated in 20% of the patients, the net acid excretion is reduced and, hence, distal renal tubular acidosis is present.[135] In chronic toluene abuse increased concentrations of NH_3 in the interstitium can lead to complement activation. Thus, toluene abuse can cause chronic interstitial diseases, and ultimately impair the ammonium excretion causing distal renal tubular acidosis.[136]

In addition to the acid-base disorders, fluid and electrolyte abnormalities are also common in the clinical presentation of toluene abuse. In fact, nausea and generalized weakness, which may result from volume contraction and hypokalemia, are the symptoms that frequently lead the patient to seek medical attention. The excretion of hippurate increases the excretion of ammonium, sodium, and potassium. About one quarter of the patients present with severe hypokalemia (potassium <2mEq per L). The degree of hypokalemia may be underestimated by the metabolic acidosis, a factor that should be anticipated during the treatment. The presence of concomitant hypophosphatemia increases the risk of rhabdomyolysis.[137]

LITHIUM

Introduction

Lithium is currently a drug of choice for treating bipolar illness and is widely used in this population. Approximately 0.1% of the U.S. population is undergoing lithium treatment for psychiatric problems and 20% to 54% of these patients have urinary symptoms during and after lithium use.[138] Approximately 30% of patients taking lithium experience at least one episode of lithium toxicity.

Chronic lithium ingestion in patients with bipolar illness has been associated with several different forms of kidney injury. The narrow therapeutic window (1 to 1.5 mEq per L during acute therapy and 0.6–1.2 mEq per L during maintenance therapy) contributes substantially to the frequency of acute and chronic toxicity. Close monitoring of serum levels is important to prevent acute and chronic kidney failure. Prevention is important and patients should be instructed to drink 10 to 12 glasses of liquid every day during lithium therapy, and keep a regular (non-low) salt diet. Patients should be oriented to contact a health care provider if fever, diarrhea, or vomiting develops. Certain drugs, especially diuretics, should be avoided with lithium use if possible. Cyclosporine and nonsteroidal anti-inflammatory drugs (NSAIDs; except low dose aspirin) potentially increase serum lithium levels and should be avoided. There is no gender or ethnic predisposition to the development of lithium toxicity, although some studies suggest that women may require fewer drugs to achieve therapeutic serum levels than men.

The most common renal side effect of lithium therapy is nephrogenic diabetes insipidus (NDI). Chronic tubulointerstitial nephropathy is the most common form of CKD associated with lithium therapy.[139] Although the majority of studies show infrequent and relatively mild renal insufficiency attributable to lithium therapy, ESRD secondary to lithium-associated chronic tubulointerstitial nephropathy does occur in a small percentage of patients, although the incidence of long-term lithium nephropathy is still a matter of debate.[139]

Renal Effects of Lithium

Lithium is a univalent cation, completely absorbed by the gastrointestinal (GI) tract. The drug is not protein bound and is completely filtered at the glomerulus. Although the majority, up to 60%, of the filtered load is reabsorbed by the proximal tubule, a significant amount is also absorbed in the loop of Henle and the early distal nephron. Lithium can act as a substitute for sodium in several sodium channels, particularly the sodium-hydrogen exchanger in the proximal tubule (NHE_3), the sodium/potassium/2chloride exchanger in the thick ascending limb of the loop of Henle ($NKCC_2$), and the epithelial channel of the cortical collecting tubule (ENaC).

Lithium nephrotoxicity can occur as soon as a month after the onset of use of the drug. The most common symptoms, polyuria and polydipsia, are reversible but can become permanent with chronically maintained high serum levels of lithium. Lithium-associated natriuresis is caused by the impaired regulation of the expression of the epithelial sodium channel in the cortical collecting tubule.[140] Lithium use partially inhibits the ability of aldosterone to increase apical membrane ENaC expression, resulting in inappropriate sodium losses.[141]

Nephrogenic diabetes insipidus is a common side effect of lithium; up to 12% of patients develop frank diabetes insipidus. Lithium impairs the ADH stimulatory effect on adenylate cyclase, and decreases cAMP levels.[142] Studies suggest that the ability of lithium to produce nephrogenic diabetes insipidus may also have an independent effect from cAMP generation and be associated with a decreased AQP2 mRNA levels.[143] Lithium most likely impairs water permeability in the principal cells by inhibiting water channel delivery and, over a prolonged period of time, by suppressing channel production.[144]

In patients with urine-concentrating defects, the improvement usually take weeks to months to occur, and can persist for years in some cases. One case report describes patients who still had diabetes insipidus 8 years after cessation of therapy. In another report, of a small subset of patients, up to 63% had persistent defects 1 year after stopping lithium.[138] The prolonged time to recover the concentrating ability may be linked to underlying renal histologic damage and may be worse with neuroleptic use and prolonged lithium therapy. Boton and colleagues, in a review, documented a 54% correlation between impaired urine-concentrating ability and the duration and total dosage of lithium treatment.[145] Chronic lithium use is also associated with a distal tubular acidification defect, exerted from the luminal side of the cell. Lithium is not known to cause significant hyperkalemia.

Acute Kidney Injury

Lithium toxicities appear to be dose and concentration dependent. Serum concentrations between 1 and 1.5 mEq per L will most likely cause impaired concentration, lethargy, irritability, muscle weakness, tremor, slurred speech, and nausea. Plasma concentrations greater than 2.5 mEq per L are associated with kidney failure. The mechanism associated with lithium acute kidney injury involve volume depletion due to natriuresis and water diuresis accompanied by elevated lithium levels, altered mental status, and subsequent poor oral intake. Cases of acute kidney injury, as a result of lithium-induced neuroleptic malignant syndrome, have also been described.[146] Adequate and timely fluid replacement can rapidly restore kidney function. Loop diuretics can decrease the lithium reabsorption in the loop of Henle and increase lithium excretion. This approach can be used in case of lithium toxicity, if adequate intravascular volume is maintained. Acetazolamide combined with sodium bicarbonate can be used because acetazolamide inhibits the reabsorption of lithium by the proximal tubules. Adequate electrolyte supplements, especially sodium and potassium, are fundamental. Lithium is entirely dialyzable and hemodialysis is the most efficient way to decrease lithium levels when patients cannot be managed medically or when kidney function is severely impaired. Dialysis is usually necessary when lithium concentrations are above 4 mmol per L. Hemodialysis increases lithium clearance to 3.0 L per hour; however, following hemodialysis, a rebound effect in the lithium concentrations can be observed. The rebound is expected to occur as lithium has a slow rate of redistribution from the peripheral tissues into the central compartment or from release of lithium from bone stores. Therefore, hemodialysis should be extended or repeated at frequent intervals.

Chronic Kidney Disease

The debate around lithium-induced CKD is the result of conflicting cross-sectional and longitudinal epidemiologic studies.[147] Some of these studies show a low incidence of kidney dysfunction in lithium-treated patients. Data from 14 studies, including 1,172 patients, estimated that the prevalence of reduced GFR, measured by different methods, was 15%.[145] The development of lithium-induced chronic tubulointerstitial nephritis was first demonstrated by Hestbech et al. in 14 patients treated with lithium for about 2 to 15 years.[148] Markowitz et al. recently reemphasized the risk of often irreversible biopsy-proven lithium toxicity being responsible for combined glomerular and tubulointerstitial damage.[139] Other studies have demonstrated interstitial fibrosis, tubular atrophy, and glomerulosclerosis among the chronic histologic changes associated with lithium. These

studies suggested that lesions correlated with the duration of lithium. However, most of the biopsy samples were obtained from patients that had a history of acute lithium toxicity, and many of the histologic changes were also identified in the control group. The histologic changes associated with acute lithium include ATN with nonspecific changes such as distal tubular flattening, proximal tubular necrosis, and cytoplasmic vacuolation and cellular and nuclear polymorphism of the distal tubular epithelial cells. Although chronic tubulointerstitial nephropathy represents a somewhat nonspecific pattern of disease, the presence of tubular cysts is highly characteristic of lithium toxicity, having been reported in up to 40% of cases.[149] Markowitz et al. revealed a chronic tubulointerstitial nephropathy in all 24 patients with biopsy-proven lithium toxicity, with associated cortical and medullary tubular cysts (62.5%) or dilatation (33.3%). The degree of tubular atrophy and interstitial fibrosis was graded as severe in 58.3%, moderate in 37.5%, and mild in 4.2% of cases. There was a surprisingly high prevalence of focal segmental glomerulosclerosis (50%) and global glomerulosclerosis (100%), sometimes of equivalent severity to the chronic tubulointerstitial disease. Despite discontinuation of lithium, seven of nine patients with initial serum creatinine values >2.5 mg per dL progressed to ESRD.[139] In 2003 a French group studied 74 patients with lithium-induced kidney failure.[150] They showed that the creatinine clearance at referral and at last follow-up was inversely related to the duration of lithium therapy in both univariate and multivariate analyses adjusting for age, gender, hypertension, and proteinuria. In 29 patients with a kidney biopsy, the degree of interstitial fibrosis was related to the lithium duration and cumulative dose. They estimated the prevalence of lithium-related ESRD as two per 1,000 dialysis patients, and the average time between onset of lithium therapy and ESRD was 20 years.[150] Although a minimal increase in the protein excretion rate has been reported in some patients who were taking lithium for at least 2 years, overt proteinuria is not a common complication. A rare association between minimal-change nephrotic syndrome and lithium administration has also been described. Renal dysfunction is often irreversible despite lithium withdrawal, and early detection is essential to prevent progression to ESRD. Although the debate around the rate of progression to CKD and ESRD associated with the chronic use of lithium continues, regular monitoring of estimated creatinine clearance is mandatory in long-term lithium-treated patients.

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