

AKI Associated with Macroscopic Glomerular Hematuria: Clinical and Pathophysiologic Consequences

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Summary

Hematuria is a common finding in various glomerular diseases. This article reviews the clinical data on glomerular hematuria and kidney injury, as well as the pathophysiology of hematuria-associated renal damage. Although glomerular hematuria has been considered a clinical manifestation of glomerular diseases without real consequences on renal function and long-term prognosis, many studies performed have shown a relationship between macroscopic glomerular hematuria and AKI and have suggested that macroscopic hematuria-associated AKI is related to adverse long-term outcomes. Thus, up to 25% of patients with macroscopic hematuria-associated AKI do not recover baseline renal function. Oral anticoagulation has been associated with glomerular macrohematuria-related kidney injury. Several pathophysiologic mechanisms may account for the tubular injury found on renal biopsy specimens. Mechanical obstruction by red blood cell casts was thought to play a role. More recent evidence points to cytotoxic effects of oxidative stress induced by hemoglobin, heme, or iron released from red blood cells. These mechanisms of injury may be shared with hemoglobinuria or myoglobinuria-induced AKI. Heme oxygenase catalyzes the conversion of heme to biliverdin and is protective in animal models of heme toxicity. CD163, the recently identified scavenger receptor for extracellular hemoglobin, promotes the activation of anti-inflammatory pathways, opening the gates for novel therapeutic approaches.

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Introduction

Glomerular hematuria, when not accompanied by mild to severe proteinuria, has been considered a benign manifestation of glomerular diseases that does not influence long-term prognosis. Nevertheless, macroscopic hematuria can induce AKI through a direct harmful effect on renal tubules. Information on pathogenesis and long-term consequences of such macrohematuria-induced AKI is remarkably scarce. The aim of this article is to review the clinical data on hematuria and glomerular disease, as well as the pathophysiology of hematuria-associated AKI.

Hematuria and Hemoglobinuria

Hematuria is defined as the presence of red blood cells (RBCs) in urine (1). Macroscopic hematuria is always pathologic and is characterized by massive presence of RBCs in urine. Microscopic hematuria is defined by the presence of more than 2 RBCs per high-power field in urine sediment in the absence of colored urine. Macroscopic hematuria may be differentiated from hemoglobinuria and myoglobinuria: a heme-positive red supernatant may contain hemoglobin or myoglobin, whereas RBCs are observed in the sediment in hematuria. Smoky gray-colored urine, the presence of RBC casts, and dysmorphic RBCs favor a glomerular origin of hematuria, and blood clots and bright red urine support a urinary tract origin.

Macroscopic Glomerular Hematuria and AKI

IgA nephropathy, Alport syndrome, and thin basement membrane disease (TBMD) are three frequent causes of glomerular hematuria. Rapidly progressive GN, vasculitis, and acute glomerular inflammation, as observed in postinfectious GN or lupus, may also be associated with glomerular hematuria. Tubules filled with RBC casts, with associated acute tubular necrosis, are common findings in these conditions, and their contribution to final renal function outcome deserves specific investigations.

AKI during gross hematuria in IgA nephropathy can be oligo-anuric and may necessitate transient hemodialysis. Reversible AKI due to glomerular macrohematuria was first reported by Kincaid-Smith and colleagues in 1983 (2). Most macroscopic glomerular hematuria-related AKI cases reported since have been IgA nephropathy (Table 1). Initially, hematuria was thought to be innocuous, and AKI, if present, was considered an infrequent feature caused by functional factors (3). In 1985, however, Praga and coworkers reported a 38% incidence of AKI during macrohematuria bouts in IgA nephropathy (4). Duration of hematuria, but not age, was a significant prognostic factor for development of AKI. All patients recovered baseline renal function 15–70 days after cessation of hematuria. The patients were particularly young: mean age in the AKI group was 24 years.

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Table 1. Macroscopic hematuria and AKI in IgA nephropathy

Author (Reference)	No. of Patients	Age (yr)	Basal sCr (mg/dl)	Peak sCr (mg/dl)	Anticoagulation	Full Recovery (%)	Duration of Macroscopic Hematuria (d)	Crescents (%)	Recovery (d)
Praga <i>et al.</i> (4)	11	24±8	NA	3±2.0	NA	100	4.8±1.2	6.5	30±19
Declaux <i>et al.</i> (5)	6	37±21	NA	4.9±1.7	NA	100	38±27	20	34
Kveder <i>et al.</i> (6)	7	56±11	NA	9.9±6.1	NA	100 ^a	4	21	NA
Gutiérrez <i>et al.</i> (7)	36	46±21	1.1±0.2	4.8±3.1	NA	75	20.0±21.5	11	42±63
Feith <i>et al.</i> (8)	3	40±23	1±0.2	5.1±3.3	NA	100	18.3±12.5	14	59±1
Martin Cleary <i>et al.</i> (11)	1	51	0.8	9	1	—	210 ^b	20	No
Foggazzi <i>et al.</i> (13)	3 ^c	40±23.5	1±0.17	5.6±3.2	NA	66%	18.3±12.5	14	59±1.4
August <i>et al.</i> (27)	1	59	NA	12.4	1	100	NA	0	30

Unless otherwise specified, data are expressed as mean ± SD. sCr, serum creatinine; NA, not available.

^aBaseline renal function not available. At last follow-up, five patients had CKD stage 2 or 3.

^bRepeated bouts of macroscopic hematuria. At last follow-up, sCr was 1.3 mg/dl.

^cOf the three patients, one had focal necrotizing lesion on biopsy. Another had ongoing hematuria at discharge.

Subsequent smaller studies did not corroborate duration of gross hematuria as a predictor of AKI (5,6). Severe AKI occurred even during brief macroscopic hematuria episodes (5). Patients in Declaux and colleagues' series were older, and although they all had complete renal function recovery, it took as long as 10 months after the end of gross hematuria (5). Older patients seemed to have longer duration of macrohematuria and recovery period. In Kveder and associates' series, baseline serum creatinine was not reported (6). Although all patients improved, at last visit, 9–57 months later, five of seven patients had CKD stage 2 or 3. In 2007, Gutiérrez and coworkers published a larger retrospective study in which 25% of the patients did not recover baseline serum creatinine (7). Univariate analysis identified duration of gross hematuria, age older than 55 years, higher baseline serum creatinine, and absence of previous macroscopic hematuria episodes as prognostic factors for incomplete recovery of renal function. Multivariate analysis, however, rendered duration of hematuria longer than 15 days as the only statistically significant variable.

We have updated this series with 16 new cases (Table 2). Again, 27% of patients did not recover baseline serum creatinine levels. Hemodialysis was necessary more frequently in the patients who did not completely recover renal function than in those with full recovery (43% versus 5%; $P<0.005$). Incomplete recovery could be related to increased age, duration of macrohematuria, severity of tubular necrosis, and interstitial fibrosis because there were no differences in histologic glomerular features. Steroids were suggested as a means of shortening the duration of gross hematuria and associated complications (4,5,7,8). In all series, proteinuria increased during macroscopic hematuria but did not exceed 3 g/d; nephrotic syndrome was not reported. Urinary sediments contained RBCs, with variable presence of hyaline and granular casts, tubular cells, and leukocytes (4,5,7,8).

Acute tubular necrosis and intraluminal obstructive RBC casts are the most salient histologic findings in AKI during macroscopic hematuria (9,10) (Figure 1 and Table 3). Hemosiderin in tubular cells and interstitial macrophages, as well as phagocytosis of RBCs by proximal tubular cells, has been observed (9–11). Acute tubular necrosis was initially reported only in those tubules that contained RBC casts (4). Other reports were consistent with these findings; those researchers observed acute tubular necrosis throughout the biopsy specimens but noted more severe lesions in tubules containing RBC casts (5). Severity of acute tubular necrosis was a significant risk factor for incomplete recovery of renal function. Contrary to the severity of tubular changes, mesangial proliferation was mild to moderate (4,5,7,8). The frequency of crescents was higher in patients with IgA nephropathy who had macroscopic hematuria-associated AKI than in those who did not (12). However, the percentage of crescents was usually <20% and was not thought to be the cause of renal failure (4–7). Furthermore, as can be observed in the updated data (Tables 2 and 3), crescents were not associated with incomplete recovery of renal function and were absent in most such patients.

The series of Bennet and Kincaid-Smith found focal and segmental proliferation to be the most frequent histologic pattern in patients with IgA nephropathy, macroscopic

Table 2. Clinical characteristics of patients with IgA nephropathy who had complete or incomplete recovery of baseline renal function after macroscopic hematuria–associated AKI

Characteristic	Complete Recovery (n=38)	Incomplete Recovery (n=14)	P Value
Age (yr)	39±18.1	68.6±9.7	0.0001
Duration of MH (d)	15±17.8	36.6±22	0.001
Renal biopsy findings (%)			
mesangial proliferation	50 (+)/50 (++)	35(+)/65 (++)	0.60
GS	5.5±10.7	13.7±20.1	0.07
glomeruli with crescents	4.3±8.4	5±9.4	0.98
tubules with RBC casts	35.3±23.9	58.1±21.2	0.01
tubular necrosis	61 (+)/29 (++)/10 (+++)	7 (+)/72 (++)/21 (+++)	0.001
interstitial fibrosis	37 (+)/58 (++)/5 (+++)	29 (-)/57 (+)/14 (++)	0.0001
Renal function			
baseline sCr (mg/dl)	0.9±0.2	1.1±0.3	0.13
peak sCr (mg/dl)	3.9±2.8	7.1±2.6	0.0001
sCr at 6 mo (mg/dl)	1±0.2	1.9±0.3	0.0001

Data were updated from reference 7 by including 16 new patients from 12 Octubre Hospital seen from 1975 to 2010. MH, macroscopic hematuria; GS, glomerulosclerosis; RBC, red blood cell; sCr, serum creatinine. +, mild; ++, moderate; +++, severe.

hematuria, and crescent formation, whereas patients without macrohematuria were more likely to have a diffuse mesangial proliferation pattern (12). The percentage of glomeruli with crescents, however, did not vary between the groups. Crescents eventually evolve to sclerotic lesions weeks after the macroscopic hematuria episode (12). Kveder and coworkers described seven patients with IgA focal proliferative GN, higher percentage of crescents (21%), and glomerulosclerosis (9%) who nevertheless improved with supportive treatment or steroids (6). Other frequent histologic findings are mild (4,13) to severe (6) interstitial infiltrates, edema, and fibrosis. Glomerulosclerosis and vascular sclerosis were also described. None of these features were as extensive as the tubular injury.

Fogazzi and associates described a heterogeneous series of seven patients with macroscopic glomerular hematuria–associated AKI, including two with IgA nephropathy and one with Henoch-Schönlein nephropathy (13). Renal biopsy showed extensive acute tubular necrosis, RBC casts, and erythrophagocytosis by tubular cells but also severe glomerular lesions. The authors concluded that severe glomerular injury may have caused AKI and delayed recovery. This series included a patient with focal necrotizing IgA nephropathy with ongoing hematuria, and partial recovery of renal function (Table 1). Of note, despite the severity of glomerular lesions, serum creatinine returned to baseline values in most other patients. It is interesting that, although the presence or intensity of microscopic hematuria has been associated with worse kidney function prognosis in IgA nephropathy (14), a history of macroscopic hematuria bouts has even been associated with a better kidney outcome (15–19). However, this association was frequently lost on multivariate analysis, probably because macroscopic hematuria was frequently observed in cases with earlier (characterized by less fibrosis) or milder glomerular injury (17).

Alport disease is a hereditary basement membrane disorder originating from alterations in type IV collagen (20). The renal manifestations consist of persistent microhematuria

and episodic gross hematuria associated with respiratory infections or exercise. ESRD usually occurs in males between ages 16 and 35 years. Gross hematuria during childhood is one of several well-established indicators of unfavorable outcome in female carriers (21). To our knowledge, there are no reports of AKI after macroscopic hematuria in Alport disease, possibly because of the rarity and underdiagnosis of the condition.

TBMD is also a hereditary nephropathy arising from mutations of type IV collagen genes. Persistent microhematuria is observed from childhood, and macroscopic hematuria can occur. The disease has excellent prognosis, and few patients progress to ESRD. A patient with TBMD who developed gross hematuria and AKI after 1 year of warfarin therapy has been described (22). The patient regained normal renal function after 6 weeks of dialysis. Renal biopsy revealed that 60% of tubules were distended with RBCs. There was no evidence of crescents, mesangial proliferation, or interstitial hemorrhage. A high prevalence of hypercalciuria, hyperuricosuria, and nephrolithiasis has been found among patients with TBMD and loin-pain hematuria syndrome (23,24). Gross hematuria and loin-pain episodes could be related to these abnormalities. Although not specifically investigated, it is generally thought that hypercalciuria and hyperuricosuria could induce the formation of intraluminal microcrystals causing tubular damage and nonglomerular bleeding (23,24).

Anticoagulation and AKI

Oral anticoagulation has been suggested to cause AKI by inducing glomerular hematuria (25). In nine patients receiving warfarin with gross hematuria and unexplained AKI, renal biopsy excluded GN. None of the biopsy specimens revealed crescents; the highest percentage of sclerosed glomeruli among them was 11%, and all specimens had variable severity scores of acute tubular necrosis and RBC casts. It was hypothesized that AKI induced by hematuria aggravated by anticoagulation was unlikely to

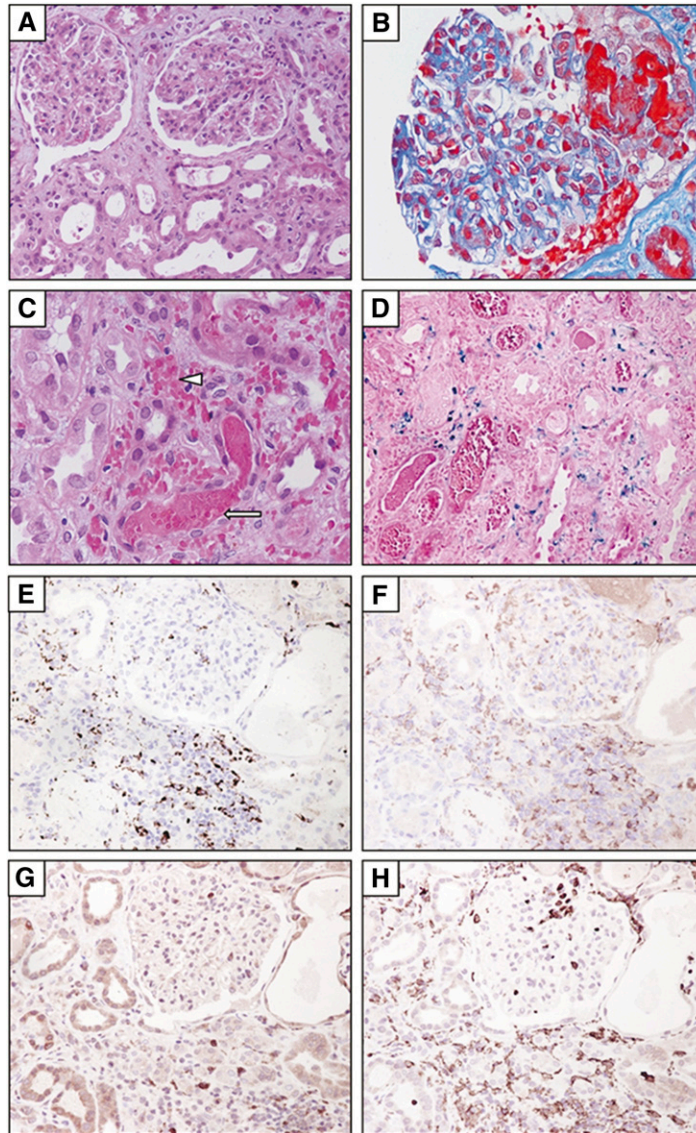


Figure 1. | Renal biopsy specimen from a patient with IgA nephropathy and macroscopic hematuria-associated AKI. Light micrographs show mesangial proliferation, increased mesangial matrix, and tubular degenerative and regenerative changes, consistent with acute tubular and glomerular necrosis (A and B). There is remarkable red blood cell extravasation in the interstitium (arrowhead) and red blood cell casts (arrow) in most tubules (C); interstitial hemosiderin, as determined by blue Perl staining (D); CD68-positive (E) and CD163-positive (F) macrophages; and oxidative stress (heme oxygenase-1 [G] and NADPH-p22 phox [H]). (A and C) Hematoxylin and eosin staining. (B) Masson trichrome. (E–H) Immunohistochemistry.

develop in a normal renal parenchyma. However, mild glomerular damage may give way to glomerular bleeding in patients receiving warfarin. The clinical outcome in this series was unfavorable: 66% of patients did not recover baseline renal function. This raises a note of caution about oral anticoagulation in patients with kidney disease. In this regard, patients with reduced renal function are at higher risk for overanticoagulation, gross hematuria, and AKI (26). Warfarin-associated gross hematuria and AKI has been reported in IgA nephropathy (27) (Table 1). More recently, AKI associated with overanticoagulation has also been reported in patients without CKD (28). In this study, mean serum creatinine failed to return to baseline values at 3 months (28).

Hemoglobinuria and AKI

AKI occurring in the course of acute hemolysis after incompatible blood transfusions or paroxysmal nocturnal hemoglobinuria (PNH) differs from glomerular bleeding-associated AKI because hematuria is absent. However, it may provide pathophysiologic clues to the molecular mechanism of kidney injury and the role of heme-containing molecules.

PNH is a rare clonal disorder characterized by chronic intravascular hemolysis and thrombotic tendency. Infections, drugs, immunization, or exercise may trigger hemolytic episodes. Reversible AKI is thought to depend on tubular hemoglobin-mediated toxicity due to hemolysis, intrarenal vasoconstriction, and intratubular obstruction

Table 3. Histologic findings in patients with IgA nephropathy who had incomplete recovery of renal function after macroscopic hematuria-associated AKI

Patient	Age (yr)	Duration of MH (d)	Mesangial Proliferation	GS (%)	Glomeruli with Crescents (%)	Tubules with RBC Casts (%)	Tubular Necrosis	Interstitial Fibrosis	Baseline sCr (mg/dl)	Final sCr ^a (mg/dl)
1	55	37	+	0	0	100	++	–	1.1	1.8
2	77	21	+	50	0	50	+++	++	1.7	2.6
3	65	11	+	61	23	50	++	+	1.5	1.9
4	59	15	++	25	19	50	++	+	1	2.1
5	58	75	++	0	25	50	++	++	1.3	1.9
6	77	60	+	0	0	50	++	+	1	2.2
7	57	17	+	0	0	30	++	+	0.7	1.2
8	83	7	+	11	0	50	++	+	1.3	1.7
9	74	60	+	0	0	50	+	–	1.3	2
10	59	49	++	4	4	60	+++	–	0.8	2
11	80	17	+	0	0	40	++	+	0.8	1.8
12	67	44	+	16	0	50	++	+	0.7	1.6
13	76	58	++	25	0	100	+++	–	0.8	1.6
14	73	42	++	0	0	75	++	+	1.4	2

Data were updated from reference 7 by including five new patients seen at 12 Octubre Hospital from 1975 to 2010. MH, macroscopic hematuria; GS, glomerulosclerosis; RBC, red blood cell; sCr, serum creatinine. –, absent; +, mild; ++, moderate; +++, severe.

^asCr 6 months after the onset of MH-associated AKI.

(29,30). AKI can be the first presenting feature. AKI is usually nonoliguric and often requires acute hemodialysis. Renal biopsy shows hemosiderin deposits in tubular cells and acute tubular necrosis. Although hemosiderin accumulates quite rapidly in tubules, its role in AKI remains controversial (30) because intense renal hemosiderosis can be found in patients with PNH who have normal renal function.

Renal ischemia from acute microvascular thrombosis may also contribute to kidney injury (30,31). Renal hemosiderosis can also be found in hemolysis due to prosthetic heart valves and sickle cell hemoglobinopathies. Superimposed AKI has been described in a patient with underlying CKD who developed intravascular hemolysis associated with mitral valve repair (32). It was hypothesized that CKD may predispose to heme-induced injury.

Blood transfusions are risk factors for AKI after cardiac surgery (33,34). Transfused RBCs may contribute to organ injury in susceptible patients because of functional and structural changes that occur after 2–3 weeks of storage. RBCs become rigid; generate less nitric oxide; have increased adhesiveness to vascular endothelium; and release procoagulant phospholipids, free iron, and hemoglobin. Transfusion of blood stored for more than 14 days was associated with greater in-hospital mortality and incidence of AKI. Renal biopsies were not reported, and whether free iron, free hemoglobin, or other pathophysiologic mechanisms are shared with macrohematuria-associated AKI is unknown.

Pathophysiology of Hematuria-Induced Renal Damage

Recent studies have provided insights into the potential mediators of tubular injury (Table 4). Initially, it was suggested that intratubular obstruction by RBCs or hemoglobin casts may induce AKI (2,9). However, recent studies did not find retro-diffusion of Tamm-Horsfall protein into glomeruli and thus did not support an obstructive hypothesis (6,13). Proximal tubular cells have a limited capacity to engulf and degrade RBCs (35), and addition of RBCs was not cytotoxic *in vitro* (36). Thus, other mechanisms have been suggested to underlie macroscopic hematuria-associated AKI. The principal mechanism proposed is the

direct tubular toxicity of hemoglobin, heme, iron, or other molecules released from RBCs. The heme group of hemoglobin may also decrease nitric oxide availability, promoting intrarenal vasoconstriction and ischemia (9). Finally, elimination of RBC debris from tubular lumens seems slow (37) and may explain the prolonged recovery period observed in some patients.

Hemolysis from any cause can result in hemoglobinuria and can induce AKI. Hemoglobin is bound to haptoglobin, forming a haptoglobin-hemoglobin complex in plasma (38). Under normal conditions, this complex is too large to be filtered by glomeruli, and it is further degraded by spleen, bone marrow, and liver. However, in conditions of intravascular hemolysis, plasma haptoglobin is consumed and its plasma concentration decreases significantly. By contrast, free hemoglobin accumulates in plasma and dissociates from tetrameric to dimeric hemoglobin, which is filtered more easily by glomeruli. In the tubular lumen, hemoglobin may be taken up by proximal tubules (38) or may be degraded, releasing heme-containing molecules and free iron (9) (Figure 2).

Under oxidant conditions, intracellular hemoglobin dissociates into heme and globin. Heme oxygenase (HO) is the enzyme that transforms heme to biliverdin, a reaction that also produces iron and carbon monoxide. Biliverdin is subsequently converted to bilirubin by bilirubin reductase, whereas iron is ultimately stored in ferritin. Increased HO activity upregulates ferritin synthesis (39). Thus, HO and ferritin decrease cellular exposure to heme and catalytically active “free” iron (40). In cells and tissues not normally involved in heme protein clearance, augmented expression of the inducible HO isoform (HO-1) is a protective mechanism against a wide variety of injurious stimuli, such as ischemia, oxidative stress, inflammation, hypoxia, and heavy metals (39). Enhanced renal HO-1 expression was observed in PNH (41), autoimmune hemolytic anemia (42), IgA nephropathy with macroscopic hematuria (11), and experimental models of heme-induced damage (39). Several data provide *in vivo* evidence that induction of HO-1 is a beneficial response from tissues exposed to heme-induced oxidative damage (39). HO-1 protection includes not only degradation of heme but also inhibition of chemokine and cell-cycle regulators, increased synthesis of ferritin, and reaction-derived products

Table 4. Mediators thought to contribute to hematuria-induced kidney injury

Promoters of injury
toxicity of hemoglobin, heme, or iron via oxidative stress and other mechanisms
hypoxia and intrarenal vasoconstriction via NO scavenging
tubular obstruction from hemoglobin precipitation and Tamm-Horsfall protein proinflammatory cytokines
Protective mechanisms
induction of heme oxygenase-1
production of carbon monoxide
biliverdin and bilirubin
ferritin-stored iron
free hemoglobin scavenging by haptoglobin/CD163
iron chelators
antioxidant defenses

NO, nitric oxide.

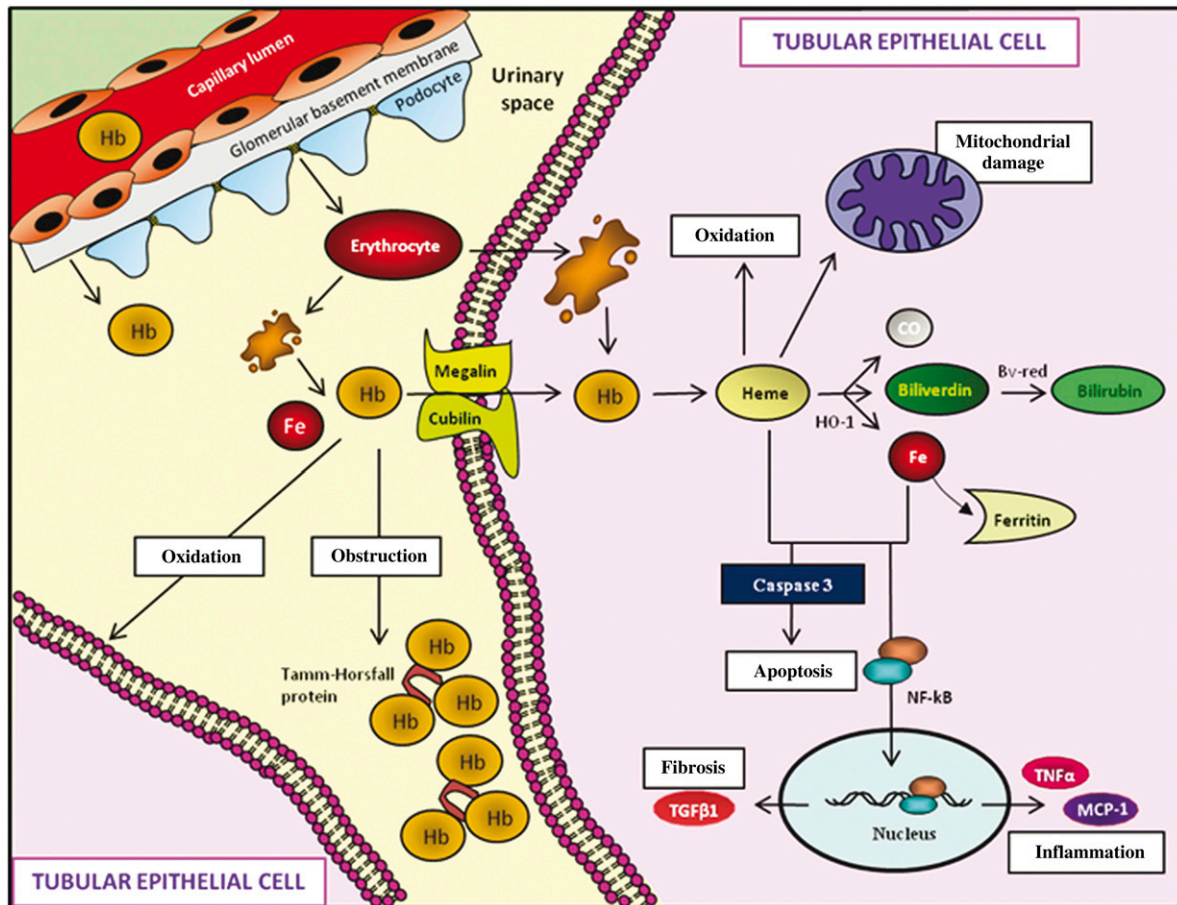


Figure 2. | Pathophysiologic pathways of hematuria-induced kidney damage. Hemoglobin (Hb) released by intratubular degradation of red blood cells or hemoglobin directly filtered by the glomerulus may be incorporated into proximal tubules through the megalin-cubilin receptor system or degraded in the tubular lumen, releasing heme-containing molecules and eventually free iron. Cell-free hemoglobin promotes lipid peroxidation and physical obstruction of the renal tubule by hemoglobin precipitation in association with Tamm-Horsfall protein under acidic conditions, which leads to intraluminal casts, increased intratubular pressure, and subsequent decreased GFR. Hemoglobin/heme/iron (Fe) accumulation within tubular cells generates reactive oxygen species, mitochondrial damage, caspase activation and apoptosis, upregulation of vascular adhesion molecules and pro-inflammatory/profibrotic cytokines (such as TNF- α , monocyte chemoattractant protein-1 [MCP-1], and TGF- β 1) through activation of NF- κ B transcription factor.

(carbon monoxide, biliverdin, bilirubin) (43). Thus, carbon monoxide has anti-inflammatory and vasorelaxant effects via induction of nitric oxide synthase (44), and bilirubin and biliverdin are potent radical scavengers (45).

Heme Toxicity

The kidney can be damaged by large amounts of heme resulting both from extrarenal heme-containing proteins (myoglobin in rhabdomyolysis and hemoglobin in hemolysis) (39,41,46) and from renal heme-proteins, as occurs after ischemic or toxic insults (47,48). Intratubular, cell-free hemoglobin induces severe oxidative damage as a consequence of heme redox cycling between ferric and ferryl states, which generates radical species and promotes lipid peroxidation (49–53). Lipid peroxidation is responsible for the intense vasoconstriction and oxidative injuries observed in disorders associated with renal accumulation of hemoproteins (54).

Myoglobin catabolism results in heme generation; therefore, the renal toxicity of myoglobin is similar to that

observed with hemoglobin (55), and it will be not discussed in depth here. Myoglobin accumulation within tubular cells generates oxygen reactive species (56), caspase activation, and apoptosis (57); upregulates pro-inflammatory cytokines (58) and vascular adhesion molecules (59); and causes vasoconstriction and tubular obstruction (48,54,60). Specifically, myoglobin-stimulated vasoconstriction is also related to a decrease in NO availability (61,62). The extent of both hemoglobin- and myoglobin-induced cell damage may be increased by an inadequate endogenous antioxidant content or a defective cytoprotective machinery. Thus, reactive oxygen scavengers and iron chelators provide protection (63,64).

Heme permeates plasma and organellar membranes, thus entering cells and facilitating cytotoxicity (65,66). Additional heme toxic mechanisms include impairment of the activity of certain glycolytic enzymes, such as glucose-6-phosphate dehydrogenase and glutathione reductase; oxidative DNA denaturation; and mitochondrial toxicity (67–70).

In addition to its direct cytotoxicity, heme can also indirectly promote chronic renal damage by inducing inflammation and fibrosis (38,71). Thus, exposure to heme proteins increases the renal expression of TNF- α , monocyte chemotactic protein-1, and TGF- β via NF- κ B transcription factor (41,46). The activation of these cytokines serves as a "positive-feedback loop" that perpetuates renal damage beyond the initial injury phase (72) and contributes to a chronic inflammatory response, as occurs in recurrent hemolytic episodes (48).

Hemoglobin Scavenging: CD163 Receptor

Recently it has been observed that haptoglobin-hemoglobin complexes are cleared by CD163, a scavenger receptor on the surface of tissue macrophages (73). In a patient with IgA nephropathy, macroscopic hematuria, and AKI, we reported extensive intratubular and interstitial RBC extravasation and interstitial hemosiderin accumulation (11). We observed an increased expression of CD163-positive macrophages and oxidative markers, which were principally observed in areas of interstitial hemorrhage and tubules filled with RBCs, showing the relationship between interstitial RBCs and oxidative stress. Renal CD163 immunostaining may reflect a compensatory role of CD163 to decrease hemoglobin-toxic effects. Binding of hemoglobin to CD163 induces anti-inflammatory pathways, increasing the IL-10 release and HO-1 synthesis that may contribute to restored tissue integrity (74).

The Road Ahead

Until recently, macroscopic hematuria in glomerular disease in the absence of nephritic syndrome was considered a mild phenomenon. However, it has become clear that it may induce AKI severe enough to warrant dialysis, and the recovery of renal function may be incomplete. Aging of the population and the widespread use of anticoagulation may increase the incidence of severe macroscopic hematuria-associated AKI. Our current understanding of potential pathogenic mechanisms derives mainly from experimental settings, and there is no current clinical application of such knowledge. Further studies that validate experimental knowledge in the clinical setting are needed in order to identify therapeutic approaches for this specific form of kidney injury. Until new specific treatments are available, early steroid administration to accelerate recovery of renal function and decrease the risk for chronic renal impairment could be suggested on the basis of observational studies. However, this approach has not been tested in randomized controlled trials. Prospective studies are needed to better define the epidemiology of hematuria-associated AKI, characterize the clinical picture, identify prognostic factors, and define a management strategy.

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