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Original Investigation

Nephropathy in Illicit Drug Abusers: A Postmortem Analysis

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Background: Illicit drug abuse is an independent risk factor for chronic kidney disease, but the pathogenic consequences of long-term exposure to illicit drugs and contaminants under unsterile conditions remains unclear.

Study Design: Case series.

Setting & Participants: All deceased persons (n = 129) who underwent forensic autopsy because of suspected connection with illicit drug abuse between January 1, 2009, and April 30, 2011, in Frankfurt/Main, Germany.

Predictor: Clinical characteristics and patterns of drug abuse.

Outcomes: Histopathologic alterations of the kidney.

Measurements: Hematoxylin and eosin, periodic acid−Schiff, Sirius, and Congo Red stainings and immunoglobulin A immunohistochemistry of all cases; additional histochemical stainings or immunohistochemistry and electron microscopy in selected cases.

Results: Individuals were mostly white (99.2%), were male (82.2%), and had intravenous drug use (IVDU) (81.4%). Median age at death was 39 years and duration of drug abuse was 17 years. The majority (79.1%) took various drugs in parallel as assessed by toxicologic analysis. Despite a young age, the deceased had a high burden of comorbid conditions, especially cardiovascular disease, liver cirrhosis, and infections. Evaluation of the kidneys demonstrated a broad spectrum of pathologic alterations predominated by arteriosclerotic and ischemic damage, mild interstitial inflammation, calcification of renal parenchyma, and interstitial fibrosis and tubular atrophy, with hypertensive-ischemic nephropathy as the most common cause of nephropathy. Interstitial inflammation (OR, 16.59; 95% CI, 3.91-70.39) and renal calcification (OR, 2.43; 95% CI, 1.03-5.75) were associated with severe IVDU, whereas hypertensive and ischemic damage were associated with cocaine abuse (OR, 6.00; 95% CI, 1.27-28.44). Neither specific glomerular damage indicative for heroin- and hepatitis C virus−related disease nor signs of analgesic nephropathy were found.

Limitations: White population, lack of a comparable control group, incomplete clinical data, and absence of routine immunohistochemistry and electron microscopy.

Conclusions: Illicit drug abuse is associated with a broad but unspecific spectrum of pathologic alterations of the kidneys. Cocaine abuse has a deleterious role in this setting by promoting hypertensive and ischemic damage.

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INDEX WORDS: Drug abuse; intravenous drug use (IVDU); cocaine; heroin; nephropathy; chronic kidney disease; histopathology; kidney biopsy.

Illicit drug abuse is associated with an extensive number of psychiatric and somatic diseases, including chronic kidney disease (CKD).[1-7] Since the 1970s, kidney disease has been linked to intravenous drug use (IVDU), mainly in the setting of heroin-associated nephropathy, characterized by nephrotic syndrome with rapid progression and focal segmental sclerosis on kidney biopsy.[1,8] Since the early 1990s, as human immunodeficiency virus (HIV)-associated nephropathy became more common, heroin-associated nephropathy almost disappeared.[9,10] However, serologic testing was not available for HIV and hepatitis C virus (HCV) until the mid-1980s and early 1990s, respectively, which made it impossible to separate the contributions of IVDU, HIV, and HCV to kidney disease. Subsequently, contemporary reports have related CKD in persons with IVDU more to common concomitant chronic HIV, hepatitis B virus (HBV), and HCV infection in this population.[6,9,11-14]

In addition, an association between cocaine abuse and chronic kidney failure has been demonstrated, although confirmation by kidney biopsy was not attained in most studies.[1-3,15]

Moreover, renal AA amyloidosis as a complication of chronic and/or recurrent inflammatory disease in

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persons with IVDU has been described consistently since the 1970s,[16,17] and recent studies have reported an increased prevalence of renal AA amyloidosis among individuals having IVDU.[5,18,19]

To date, few data are available about the burden of CKD in persons with IVDU and results have been contradictory because medical management of this population is challenging. Patients frequently do not appear for follow-up and ask for medical advice only when they are acutely sick. Kidney biopsy is performed infrequently and the diagnosis of underlying kidney disease often is established only clinically. Hence, insight obtained is derived from small case series and kidney biopsy studies with only a small number of individuals included.[5,12,13,17,20] The small sample size and patient selection may explain the discordant results presented by different studies. Moreover, larger autopsy studies that have been conducted mainly predated the surveillance of HCV and HIV.[1,16,20] Thus, it is unclear whether the drugs themselves or other aspects of drug abuse put users at risk for kidney disease.

We conducted a postmortem analysis in illicit drug abusers, unselected for pre-existing kidney disease, to examine the impact of illicit drug abuse on kidney integrity and evaluate the associations between clinical characteristics, as well as patterns of drug abuse, and renal pathologic alterations.

METHODS

Study Design and Cohort

The Institute of Legal Medicine of Goethe University is responsible for autopsies in the Frankfurt/Main metropolitan area (3.5 million inhabitants), Germany. All individuals who underwent forensic autopsy by order of the judicial authorities between January 1, 2009, and April 30, 2011, because of suspected connection with illicit drug abuse were identified using the databases of the Institute of Legal Medicine. All cases were analyzed retrospectively using investigational reports provided by the judicial authorities. Investigation at the scenes was done by the criminal investigation department of the police, including securing evidence and interviewing witnesses, relatives, and general practitioners regarding various parameters, for example, age, sex, and information about abuse behavior.

Additionally, previous medical records from outpatient clinics and hospitalizations were retrieved from patient databases of the Goethe University hospital and affiliated teaching hospitals. Medical diagnoses of pre-existing disease conditions and drug dependency are based on *International Classification of Diseases, 9th and 10th Revisions*, respectively. Cause of death was rated in synopses of police investigations, autopsy findings, and toxicologic analyses in the final medico-legal report. Approval for this study was obtained from the institutional ethics committee of Goethe University.

Autopsy

All autopsies were performed by 2 forensic medical physicians according to Section 87 subs. 2 of the German Code of Criminal Procedure in accordance with the rules of the European Council in Legal Medicine regarding medico-legal autopsies[21] and the DIN EN ISO 17025 standard, including the collection of hair, gastric contents, and urine and blood samples (obtained from the cardiac chambers and femoral veins) for further toxicologic analysis (Item S1, available as online supplementary material).

Remnant blood samples were analyzed further for HBV surface antigen, HCV antibodies, and HIV 1 and 2 antibodies by chemiluminescent microparticle immunoassays and defined as positive when confirmed by western blot (HCV antibodies and HIV antibodies) or neutralization test (HBV surface antigen). Antigen detection by polymerase chain reaction could not be performed because of the high viscosity of postmortem blood samples. Tissue samples were obtained from all organs, including the kidneys, and formalin fixed for further evaluation.

Histologic Evaluation of the Kidneys

Histologic specimens of 129 drug abusers were evaluated. For every paraffin block, hematoxylin and eosin, periodic acid−Schiff, Sirius, Congo Red, and, when calcifications were seen, von Kossa staining were performed. Additionally, immunoglobulin A (IgA) immunohistochemistry was performed for every case using an IgA-specific polyclonal rabbit anti-human antibody (1:150,000 dilution; Dako Cytomation) on a Ventana BenchMark ULTRA stainer immunohistochemistry device (Roche). In selected cases, additional immunohistochemical staining was performed, with polyclonal antibodies specific for IgG (1:100,000 dilution; Dako) and complement component C3c (1:75,000 dilution; Dako) were performed when glomerulonephritis was suspected. A monoclonal antibody specific for amyloid A (1:500 dilution, clone mc1; Dako) was applied in amyloidosis cases.

The following histologic parameters were evaluated: number of obliterated glomeruli per 100 counted glomeruli; presence of segmental sclerosis/scarring/segmentally accentuated increase in cellularity and matrix (yes/no), increase in mesangial matrix (yes/no), and signs of glomerular ischemia (wrinkling of basement membranes and widened multilayered Bowman capsules; yes/no); degree of interstitial fibrosis and tubular atrophy estimated as a percentage and arteriosclerosis and arteriolosclerosis semiquantitatively separated into 6 groups (0, no sclerosis; 1, mild; 2. mild to moderate; 3, moderate; 4, moderate to severe; and 5, severe); presence of interstitial inflammation (yes/no) with all degrees, even very mild, of inflammation included, except for minimal infiltration in the proximity of larger vessels; presence of parenchymal calcifications (yes/no) and whether they were located in the renal papillae/deep medulla or along tubular basement membranes; and, as signs of analgesic nephropathy, capillary sclerosis of the medulla/papillae and suburothelial soft tissue of the pelvis when present ($n = 50$) and signs of papillary necrosis tips of the papillae when present ($n = 46$).

Because of autolysis, the degree of tubular damage (acute tubular necrosis) was not evaluated. Additional electron microscopic investigations were performed for 7 cases, if the light microscopic diagnosis was ambiguous or in order to confirm amyloidosis.

Statistical Analysis

Demographic, clinical, and laboratory variables were expressed as median with interquartile range (IQR) or as proportion, as appropriate. Continuous and categorical variables were compared for univariable analysis between groups using t test or Mann-Whitney U test and Fisher exact test, respectively. Associations between the presence of renal damage and demographic, clinical, and laboratory variables were estimated by stepwise multivariable logistic regression with an elimination criterion > 0.1. All P values reported are 2 sided. Statistical significance was assumed for $P < 0.05$. All statistical analyses were performed using BiAS, version 10.04 (Epsilon-Verlag).

RESULTS

Study Cohort and Clinical Characteristics According to Premortem Medical Records

A total of 139 deceased persons were referred for forensic autopsy because death was suspected to be in the context of illicit drug abuse. Ten deceased were excluded; 6 had no history of drug abuse but died because of intoxication with analgesics or narcotics prescribed in the setting of advanced chronic illness, for example, malignancy, mostly with suicidal intention, and in 4, histologic evaluation of the kidney was not possible because the corpse was in an advanced stage of decomposition when it was found. Thus, 129 deceased individuals were included in this study.

A summary of characteristics of the study cohort according to premortal medical records is shown in Table 1. All the deceased, except for 1 of African descent, were white (99.2%) and mostly men (82.2%). Median age at time of death was 39 (IQR, 32-46) years and documented duration of drug abuse was 17 (IQR, 10-24) years. The majority were known to have had IVDU (81.4%). Diagnosis of various types of chronic diseases had been established in <10% of individuals during their lifetimes, with the exception of chronic HCV infection (41.9%) and hypertension (24.0%). Seven individuals (5.4%) had been given a diagnosis of CKD, none biopsy proven because the deceased had not been preselected for kidney disease in this study.

Table 1. Characteristics of Study Cohort According to Premortem Medical Records

Characteristic	Value
Total no. of individuals	129
Age at death (y)	39 [32-46]
Male sex	106 (82.2)
Documented duration of drug abuse (y)	17 [10-24]
No. with IVDU	105 (81.4)
Documented duration of IVDU (y)	16 [5-24]
History of opioid abuse	103 (79.8)
Opioid maintenance therapy	51 (39.5)
Duration of opioid maintenance therapy (y)	4 [1-11]
History of cocaine abuse	41 (31.8)
Alcoholic	68 (52.7)
Smoker	113 (87.6)
Latest available eGFR (mL/min/1.73 m^2)[a]	91 [78-111]
Time between latest eGFR and death (y)	2.7 [0.8-4.6]
Known medical history	
Chronic hepatitis B virus infection	4 (3.1)
Chronic hepatitis C virus infection	54 (41.9)
HIV infection	9 (7.0)
Hypertension	31 (24.0)
Coronary heart disease	3 (2.3)
Diabetes mellitus	2 (1.6)
Chronic kidney disease	7 (5.4)
Resuscitation measures after corpse found	43 (33.3)
Drugs/injection equipment at place corpse found	82 (63.6)

Note: Unless otherwise indicated, values for categorical variables are given as number (percentage); values for continuous variables, as median [interquartile range].

Abbreviations: eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; IVDU, intravenous drug use.

[a]eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration creatinine equation[43].

Autopsy Findings

In external examination, 64.3% had injection sites, which might be attributable to IVDU but also to medical treatment, whereas 29.5% had injection tracks as markers for severe and long-time IVDU (Table 2). Deceased drug abusers were found to have a high burden of morbidities on autopsy, including cardiovascular disease (left ventricular hypertrophy, 62.0%, and coronary heart disease, 21.7%), liver cirrhosis (20.9%), and acute infections (30.2%). HCV antibody testing was positive in the majority of deceased (66.7%), whereas HBV surface antigen and HIV antibodies were detected in only individual cases.

Toxicologic Results of Drug Intake and Causes of Death

Toxicologic analysis of blood for determination of acute drug intake prior to death and hair for determination of drug abuse behavior in the weeks prior to death demonstrated a broad spectrum of substances abused (Table 3). Among illicit drugs, opioid and cocaine intake were most frequent. Additionally, alcohol consumption was verified in the majority of cases (60.7%). Most patients had consumed different types of drugs in parallel because 2 or more different drugs were found in 102 cases (79.1%).

Drug intoxication was the predominant cause of death according to the final medico-legal report (78.3%), with opioids being the predominant drug in 70.5% (Table S1, available as online supplementary material). Other causes of death were attributable mainly to cardiovascular disease (5.5%), pneumonia (6.2%), and trauma (6.2%).

Pathologic Alterations of the Kidneys

A detailed histologic analysis of renal parenchyma collected during the autopsy was performed for all 129 deceased individuals. Frequencies of morphologic changes are summarized in Table 4. The diagnosis of hypertensive-ischemic nephropathy was made in cases with morphologic changes indicative of hypertensive injury, including atherosclerosis (at least moderate), and when arterial hypertension was diagnosed during life time (12 cases), left ventricular hypertrophy was present (2 cases) or atheromatosis/atherosclerosis was

Table 2. Postmortem Macroscopic Findings

Characteristic	Value
Total no. of individuals	129
BMI (kg/m^2)	23.6 [21.3-26.9]
Injection sites	83 (64.3)
Injection tracks	38 (29.5)
Left ventricular hypertrophy	80 (62.0)
Right ventricular hypertrophy	14 (10.9)
Coronary heart disease	28 (21.7)
Myocardial scarring	8 (6.2)
Valvular vegetation or artificial heart valve	5 (3.9)
Atheromatosis of aorta	55 (42.6)
Atherosclerosis of aorta	34 (26.4)
Cerebral scarring	4 (3.1)
Lung emphysema	15 (11.6)
Pleural adhesion	18 (14.0)
Pancreatic scarring	9 (7.0)
Liver steatosis	33 (25.6)
Liver cirrhosis	27 (20.9)
Splenomegaly	42 (32.6)
Site of infection	39 (30.2)
Skin	4 (3.1)
Tonsil	5 (3.9)
Bronchopulmonary system	35 (27.1)
Endocard	3 (2.3)
Other	4 (3.1)
Kidney weight	
Right (g)	160 [140-180]
Left (g)	165 [145-186]
HBsAg positive	3/96 (3.1)
HCV antibody positive	64/96 (66.7)
HIV antibody positive	10/129 (7.8)

Note: Unless otherwise indicated, values for categorical variables are given as number (percentage) or n/N (percentage); values for continuous variables, as median [interquartile range].

Abbreviations: BMI, body mass index; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

documented (2 cases). Histologic changes were considered sufficient for the diagnosis of relevant hypertensive-ischemic damage when at least one of the following 3 characteristics was found: >10% obliterated glomeruli, >10% interstitial fibrosis and tubular atrophy, and severe arteriosclerosis. In conclusion, in 16 cases, presumptive hypertensive-ischemic nephropathy was diagnosed (Fig 1A), with signs of subacute thrombotic microangiopathy in one case. Mesangioproliferative IgA glomerulonephritis was seen in 6 cases, of which in 5, IgA immunohistochemistry (Fig 1B) was clearly positive; in the sixth case, IgA staining was very faintly positive and focal osmiophilic deposits were found in the mesangia by electron microscopy. In 2 HIV-positive persons, AA amyloidosis was diagnosed (Fig 1C and D). In one

Table 3. Toxicologic Results From Postmortem Analysis

Result	Value
No. with ≥1 drug test positive in hair and/or blood analysis	129 (100)
Hair analysis	117 (90.7)
Opioids	91 (77.8)
Morphine and/or monoacetylmorphine	62 (53.0)
Methadone	57 (48.7)
Other opioid	19 (16.2)
Cocaine	75 (64.1)
Amphetamine	18 (15.4)
Tetrahydrocannabinol	28 (23.9)
Benzodiazepines	11 (9.4)
Other	6 (5.1)
Blood analysis	122 (94.6)
Opioids	91 (74.6)
Morphine	85 (69.7)
Methadone	47 (38.5)
Cocaine and/or metabolites	31 (25.4)
Alcohol test positive from blood and/or urine	74 (60.7)

Note: Values are given as number (percentage) of those tested.

case, chronic interstitial inflammation suspected to be chronic interstitial nephritis was observed. In all other cases, the interstitial inflammation was too mild to justify the diagnosis of interstitial nephritis. In 12 patients, segmental sclerosis, segmental scarring, or a segmentally accentuated hypercellularity/matrix increase restricted to single glomeruli was observed. In one case reminiscent of genuine focal segmental glomerulosclerosis (FSGS), electron microscopy was

Table 4. Pathologic Alterations of the Kidney

Alteration	Value
>10% obliterated glomeruli	13/127 (10.2)
Segmental glomerular scarring	12/126 (9.5)
Signs of glomerular ischemia	49/117 (41.9)
IF/TA > 10%	20/127 (15.7)
Arteriosclerosis > 2[a]	67/128 (52.3)
Arteriolosclerosis > 2[a]	33/119 (27.7)
Interstitial inflammation	28/125 (22.4)
Calcifications of renal parenchyma	75/129 (58.1)
Diagnosis of nephropathy	
Hypertensive-ischemic nephropathy	16/129 (12.4)
IgA glomerulonephritis	6/129 (4.6)
AA amyloidosis	2/129 (1.6)
Chronic interstitial nephritis	1/129 (0.8)

Note: Values are given as n/N assessed (percentage).

Abbreviations: AA, serum amyloid A; IF/TA, interstitial fibrosis/tubular atrophy; IgA, immunoglobulin A.

[a]Arteriosclerosis and arteriolosclerosis were semiquantitatively separated into 6 groups (0, no sclerosis; 1, mild; 2. mild to moderate; 3, moderate; 4, moderate to severe; and 5, severe).

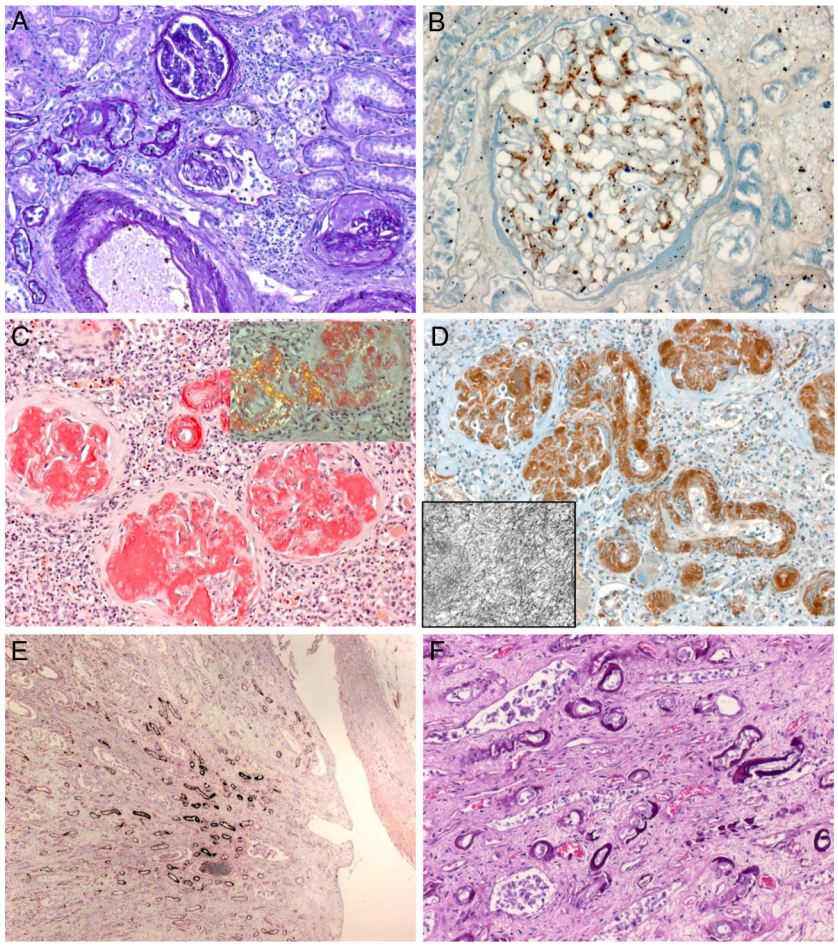

Figure 1. (A) Periodic acid–Schiff stain (original magnification, ×100) of a kidney with hypertensive-ischemic damage with global glomerulosclerosis, signs of glomerular ischemia, tubular atrophy, and arteriosclerosis. (B) Immunoglobulin A (IgA) immunohistochemistry (original magnification, ×400) of a kidney with distinct granular IgA deposits in the mesangia. Deposits are clearly seen despite signs of autolysis. (C) Congo Red stain (original magnification, ×200) of a kidney with AA amyloidosis. The inlay shows birefringence in polarization microscopy in a corresponding area of the section. (D) Amyloid A immunohistochemistry (original magnification, ×200) of the amyloidosis depicted in C. In the inlay, fibrillary deposits with a periodicity typical of amyloid are seen in electron microscopy (original magnification, ×31,500). (E) Conspicuous calcification in the papilla of a renal specimen accentuated along the tubular basement membranes in von Kossa stain (original magnification, ×50). No prominent capillary sclerosis in the renal medulla or the suburothelial soft tissue is found. (F) Hematoxylin and eosin stain (original magnification, ×200) of papillary calcifications with prominent circular deposits at the tubular basement membranes. All pictures were taken on a Zeiss Axio Imager A1.

performed, but despite autolysis, the findings did not justify the diagnosis of a primary podocytopathy. None of the kidneys showed membranoproliferative glomerulonephritis (MPGN). The case classified as subacute thrombotic microangiopathy was the only case with a picture reminiscent of MPGN with mesangial increase of matrix and thickened, questionably double-contoured basement membranes. However, C3c and IgG immunohistochemistry yielded negative results and electron microscopy showed no characteristics of MPGN, but rather of thrombotic microangiopathy.

Conspicuous calcifications of the renal parenchyma were seen in numerous cases (58.1%). In 15 cases, calcium deposits along the tubular basement membranes were observed in renal papillae (Fig 1E and F). No capillary sclerosis of medulla/papillae or pelvic soft tissue and no papillary necroses were observed as signs of analgesic nephropathy.

Clinical Characteristics and Patterns of Drug Abuse With or Without Renal Pathologic Alterations

The deceased were grouped according to the presence or absence of different histologic pathologic states as indicated in Table 4 and compared for clinical characteristics and modalities of drug abuse, including severity of drug use according to toxicologic measurements.[22,23]

Patients with and without different parameters of kidney pathology were comparable for most clinical parameters (data not shown). Parameters associated significantly with different types of renal pathology in univariable analysis included age, duration of drug abuse, and IVDU, as well as positive testing for HCV antibodies and cocaine (Table 5). When using stepwise multivariable logistic regression, the presence of injection tracks was associated positively with >10% obliterated glomeruli, >10% interstitial fibrosis and tubular atrophy, interstitial inflammation, and calcification of renal parenchyma, whereas a positive test result for cocaine was associated with signs of glomerular ischemia, arteriosclerosis greater than 2, and diagnosis of hypertensive-ischemic nephropathy only. In addition, interstitial inflammation was associated with longer duration of IVDU, and diagnosis of hypertensive-ischemic nephropathy was associated with longer duration of drug abuse (all $P < 0.05$).

Table 5. Associations Between Clinical Characteristics or Patterns of Drug Abuse and Renal Pathologic Alterations

	Univariable		Multivariable	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
>10% obliterated glomeruli (n = 127)				
Age (per 1-y older)	0.88 (0.82-0.96)	0.003		
Duration of drug abuse (per 1-y longer)	0.87 (0.80-0.95)	0.001		
Duration of IVDU (per 1-y longer)	0.92 (0.86-0.98)	0.02		
Injection tracks	15.69 (3.22-76.33)	<0.001	26.63 (2.97-239.02)	0.003
Segmental glomerular scarring (n = 126)				
Injection tracks	4.93 (1.37-17.80)	0.02		
Signs of glomerular ischemia (n = 117)				
Age (per 1-y older)	0.94 (0.91-0.99)	0.02		
Duration of drug abuse (per 1-y longer)	0.93 (0.89-0.98)	0.004		
Duration of IVDU (per 1-y longer)	0.96 (0.92-0.99)	0.02		
Cocaine testing positive	3.08 (1.35-7.01)	0.007	3.34 (1.37-8.14)	0.01
HCV-antibody positive	3.19 (1.46-6.99)	0.04		
IF/TA > 10% (n = 127)				
Age (per 1-y older)	0.87 (0.79-0.96)	0.006		
Duration of drug abuse (per 1-y longer)	0.87 (0.79-0.96)	<0.001		
Duration of IVDU (per 1-y longer)	0.84 (0.77-0.93)	0.005		
Injection tracks	17.22 (3.53-84.12)	<0.001	16.73 (1.81-154.56)	0.01
HCV-antibody positive	8.71 (1.07-70.87)	0.04		
Arteriosclerosis > 2 (n = 128)[a]				
Age (per 1-y older)	0.91 (0.86-0.96)	<0.001		
Duration of drug abuse (per 1-y longer)	0.90 (0.85-0.95)	<0.001		
Duration of IVDU (per 1-y longer)	0.94 (0.91-0.98)	0.001		
Cocaine testing positive	2.35 (1.08-5.11)	0.02	3.88 (1.49-9.92)	0.005
Injection tracks	2.95 (1.27-6.82)	0.01		
Interstitial inflammation (n = 125)				
Age (per 1-y older)	0.91 (0.85-0.96)	<0.001		
Duration of drug abuse (per 1-y longer)	0.89 (0.84-0.95)	<0.001		
Duration of IVDU (per 1-y longer)	0.95 (0.91-0.99)	0.03	1.17 (1.05-1.30)	0.003
Injection tracks	8.88 (3.34-23.58)	<0.001	16.59 (3.91-70.39)	<0.001
HCV-antibody positive	3.63 (1.45-9.07)	0.01		
Calcifications of renal parenchyma (n = 129)				
Duration of drug abuse (per 1-y longer)	0.95 (0.90-0.99)	<0.001		
Duration of IVDU (per 1-y longer)	0.96 (0.92-0.99)	0.03		
Injection tracks	3.00 (1.32-6.81)	<0.001	2.43 (1.03-5.75)	0.04
HCV-antibody positive	2.60 (1.21-5.62)	0.01		
Hypertensive-ischemic nephropathy (n = 129)				
Age (per 1-y older)	0.88 (0.82-0.95)	0.004		
Duration of drug abuse (per 1-y longer)	0.94 (0.89-0.99)	0.03	1.12 (1.02-1.23)	0.02
Duration of IVDU (per 1-y longer)	0.84 (0.76-0.94)	<0.001		
Cocaine testing positive	5.42 (1.17-25.20)	0.02	6.00 (1.27-28.44)	0.02

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; IF/TA, interstitial fibrosis/tubular atrophy; IVDU, intravenous drug use; OR, odds ratio.

[a]Arteriolosclerosis was semiquantitatively separated into 6 groups (0, no sclerosis; 1, mild; 2, mild to moderate; 3, moderate; 4, moderate to severe; and 5, severe).

DISCUSSION

The pathogenic potential of long-term exposure to illicit drugs and their accompanying contaminants under unsterile conditions remains incompletely understood. In this postmortem study in an unselected cohort of illicit drug abusers, we found a high burden of kidney pathologic states, although only a few individuals had known CKD. This is analogous to the high frequency of other comorbid conditions, especially cardiovascular diseases, not diagnosed premortem in the individuals of our cohort, emphasizing the notion that many addicts seek medical advice only when acutely ill.[24] The spectrum of kidney alterations was wide, with arteriosclerotic and ischemic damage, interstitial inflammation, calcifications, and interstitial fibrosis and tubular atrophy being the most frequent,

however unspecific, findings. Hypertensive-ischemic kidney disease, associated with cocaine abuse, was the predominant form of CKD, affecting >10% of the deceased. Other specific diagnoses, namely, IgA glomerulonephritis, AA amyloidosis, and chronic interstitial nephritis, were found in individual cases only.

In a series of diagnostic kidney biopsies, a 1.7% frequency of amyloidosis has been reported and reactive AA amyloidosis made up 40.3% of cases.[25] Because biopsy indication is based on renal symptoms, thus causing preselection, a 1.6% frequency of AA amyloidoses in our unselected cohort is unexpectedly high. Our finding is in accordance with reports of high rates of renal AA amyloidosis in persons with IVDU.[5,16,18,19] On the contrary, IgA nephropathy, that is, mesangial IgA deposits, was found in 4.6% of cases, which is consistent with a consecutive autopsy study in which 4.8% of kidneys showed mesangial IgA deposits,[26] indicating that drug abuse does not promote this disease.

The predominance of renal chronic vascular changes is in line with a consecutive autopsy study.[27] However, our cohort in comparison was nearly 40 years younger and vascular changes should increase with age.[28] Given a prevalence of hypertension of 21%-33% in men at corresponding age in established market economies,[28] a frequency of 12.4% hypertensive nephropathies and 52.3% individuals with at least moderate arteriosclerosis as found in our study appears unexpectedly high. We found cocaine abuse to be a strong independent risk factor for ischemic and hypertensive renal damage. Similar findings were reported in a biopsy study of HIV-infected persons with IVDU.[15] Because cocaine is a potent vasoconstrictor known to cause cardiovascular disease, a relationship between cocaine use and kidney failure is plausible.[1,29] Mechanisms underlying cocaine-related renal damage were suggested to involve hemodynamic changes, alterations in glomerular matrix synthesis, degradation, and oxidative stress, leading to ischemic nephropathy, secondary hypertension, and induction of renal atherogenesis.[1,2,3,15,29-34] However, hypertensive renal damage has been described in cocaine abusers even in the absence of systemic hypertension.[2,15] It has been suggested that there is a vicious circle of cocaine use and accelerated progression to kidney failure by hypertension, which is exacerbated and possibly triggered by sustained cocaine-induced vasoconstriction.[15,35]

We could not detect glomerular damage indicating specific heroin- and HCV-related disease, for example, FSGS or MPGN, or signs of analgesic nephropathy, which is at least in part in contrast to previous studies in persons with IVDU.[9,12,13,16,20] How could this be explained?

Both intravenous heroin abuse and chronic hepatitis have been associated with kidney disease, but their relative contribution is not well described. The predominant renal lesion reported in heroin users of African descent is FSGS, and in whites, it is MPGN.[1] However, reports of heroin-associated nephropathy predated the surveillance of HCV and HIV, infections frequently found in persons with IVDU, and thus renal changes might originate from concomitant viral effects.[1,10] Because FSGS in heroin users and nonusers cannot be distinguished on morphologic grounds, it also has been speculated that other conditions, for example, ethnic, socioeconomic, or behavioral factors, may be of pathogenetic relevance rather than heroin's pharmacologic properties.[1,8,36] Subsequent studies found only nonspecific renal findings and no uniform pattern of renal injury in heroin abusers.[9,15,20,37] We found no case of FSGS, but this entity has been described almost exclusively in African descendants,[1,8,11] a group that is not represented in our cohort.

Similarly, contemporary studies found MPGN to be related to chronic HCV infection rather than an independent association with IVDU.[5,7,9,12-14,16] Although HCV infection was frequent in our cohort, in contrast to kidney biopsy studies, we found no case of HBV- or HCV-associated MPGN.[5,12,13,14] However, in these studies, kidney biopsy was performed for nephrotic syndrome in most cases, whereas our cohort was not preselected for renal symptoms. An autopsy study of patients with chronic HCV infection found MPGN in <3% of patients, all of African American descent,[38] indicating that even in the context of HCV infection, MPGN develops infrequently, in accordance with our observations, and may be dependent on ethnicity. In contrast, McGuire et al[39] reported immune complex glomerulonephritis in >80% of HCV patients with liver cirrhosis, often without clinically evident kidney disease. As in our study, immunohistochemistry other than IgA staining was performed in only morphologically suspect cases and, because autolytic changes were common, very early cases of immune complex glomerulonephritis, for example, membranous glomerulonephritis, might have been missed. However, immune complex glomerulonephritis in the earlier report[39] showed an interesting peculiarity, with >95% being IgA positive. Therefore, it appears improbable that a substantial number of such cases were overlooked in our analysis because we found only 6 cases with IgA deposits in a pattern typical of IgA nephropathy. Moreover, these cases were not associated significantly with the presence of HCV infection (data not shown). Although anti-HCV antibodies were observed more frequently in individuals with pathologic kidney alterations, these differences diminished

after adjustment for age and parameters of drug abuse. It therefore appears possible that the presence of HCV infection is a surrogate for severity of abuse rather than an independent risk factor per se.

Comparing for the presence of metabolic lesions of the kidney, one autopsy study found nephrocalcinosis ("mainly of minor degree") in 5.5% of cases.[27] In our much younger cohort, calcifications of renal parenchyma were found in 58.1%. This might indicate an imbalance in electrolyte metabolism in drug abusers. This idea could be supported by reports of cocaine and heroin abusers exhibiting soft-tissue and thymus calcifications, especially in the course of rhabdomyolysis.[40-42] One therefore could hypothesize that even without rhabdomyolysis, such mechanisms might take place on a much smaller scale in drug addicts, promoting the development of renal calcifications. Because nonsteroidal anti-inflammatory drugs are used as adulterants in intravenous drugs, one could hypothesize that this might make intravenous drug abusers prone to interstitial nephritis or analgesic nephropathy. However, only one individual had interstitial inflammation sufficient to postulate interstitial nephritis. Moreover, no case of analgesic nephropathy was detected, which is in line with the idea that phenacetin, but not its metabolite paracetamol, causes analgesic nephropathies.[27]

One limitation of our study is the lack of a control group. However, individuals with a comparably young age at the time of death mostly die in the setting of incurable diseases or severe trauma, when a complete autopsy usually is not performed; thus, adequate controls are lacking. Second, this is a single-center study and results may not be transferrable to other populations because drug abuse behaviors and quality or type of drugs may differ. Moreover, our white cohort may not be representative of other ethnicities, which might explain in part the lack of certain renal pathologic states reported in other studies. Third, there is no binary concept of being a drug addict to one specific type of drug alone because consumption of several drugs in parallel is the rule, not the exception.[3,6] Even by applying toxicologic analyses, type and severity of drug abuse can be established for only the time range of the last 2 months and does not fully reflect the severity of abuse through all past years of addiction, but the development of renal pathology in this setting appears to be a dose- and time-dependent effect.[6,7]

In summary, we found that illicit drug abuse was associated with a broad and unspecific spectrum of pathologic alterations, such as glomerular obliteration, interstitial inflammation, calcifications, and interstitial fibrosis and tubular atrophy. We could not establish a link between one uniform glomerular disease and parameters of drug abuse or concomitant chronic infectious diseases. It therefore appears likely that repeated insults to the kidney caused by multiple pharmacologic challenges due to adulterants, diluents, and/or specific drugs themselves and possibly also antigenic challenges in the setting of repeated nonsterile IVDU induce chronic progressive kidney failure. In addition, our data demonstrate the deleterious role of cocaine abuse in inducing hypertensive and ischemic damage and thus promoting the progression of kidney disease.

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SUPPLEMENTARY MATERIAL

Table S1: Cause of death according to postmortem examination.

Item S1: Autopsy evaluation and toxicological assessment of drug intake.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.01.428) is available at www.ajkd.org

REFERENCES

1. Jaffe JA, Kimmel PL. Chronic nephropathies of cocaine and heroin abuse: a critical review. *Clin J Am Soc Nephrol*. 2006;1(4):655-667.

2. Norris KC, Thornhill-Joynes M, Robinson C, et al. Cocaine use, hypertension, and end-stage renal disease. *Am J Kidney Dis*. 2001;38(3):523-528.

3. Perneger TV, Klag MJ, Whelton PK. Recreational drug use: a neglected risk factor for end-stage renal disease. *Am J Kidney Dis*. 2001;38(1):49-56.

4. Milroy CM, Parai JL. The histopathology of drugs of abuse. *Histopathology*. 2011;59(4):579-593.

5. Jung O, Haack HS, Buettner M, et al. Renal AA-amyloidosis in intravenous drug users—a role for HIV-infection? *BMC Nephrol*. 2012;13:151.

6. Yanik EL, Lucas GM, Vlahov D, Kirk GD, Mehta SH. HIV and proteinuria in an injection drug user population. *Clin J Am Soc Nephrol*. 2010;5(10):1836-1843.

7. Rhee MS, Schmid CH, Stevens LA, Forrester JE. Risk factors for proteinuria in HIV-infected and -uninfected Hispanic drug users. *Am J Kidney Dis*. 2008;52(4):683-690.

8. Rao TK, Niccastri AD, Friedmann EA. Natural history of heroin associated nephropathy. *N Engl J Med*. 1974;290(1):19-23.

9. Dettmeyer R, Wessling B, Madea B. Heroin associated nephropathy—a post-mortem study. *Forensic Sci Int*. 1998;95(2):109-116.

10. Friedman EA, Tao TK. Disappearance of uremia due to heroin-associated nephropathy. *Am J Kidney Dis*. 1995;25(5):689-693.

11. Lucas GM, Mehta SH, Atta MG, et al. End-stage renal disease and chronic kidney disease in a cohort of African-American HIV-infected and at-risk HIV-seronegative participants followed between 1988 and 2004. *AIDS*. 2007;21(18):2435-2443.

12. do Sameiro Faria M, Sampaio S, Faria V, Carvalho E. Nephropathy associated with heroin abuse in Caucasian patients. *Nephrol Dial Transplant*. 2003;18(11):2308-2313.

13. Cheng JT, Anderson HL Jr, Markowitz GS, et al. Hepatitis C virus-associated glomerular disease in patients with human immunodeficiency virus coinfection. *J Am Soc Nephrol*. 1999;10(7):1566-1574.

14. Johnson RJ, Gretch DR, Yamabe H, et al. Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. *N Engl J Med*. 1993;328(7):465-470.

15. Fine DM, Garg N, Haas M, et al. Cocaine use and hypertensive renal changes in HIV-infected individuals. *Clin J Am Soc Nephrol*. 2007;2(6):1125-1130.

16. Menchel S, Cohen D, Gross E, Frangione B, Gallo G. AA protein-related renal amyloidosis in drug addicts. *Am J Pathol*. 1983;112(2):195-199.

17. Dubrow A, Mittman N, Ghali V, Flamenbaum W. The changing spectrum of heroin-associated nephropathy. *Am J Kidney Dis*. 1985;5(1):36-41.

18. Connolly JO, Gillmore JD, Lachmann HJ, Davenport A, Hawkins PN, Woolfson RG. Renal amyloidosis in intravenous drug users. *QJM*. 2006;99(11):737-742.

19. Manner I, Sagedal S, Røger M, Os I. Renal amyloidosis in intravenous heroin addicts with nephrotic syndrome and renal failure. *Clin Nephrol*. 2009;72(3):224-228.

20. Treser G, Cherubin C, Longergan ET, et al. Renal lesions in narcotic addicts. *Am J Med*. 1974;57(5):687-694.

21. Brinkmann B. Harmonization of medico-legal autopsy rules. Committee of Ministers. Council of Europe. *Int J Legal Med*. 1999;113(1):1-14.

22. Pépin G, Gaillard Y. Concordance between self-reported drug use and findings in hair about cocaine and heroin. *Forensic Sci Int*. 1997;84(1-3):37-41.

23. Schulz M, Schmoldt A. Therapeutic and toxic blood concentrations of more than 800 drugs and other xenobiotics. *Pharmazie*. 2003;58(7):447-474.

24. Simmedinger R, Stoever H. Auswertung der Frankfurter Konsumraumdokumentation 2011. Dokumentationszeitraum 01. 01-31.12.2010. Frankfurt, Germany: ISFF 2011; ISNN 1867-531X.

25. von Hutten H, Mihatsch M, Lobeck H, Rudolph B, Eriksson M, Röcken C. Prevalence and origin of amyloid in kidney biopsies. *Am J Surg Pathol*. 2009;33(8):1198-1205.

26. Waldherr R, Rambausek M, Duncker WD, Ritz E. Frequency of mesangial IgA deposits in a non-selected autopsy series. *Nephrol Dial Transplant*. 1989;4(11):943-946.

27. Mihatsch MJ, Khanlari B, Brunner FP. Obituary to analgesic nephropathy—an autopsy study. *Nephrol Dial Transplant*. 2006;21(11):3139-3145.

28. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365(9455):217-223.

29. Dressler FA, Malekzadeh S, Roberts WC. Quantitative analysis of amounts of coronary arterial narrowing in cocaine addicts. *Am J Cardiol*. 1990;65(5):303-308.

30. Bemanian S, Motallebi M, Nosrati SM. Cocaine-induced renal infarction: report of a case and review of the literature. *BMC Nephrol*. 2005;6:10.

31. Lange RA, Hillis LD. Cardiovascular complications of cocaine use. *N Engl J Med*. 2001;345(5):351-358.

32. Nzerue CM, Hewan-Lowe K, Riley LJ Jr. Cocaine and the kidney: a synthesis of pathophysiologic and clinical perspectives. *Am J Kidney Dis*. 2000;35(5):783-795.

33. Brecklin CS, Gopaniuk-Folga A, Kravetz T, et al. Prevalence of hypertension in chronic cocaine users. *Am J Hypertens*. 1998;11(11, pt 1):1279-1283.

34. Braun BL, Murray DM, Sidney S. Lifetime cocaine use and cardiovascular characteristics among young adults: the CARDIA Study. *Am J Public Health*. 1997;87(4):629-634.

35. Dunea G, Arruda JA, Bakir AA, Share DS, Smith EC. Role of cocaine in end-stage renal disease in some hypertensive African Americans. *Am J Nephrol*. 1995;15(1):5-9.

36. Cunningham EE, Zielezny MA, Venuto RC. Heroin-associated nephropathy. A nationwide problem. *JAMA*. 1983;250(21):2935-2936.

37. May DC, Helderman JH, Eigenbrodt EH, Silva FG. Chronic sclerosing glomerulopathy (heroin-associated nephropathy) in intravenous T's and Blues abusers. *Am J Kidney Dis*. 1986;8(6):404-409.

38. Gopalani A, Ahuja TS. Prevalence of glomerulopathies in autopsies of patients infected with the hepatitis C virus. *Am J Med Sci*. 2001;322(2):57-60.

39. McGuire BM, Julian BA, Bynon JS Jr, et al. Brief communication: glomerulonephritis in patients with hepatitis C cirrhosis undergoing liver transplantation. *Ann Intern Med*. 2006;144(10):735-741.

40. Castelao AM, Romero R, Gil-Vernet S, Gonzalez MT, Alsina J. Cocaine, rhabdomyolysis and metastatic calcifications. *Nephrol Dial Transplant*. 1989;4(7):675.

41. Kumar R, West DM, Jingree M, Laurence AS. Unusual consequences of heroin overdose: rhabdomyolysis, acute renal failure, paraplegia and hypercalcaemia. *Br J Anaesth*. 1999;83(3):496-498.

42. Glavina-Durdov M, Definis-Gojanovic M. Thymus alterations related to intravenous drug abuse. *Am J Forensic Med Pathol*. 1999;20(2):150-153.

43. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.