

Editorial Reviews

Haematuria: the forgotten CKD factor?

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Abstract

Haematuria is a frequent manifestation of glomerular disease. However, nephrologists devote more attention to the monitoring and therapeutic targeting of another key manifestation of glomerular injury, proteinuria. Recent reports have propelled haematuria to the forefront of clinical nephrology. Thus, glomerular macroscopic haematuria is associated with the development of acute kidney injury (AKI) with predominant tubular cell damage and there is increasing evidence for the negative impact of glomerular haematuria-associated AKI on long-term renal function outcome both in the context of IgA nephropathy and in anticoagulated patients. In addition, an epidemiological association between isolated microscopic haematuria in young adults and long-term incidence of end-stage renal disease has been described. Finally, a clearer understanding of how haematuria may cause tubular injury is emerging through detailed histological assessment of human biopsies and experimental models of haemoglobin-mediated nephrotoxicity.

Keywords: chronic kidney disease; haematuria; warfarin

Haematuria was the first sign of glomerular injury to be noted by ancient physicians. However, the development of a proteinuria-centric vision of chronic kidney disease (CKD) in the last decades has relegated haematuria to secondary actor status and its presence is usually not mentioned in large epidemiological studies of CKD. Recent information has propelled haematuria to the forefront of clinical nephrology, such as increasing evidence for the existence of haematuria-associated acute kidney injury (AKI) and its negative prognostic implications [1], the description of warfarin-related nephropathy (WRN) [2–4], the epidemiological evidence of an association between microscopic haematuria and long-term incidence of end-stage renal disease (ESRD) [5] and a clearer understanding of how haematuria may cause tubular injury [6, 7].

The pathogenesis of glomerular haematuria

The presence of glomerular haematuria indicates a defect in the glomerular basement membrane (GBM) through which red blood cells (RBCs) egress from the glomerular capillary into the urinary space [8]. The precise mechanism responsible for GBM alteration or rupture remains unclarified. In glomerulonephritis, where leucocytes infiltrate the glomerulus, electron microscopy has revealed GBM alterations, such as thickening, generalized attenuation, irregularity, wrinkling, notching and rupture. Immune complex deposits are thought to interfere with the GBM structure, rendering it weak and easily ruptured. In addition, matrix metalloproteinases and gelatinases released by infiltrating leucocytes or activated glomerular cells further damage the weakened GBM.

In non-inflammatory glomerular injury, which includes thin basement membrane disease (TBMD), early Alport syndrome and loin pain haematuria syndrome, electron microscopy reveals a diffuse thinning of the GBM while the structure remains apparently intact. The GBM width may be reduced to a third of normal, and the defect is more often diffuse and extensive, although it can be focal [9]. In Alport syndrome, GBM injury can progress to thickening, splitting or basket weaving of the lamina densa [10]. Abnormalities in the GBM molecular composition are thought to account for these alterations. In TBMD, Type IV collagen is slightly more compact and the GBM has less non-collagenous molecules [8]. In Alport syndrome, a genetic defect in adult GBM Type IV collagen chains ($\alpha 3$, $\alpha 4$ or $\alpha 5$) leads to the persistent expression of foetal GBM Type IV collagen chains ($\alpha 1/\alpha 2$) which are more sensitive to proteases, rendering the GBM more unstable [11]. In loin pain haematuria syndrome, thick or thin GBMs have been observed [12]. However, the precise molecular mechanisms responsible for the abnormal GBM were not fully described.

Whatever the cause of GBM injury, electron micrographs have shown dysmorphic RBCs traversing through

GBM ruptures in lupus nephritis Class IV nephropathy [13] or through gaps in the glomerular capillary walls in sporadic microhaematuria with thin GBM [14]. Therefore, the presence of glomerular haematuria is an indicator of glomerular injury and most evidence points it to be a marker of a damaged GBM.

The consequences of glomerular haematuria

Glomerular haematuria, similar to proteinuria, may result in tubular injury. This evidence rests on insights from basic research on the molecular mechanisms of haemoglobinuria- and myoglobinuria-induced tubular injury as well as on the clinical evidence of macrohaematuria-associated AKI in the context of IgA nephropathy or anticoagulation. Recent detailed immunohistochemical evaluation of human renal biopsies serves as a link between basic research on haem toxicity and clinical findings in the context of glomerular haematuria.

Insights from basic research

The experimental evidence supports the role of haemoglobin (Hb), haem, iron or other molecules released by RBC in the pathogenesis of tubular injury (Figure 1). Cell-free Hb in the tubular lumen generates reactive oxygen species and lipid peroxidation [15] and may decrease nitric oxide availability, inducing intra-renal vasoconstriction and ischaemia and, in the last instance, renal damage [16]. Hb could also be incorporated into proximal tubules via the megalin–cubilin

receptors [17]. Intracellular Hb increases iron-derived hydroxyl radicals [18], caspase activation and apoptosis [19] and induces pro-inflammatory cytokine secretion [20]. Under oxidant conditions, intracellular Hb dissociates into globin and haem. Haem is also a potent oxidant that induces pro-inflammatory and profibrotic pathways, contributing to a chronic inflammatory response in the kidney, as observed in recurrent haemolytic episodes [17, 21]. Haem oxygenase (HO) decreases cellular exposure to haem by transforming haem to biliverdin, a reaction that additionally releases carbon monoxide and catalytically active ‘free’ iron. Interestingly, HO induction activates ferritin synthesis, the principal protein implicated in iron storage [22]. Experimental models have shown that induction of the HO-1 isoform is a beneficial response towards haem-induced oxidative stress [23]. HO-1 protection is multifactorial since reaction-derived products (carbon monoxide and biliverdin) have beneficial effects as well. Carbon monoxide induces nitric oxide synthase, which has anti-inflammatory and vasorelaxant effects [24], while biliverdin is a potent peroxyl radical scavenger [25]. In tissues, Hb is thought to be cleared in part by CD163, a scavenger receptor present in resident macrophages [26]. Binding of Hb to CD163 prompts anti-inflammatory responses such as interleukin-10 and HO-1 synthesis [27]. It is hypothesized that CD163 responds to Hb-derived oxidant injury in a way that could contribute to restore tissue integrity. There is clinical evidence that such processes also occur in human haemoglobinuria. Thus, renal HO-1 expression has been observed in haemolytic disorders, such as paroxysmal nocturnal haemoglobinuria [7] and autoimmune haemolytic

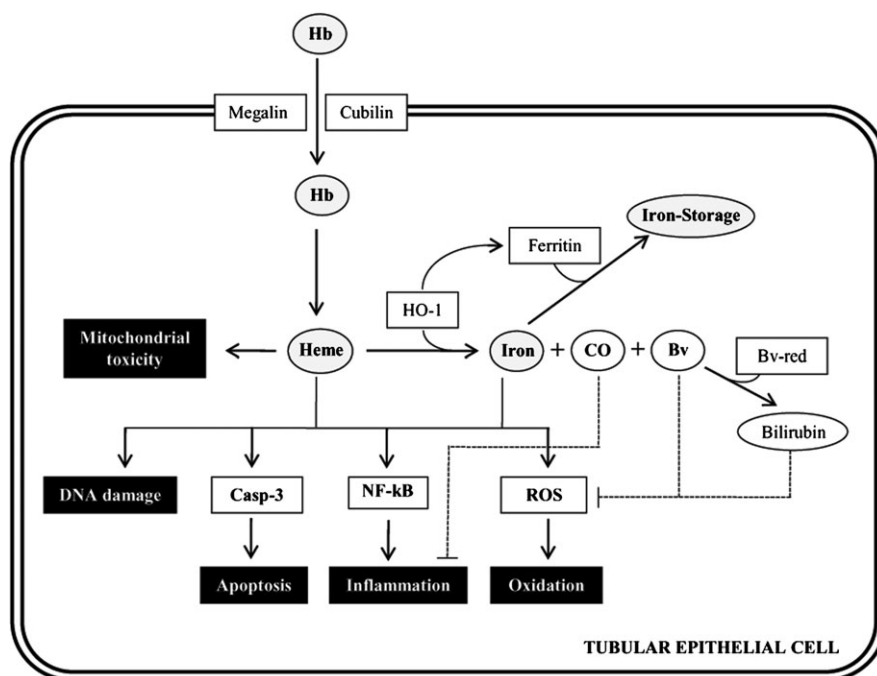


Fig. 1. Pathogenetic mechanisms of tubular epithelial cell injury by haemoglobin. Tubular epithelial cells uptake haemoglobin (Hb) by the megalin–cubilin receptor system. Intracellular Hb dissociates into globin and haem. Haem oxygenase-1 (HO-1) degrades haem to biliverdin (Bv), iron and carbon monoxide (CO). Haem and iron accumulation in the cell produces reactive oxygen species (ROS), mitochondrial damage, caspase activation and apoptosis and pro-inflammatory cytokine release via NF- κ B transcription factor. To decrease these injurious effects, free-active iron is ultimately stored in ferritin, and biliverdin is subsequently converted to bilirubin by biliverdin reductase (Bv-red). It is important to note that ferritin synthesis is increased by HO-1 activity and that products generated by HO-1 activity, such as CO has anti-inflammatory effects, whereas bilirubin and biliverdin are potent antioxidants.

anaemia [28], and infiltrating CD163-expressing macrophages are present in paroxysmal nocturnal haemoglobinuria [7] (Figure 2).

Glomerular haematuria-associated AKI

In addition to the experimental evidence supporting a tubule toxic effect of haemoglobin, clinical data have reported the association between glomerular macroscopic haematuria and AKI [29]. Bouts of macroscopic haematuria are a typical manifestation of IgA nephropathy. The real incidence of AKI during episodes of gross haematuria in IgA nephropathy is unknown, although some studies have reported that it can be >35% [29]. AKI has also been reported during gross haematuria bouts of some clinical

entities pathogenically related with IgA nephropathy, such as Henoch–Schönlein vasculitis and glomerulonephritis of cirrhotic patients [30, 31]. Further emphasizing the pathogenic role of haematuria, both the likelihood and the severity of AKI are increased in parallel with the duration of gross haematuria [1, 29]. Most of these macrohaematuria-related AKI are non-oliguric and accompanied by a non-nephrotic proteinuria; hypertension is absent or mild. Severity of AKI is very variable, oscillating between mild renal function deterioration (likely undetected in many episodes) and severe AKI requiring dialysis.

Case studies and series have shown that acute tubular necrosis (ATN) and intraluminal obstructive RBC casts are the most prominent histological features in haematuria-associated AKI. Glomerular lesions are characteristically mild and crescents may be present but usually in <15–20% of glomeruli [29]. Indeed, gross haematuria or the presence of >1 000 000 RBC/mL of urine is associated with a high likelihood of crescents in the renal biopsy [32]. Initially, it was thought that gross haematuria-related AKI was secondary to tubular obstruction. However, new detailed immunohistochemical analysis suggested a more complex picture. Thus, we recently reported in an over-coagulated patient with IgA nephropathy and macroscopic haematuria-associated AKI, iron in tubular cells and macrophages, increased HO-1 expression and presence of CD163-positive macrophages in iron-loaded areas. Additionally, macrophages stained positively for NADPH-p22 phox, an oxidative stress marker [6]. These findings recapitulate many of the features of experimental and clinical haemoglobinuria-associated AKI [7] and suggest the involvement of haemoglobin nephrotoxicity in the pathogenesis of glomerular haematuria-associated AKI.

General supportive care, as in other types of AKI, is recommended for patients with haematuria-induced AKI. Since the severity and the long-term consequences of AKI are clearly related with haematuria duration, any therapeutic measure able to shorten haematuria could be beneficial. Preliminary observations of our group suggest that intravenous corticosteroid pulses reduce duration of gross haematuria, hastening renal function recovery. On the other hand, it is important to stress that a renal biopsy is necessary for an accurate diagnosis in patients with AKI and macroscopic haematuria, after excluding urological and vascular diseases. Crescentic glomerulonephritis (crescents in >50% of glomeruli) is another possible presentation of IgA nephropathy, although less common than haematuria-induced AKI. Clinical manifestations of both IgA nephropathy presentations can be very similar, although prognosis is remarkably poorer in crescentic forms. High-dose corticosteroids and cyclophosphamide have been used with favourable results in some patients with crescentic IgA nephropathy, but there is a need for more robust clinical information. Finally, other different types of acute and severe glomerular diseases (other types of crescentic glomerulonephritis, vasculitis, lupus nephritis, acute post-infectious and membranoproliferative glomerulonephritis) can also present with gross haematuria and AKI and should be correctly diagnosed by means of a renal biopsy.

In recent years, episodes of AKI during gross haematuria bouts in patients taking oral anticoagulation have been increasingly recognized and have raised considerable interest.

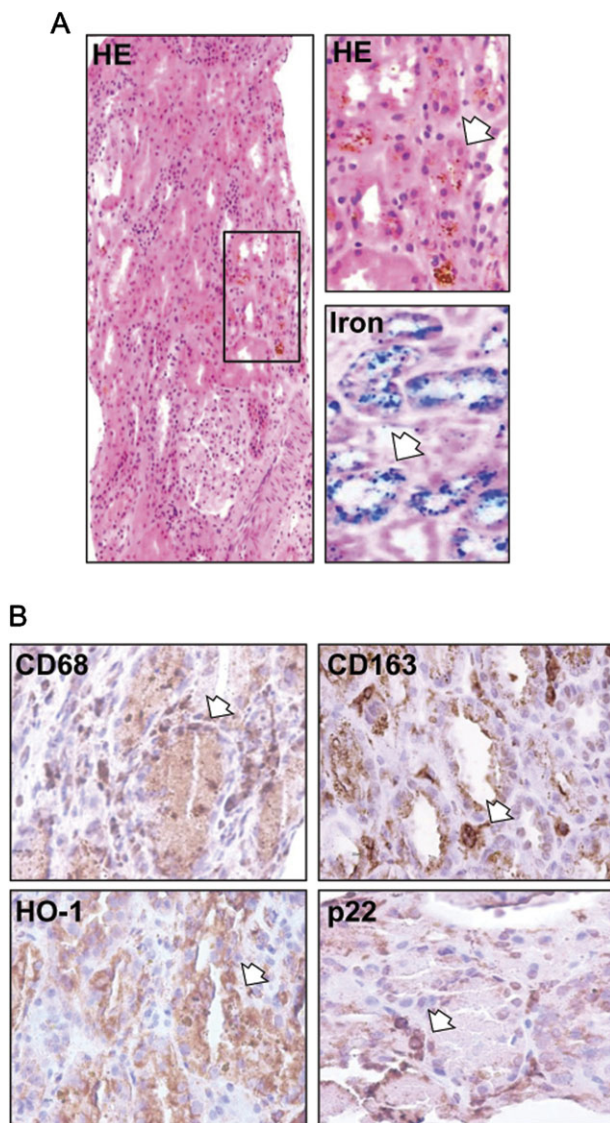


Fig. 2. Haemoglobinuria-associated kidney injury. Renal biopsy from a patient with haemoglobinuria-associated AKI. (A) Light micrographs showing acute haemolysis as determined by the presence of brown deposits in the tubular epithelium [haematoxylin and eosin (HE) stain] and haemosiderin (Iron) deposits in tubular cells (blue, Perl's staining). (B) CD68 (total macrophages) and CD163 (anti-inflammatory macrophages) and oxidative stress [haem oxygenase-1 (HO-1) and NADPH-p22 phox (p22)].

Table 1. Predictors of ESRD in IgAN^a

Author	Year	Type of study	N	Follow-up	Morphological classification	Gender	Age	Scr/GFR	Proteinuria	High BP	Histology	Gross haematuria	Microhaematuria
Espinosa	2009	Retrospective cohort	19 versus 40	1992–2006	<i>Ad hoc</i>	Male ^b	+ ^b	+ ^b	+ ^b	+ ^b	+ ^b	– ^b	+ ^b
D’Amico	2000	Review	30 Studies	–	Lee or Haas	Male ^b	+ ^b	+	+	+	+	– ^b	ND
Haas	1997	Retrospective	244	1980–94	Haas	ND	ND	+ ^b	+ ^b	+ ^b	+ ^b	– ^b	ND
Frimat	1997	Prospective longitudinal	210	5.6 ± 2.6	Lee	Male	ND	+	+	+	+	+ ^b	ND
Beukhof	1986	Retrospective	75	1967–83	–	ND	ND	+	+	+	ND	–	+

^a(+), positive association with ESRD; (–), negative association with ESRD; NS, non-significant; ND, no data/not studied.

^bOnly in univariate analysis.

To our knowledge, the first report of gross haematuria-associated AKI in such patients was a TMBD patient on warfarin who recovered renal function 6 months later [33]. Transient AKI was further documented in an anticoagulated patient with inactive Class III lupus nephritis [34]. A case series of warfarin-treated patients with gross haematuria-associated AKI showed ATN and underlying CKD in all biopsies and excluded acute or active glomerulonephritis as a cause of AKI [4]. Therefore, it was suggested that anticoagulated patients with underlying kidney diseases and abnormal parenchyma were at higher risk of haematuria-associated AKI [4]. Recently, the clinical and morphological findings observed in patients with WRN have been reproduced in an animal model of acute excessive anticoagulation in 5/6-nephrectomized rats but not in controls [35].

Haematuria as a prognostic factor

The prognostic importance of haematuria has been most thoroughly studied in IgA nephropathy. Most but not all studies found a negative association between macroscopic haematuria and long-term renal prognosis (Table 1). However, this negative association frequently disappeared on multivariate analysis [36, 37]. A potential explanation for this observation is that gross haematuria should be most prevalent in histological subclasses with a minimal increase in mesangial cellularity or focal proliferative glomerulonephritis, but it is a rare finding in more advanced processes such as focal segmental glomerulosclerosis-like and advanced chronic glomerulonephritis [38]. In addition, gross haematuria bouts are more frequent during the earlier stages of the disease, whereas they tended to be progressively uncommon in more advanced stages, when renal function deterioration starts. Although the initial report described full recovery of baseline renal function following haematuria-associated AKI in IgA nephropathy [29], a subsequent evaluation of a larger series disclosed that up to 25% of patients may not recover baseline serum creatinine [1]. Duration of haematuria over 15 days was the only significant prognostic factor for incomplete recovery by multivariate analysis. Age >55 years, male sex, higher baseline serum creatinine and absence of previous macroscopic haematuria bouts were also significant risk factors for the persistence of renal insufficiency after macroscopic haematuria disappearance by univariate analysis [1]. Elderly patients appear to be particularly prone to an incomplete recovery of previous renal function after such episodes. Histological severity of ATN was also a significant risk factor for partial recovery of AKI [1, 16].

The relation between microhaematuria and a worse renal outcome has been reported in several studies [39–41]. The largest body of evidence about long-term outcome of persistent isolated microhaematuria is the Israeli nationwide retrospective study [5]. The incidence of asymptomatic isolated (in the absence of proteinuria) persistent microhaematuria in the young Israeli population was 0.3%. The incidence of treated ESRD in the cohort with isolated microhaematuria was 34 per 1 00 000 person-year versus 2 per 1 00 000 person-year in the no-haematuria cohort, rendering an adjusted hazard ratio for treated ESRD of 18.5.

Patients with microhaematuria required ESRD treatment earlier than those without haematuria. This difference was suggested to represent the underlying fundamental kidney diseases in both groups [5]. Of note, 15% of patients with isolated microscopic haematuria and treated ESRD had IgA nephropathy. While this report draws attention to the screening value of dipstick haematuria and the higher incidence of ESRD in microhaematuria may represent long-standing progressive glomerular injury, the potential implication of persistent haematuria in promoting the progression of CKD should be further explored. Nevertheless, it is important to remark that the majority of patients with TBMD show persistent isolated microscopic haematuria throughout their entire life without any repercussion in renal function unless proteinuria develops [30].

Up to 66% of patients with anticoagulant-associated macrohaematuria and AKI did not recover baseline renal function, suggesting that outcome was frequently unfavourable [4]. This was consistent with a subsequent study, in which over-coagulated CKD patients with an associated increase in serum creatinine experienced a more rapid progression towards CKD [3]. Brodsky *et al.* [2] clinically defined those patients having an international normalized ratio (INR; an assessment of prothrombin time to monitor the effects of warfarin) >3 and an increase in sCr ≥ 0.3 mg/dL within 1 week of the high INR, in the absence of haemorrhage, as having WRN. WRN occurred in 33% of CKD and 16% of non-CKD over-coagulated patients. As a group, WRN patients failed to recover baseline serum creatinine by 3 months of follow-up and, most importantly, had a lower survival rate at 1 year than over-coagulated patients without AKI, even after controlling for covariates [2]. Survival at 1 year was lower in CKD than in non-CKD patients with WRN. On the other hand, the dangerous interplay between CKD and anticoagulation has been illustrated by a prospective study where patients with severe CKD (estimated glomerular filtration rate <30 mL/min or on dialysis) had worse anticoagulation control (higher incidence of over-coagulation and undercoagulation), needed lower warfarin dose and had a higher risk of major haemorrhagic events in comparison to moderate and mild CKD, even after adjustment for clinical and genetic factors [42].

Pitfalls and confounding factors

In summary, on one hand, there is accumulating evidence for an adverse influence of glomerular haematuria on renal function: macroscopic haematuria may cause partially reversible AKI and isolated microscopic haematuria is associated with an increased incidence of ESRD [1, 5]. On the other hand, macroscopic haematuria bouts have generally been associated with improved outcomes in univariate analysis in IgA nephropathy. This discrepancy suggests an insufficient understanding of the interaction between causes and consequences of haematuria, the presence of confounding factors or pitfalls in the assessment of haematuria. Indeed, several of these can be envisioned:

a) The relative role of haematuria as a marker of the severity of glomerular injury versus haematuria as a pro-

moter of tubular injury. Haematuria and its intensity may both represent the severity and chronicity of the underlying glomerular injury, but at the same time, promote tubular injury. In this regard, macroscopic haematuria is frequently encountered in severe crescentic or necrotizing glomerular injury, where glomerular injury itself is thought to be the main contributor to decreased renal function. However, in the absence of such dramatic glomerular changes, macroscopic haematuria is more frequently associated with early stages of IgA nephropathy, when glomerulosclerosis is still not present [38]. This association of macroscopic haematuria with early stage IgA nephropathy may confound the study of the prognostic value of macroscopic haematuria since this symptom would be infrequent in patients diagnosed at a more advanced stages of the disease.

b) There are also pitfalls in quantifying haematuria. Firstly, assessment of glomerular haematuria may be interfered with by the presence of non-glomerular haematuria. Microhaematuria is not routinely quantified in the accurate fashion that albuminuria or proteinuria are determined, thus rendering it more difficult to assess in a quantitative way the impact of therapy on haematuria or the impact of haematuria on outcomes. Although haematuria is defined by the presence of >2 RBCs per high power field in a spun urine sediment, some clinicians prefer to define haematuria as RBCs per millilitre by quantitative counting of RBCs in a haemocytometer chamber. Fairley *et al.* popularized the Fuchs–Rosenthal counting chamber which measures RBC counts per unit of uncentrifuged urine volume. This chamber avoids the loss of RBCs that may stick to the tube during centrifugation and loss of RBCs as the supernatant is discarded [43, 44].

Although there is day-to-day variation in albuminuria, this parameter is routinely accurately measured and normalized for time of urine collection or urinary creatinine in order to account for variations in urine concentration [45]. However, haematuria is frequently assessed in semi-quantitative fashion and not normalized for urine concentration. This difference in our ability to quantify the phenomenon has impacted clinical practice. At present, the therapeutic response of all glomerulonephritis (with or without haematuria) is based mostly on proteinuria and serum creatinine. In the absence of hard data on the long-term prognostic impact of haematuria and of haematuria-guided therapy, it is difficult to make recommendation on the specific amount of haematuria that should impact treatment decision making. However, in our view, disappearance of haematuria should also be added to the definition of complete remission in subjects with glomerular disease (such as in lupus nephritis or IgA nephropathy).

Conclusions and unsolved issues

There is increasing evidence for an association between haematuria and adverse renal outcomes, as well as for a biological basis that explains the association, implying haemotoxicity in tubular cell injury through oxidative stress. Prospective studies should explore how to more accurately monitor haematuria, whether monitoring of haematuria and tweaking therapy according to these results will improve

kidney outcomes and whether specific interventions to decrease haematuria or protect from its adverse effects improve renal function outcomes in haematuria-induced AKI or CKD.

Acknowledgements. Funding. FIS (Programa Miguel Servet) to J.A.M. ISCIII and FEDER funds CP04/00060, PS09/00447, Sociedad Española de Nefrología, ISCIII-RETIC REDinREN/RD06/0016, Comunidad de Madrid/FACM/S-BIO0283/2006, Programa Intensificación Actividad Investigadora (ISCIII) to A.O., FIS 10/02668, FIS 10/02581 and AITER (Asociación para el Estudio y Tratamiento de las Enfermedades Renales) to E.G. and M.P. and ISCIII-Redes RECAVA (RD06/0014/0035), EUS 2008/03565, ISCIII PI10/00072 and Fundación Lilly to J.E.

Conflict of interest statement. None declared.

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Received for publication: 5.10.11; Accepted in revised form: 23.11.11