



EDITORIAL COMMENT

Sickle cell disease and albuminuria: recent advances in our understanding of sickle cell nephropathy

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Abstract

Albuminuria is considered to be a relevant biomarker for the detection of early glomerular damage in patients with sickle cell disease (SCD). Improvements in our understanding of the pathophysiological processes and molecular mechanisms underlying albuminuria are required, because increasing numbers of patients with SCD are developing chronic kidney disease. The early recognition of sickle cell nephropathy (SCN) and studies of the natural course of this emerging renal disease are therefore crucial, together with identification of the associated clinical and biological risk factors, to make it possible to initiate kidney-protective therapy at early stages of renal impairment. The pathophysiological process underlying SCN remains hypothetical, but chronic haemolysis-related endothelial dysfunction and the relative renal hypoxia triggered by repeated vaso-occlusive crises have been identified as two potential key factors. The optimal preventive and curative management of albuminuria in the context of SCD is yet to be established, but recent studies have suggested that hydroxyurea therapy, the cornerstone of SCD treatment, could play a key role in reducing albuminuria. The place of conventional kidney-protecting measures, such as renin-angiotensin system inhibitors, in the treatment of SCD patients also remains to be determined.

Key words: albuminuria; chronic renal failure; endothelial dysfunction; ischemia reperfusion injury; sickle cell disease

Sickle cell nephropathy: a global emerging renal disease

Sickle cell disease (SCD), the most common haematological hereditary disorder, is caused by a single-base pair substitution in the β -globin gene resulting in the production of an abnormal

haemoglobin molecule (haemoglobin S) that polymerizes under deoxygenation conditions, disrupting the normal architecture of erythrocytes, thereby impairing oxygen supply to some tissues [1]. The major clinical features of SCD are acute vaso-occlusive manifestations and chronic haemolytic anaemia, leading to acute and/or chronic tissue damage and organ

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dysfunction [1]. Improvements in care over the last 20 years have resulted in a longer lifespan for SCD patients. This increase in life expectancy has resulted in a higher frequency of long-term complications, such as chronic organ damage, which may affect the liver, heart, lungs and kidneys. The prevalence of chronic kidney disease (CKD) has significantly increased and renal involvement constitutes a major independent risk factor for death in these patients [2, 3]. In a retrospective study, patient survival was shorter and the likelihood of receiving a kidney graft was lower for SCD patients on dialysis than for patients without SCD [4]. The spectrum of renal manifestations occurring in SCD patients includes an impairment of urinary concentrating ability, defects of urine acidification, renal papillary necrosis and acute kidney injury (AKI) [5, 6]. Glomerular involvement, one of the most prominent renal manifestations observed in SCD patients, is characterized by an early increase in glomerular filtration rate (GFR) associated with micro- or macroalbuminuria, followed by a gradual decline of GFR and chronic renal failure [5, 6]. In this issue of the *Clinical Kidney Journal*, Aloni et al. report the prevalence and determinants of microalbuminuria in children with SCD living in the Democratic Republic of Congo. In this cross-sectional study, microalbuminuria, defined on the basis of urine albumin/creatinine ratio (ACR), was detected in 18.5% of 150 children with homozygous SCD, in whom it ranged from 30 to 299 mg/g [7]. Information about sickle cell nephropathy (SCN) in Sub-Saharan Africa is scarce, but Ranque et al. carried out a prospective multicentre study in which they evaluated the prevalence of early kidney damage in 2582 patients with SCD [8]. They reported a high urinary ACR in 144 of 527 children (27%) under the age of 10 years tested. Many studies have assessed the prevalence of proteinuria in children and adults with SCD. Microalbuminuria, with or without hyperfiltration, is currently the earliest renal symptom reflecting probable glomerular injury detectable in adults and children with SCD [9]. The prevalence of albuminuria in SCD patients increases with age, from 4.5% to 26% in patients under the age of 21 years, to between 26% and 68% in older patients [9]. In a cross-sectional study of 410 patients aged between 2 and 21 years, abnormal albuminuria was found in 20.7% of patients, and the level of albuminuria was closely correlated with age [10]. Guasch et al. found that 68% of 300 SCD adult patients had high rates of urinary albumin excretion, with 26% of these patients displaying macroalbuminuria (defined as urine albumin excretion rate >300 mg/g creatinine) [11]. In the cohort of 424 adult British patients of African origin studied by Day et al., microalbuminuria was detected in 28% of the patients aged 16–25 years, 38% of the patients aged 26–35 years and 50% of those aged 36–45 years [12]. Aloni et al. showed, by bivariate analysis, that age was the main determinant of microalbuminuria in children with SCD [7]. These findings suggest that SCN is a progressive condition that begins during childhood, although the long-term outcome and the natural course of kidney disease in SCD patients with albuminuria remain largely unknown. In the absence of treatment, albuminuria probably increases over time, as reported in other proteinuric kidney diseases. In a retrospective study of 38 patients with albuminuria aged up to 21 years, 10.5% of those included were found to have progressive renal disease after approximately 20 months of follow-up [13]. A more recent study demonstrated that, after a mean follow-up of 5 years, the frequency of CKD had increased to 41.8%, and multivariate analysis identified baseline albuminuria levels and each 1-mmHg increase in systolic blood pressure as key risk factors for subsequent CKD development [14]. The close relationship between the decline in GFR and the increase

in albuminuria was recently confirmed in the Jamaica Sickle Cell Cohort Study, which assessed longitudinal changes in GFR over time in individuals with homozygous SCD [15]. In a retrospective study, nephrotic syndrome, which affected 4% of SCD patients, was found to be associated with poor renal survival [16]. A broad spectrum of glomerular diseases has been described in SCD patients, with significant proteinuria and isolated glomerular enlargement and focal segmental glomerulosclerosis (FSGS) reported to be the most frequent glomerular lesions identified on renal biopsy specimens [9]. We have previously shown that, regardless of the underlying glomerular lesions associated with SCD, a progressive deterioration of renal function is frequently observed in SCD patients with biopsy-proven glomerular involvement [17].

Pathogenesis of albuminuria in SCD patients: one or many pathophysiological processes?

Despite significant advances in our understanding of the spectrum of renal manifestations associated with SCN development over the last 20 years, many questions remain unresolved. For example, the pathophysiological processes underlying the occurrence of albuminuria remain incompletely understood. As demonstrated by Aloni et al., the prevalence of abnormal albuminuria increases with patient age. Prolonged hyperfiltration is probably another contributing factor associated with the occurrence of albuminuria. Aloni et al. showed, with the Schwartz equation, that 22% of patients with microalbuminuria had glomerular hyperfiltration [7]. Hyperfiltration is a common finding in children with SCD [18]. It is also frequently observed in adult patients, but the optimal method for determining GFR in this population remains to be established. Hayman et al., in their study of 280 adult patients with homozygous SCD, showed that the prevalence of hyperfiltration (defined as $eGFR > 130 \text{ mL/min/1.73 m}^2$ for women and $> 140 \text{ mL/min/1.73 m}^2$ for men), as assessed by the Modification of Diet in Renal Disease equation for estimating GFR, was 51% (36% and 15% of the patients with hyperfiltration had associated microalbuminuria or macroalbuminuria, respectively) [19]. Another study, in Caribbean patients and European patients of African descent, demonstrated that the CKD-EPI equation without adjustment for ethnicity was the best method for estimating GFR in adult SCD patients [20]. Nevertheless, it should be borne in mind that whatever the formula used to estimate GFR, accuracy remains low for high values of GFR. This is particularly true for sickle cell patients, who may have high tubule creatinine secretion levels [19]. It is tempting to speculate that glomerular hyperfiltration is a key factor in subsequent FSGS occurrence and an important determinant of CKD progression in SCD patients, but prospective studies are required to demonstrate the validity of this relationship. Some clinical studies on adults and children with SCD have reported strong associations between biological markers of haemolysis and high levels of albuminuria, suggesting that chronic haemolysis-related endothelial dysfunction is probably a crucial risk factor associated with glomerular injury [5, 12, 21, 22]. Consistent with this hypothesis, Ataga et al. found a close positive relationship between urinary albumin excretion and serum concentrations of soluble fms-like tyrosine kinase 1 (sFLT-1), a member of the vascular endothelial growth factor receptor family [23]. Another study confirmed the hypothesis that albuminuria is associated with endothelial dysfunction, by measuring endothelium-dependent dilation of the brachial artery [24]. Assessments of endothelial dysfunction based on the

measurement of carotid-femoral pulse wave velocity (cf-PWV) showed that microalbuminuria was closely related to this parameter [25]. Moreover, haemoglobinuria has recently been shown to be associated with CKD progression, suggesting that the decline of renal function is closely related to intensity of haemolysis [26]. Higher haemolysis rates may also promote higher levels of iron deposition in tissues. In some SCD patients, magnetic resonance imaging (MRI) may reveal iron accumulation in the kidney parenchyma [27, 28]. This finding is generally consistent with renal biopsy data, with abundant haemosiderin deposits in proximal tubule epithelial cells frequently observed in association with glomerular injury in SCD patients [17]. One important issue is whether iron deposits in the renal cortex are exclusively a marker of chronic haemolysis, or whether they may also promote direct kidney injury. We recently reported the case of a 32-year-old man with iron overload in the renal cortex [29]. A second MRI scan 16 months after the initiation of hydroxyurea (HU) treatment showed a normalization of the cortical signal on T2* gradient images, concomitant with a significant decrease in albuminuria. The disappearance of iron deposits on MRI may be a direct marker of the decrease in haemolysis on HU treatment, but these findings suggest that HU may modulate albuminuria by decreasing iron deposition in tubule cells. As demonstrated in experimental mouse models of SCD, relative renal hypoxia triggered by repeated vaso-occlusive crises (VOCs) might be one of the factors underlying the progressive renal impairment and proteinuria observed in SCD patients [5]. This hypothesis was tested in a previous study which showed that AKI was rare during sickle cell crises but was closely related to the severity of VOC [30]. Nevertheless, subclinical tubular injury may occur during VOCs, as revealed by the significant increase in urinary neutrophil gelatinase-associated lipocalin (NGAL) (a relevant biomarker of tubule injury) during VOC relative to steady state [31]. In this study, ACR levels were similar during VOC and in steady state, suggesting that ischaemia-reperfusion injury during VOCs does not directly affect glomerular permeability. We recently performed a prospective single-centre pilot study to investigate the potential value of blood oxygen level-dependent (BOLD), diffusion-weighted (DW) and intravoxel incoherent motion (IVIM) MRI techniques for the assessment of kidney oxygenation and the detection of potential changes to tissue perfusion and cellular integrity during VOCs [32]. We compared SCD patients at steady state (with normal renal function and without macroalbuminuria) with healthy subjects and the same patients during VOCs. MRI findings suggested that the renal parenchyma of SCD patients was in a state of hypoxia relative to that in healthy subjects, and revealed significant changes in kidney perfusion during VOC. Further clinical studies are required to demonstrate the relevance of this relative renal hypoxia state and of the changes to the microcirculation triggered by repeated VOC, which may lead to a chronic inflammatory state in the renal parenchyma, resulting in progressive tubulointerstitial and glomerular damage.

Current therapies to reduce albuminuria in SCD patients

The therapeutic management of SCD patients with albuminuria remains challenging, and the optimal approach is yet to be established, but is of crucial importance for preventing CKD progression [6]. Renin-angiotensin system inhibitors and/or HU, the standard of care for preventing VOC in SCD patients, should

probably be considered to prevent kidney disease progression in this population. In 10 patients, the administration of enalapril for 2 weeks was found to be associated with a 57% decrease in proteinuria, which was followed by a rebound after treatment withdrawal [33]. In a randomized trial carried out in 22 patients, Foucan *et al.* confirmed that usual renal protective measures can reduce proteinuria in SCD patients [34]. The long-term effects and tolerance of angiotensin-converting enzyme inhibitors in SCD patients remain unknown, although current recommendations include the use of renin-angiotensin system inhibitors in SCD patients with macroalbuminuria >100 mg/mmol [6]. HU is one of the cornerstone treatments for the management of SCD patients and its efficacy is generally attributed to its ability to boost the levels of foetal haemoglobin. HU is known to decrease the frequency of acute pain episodes and acute chest syndrome, the need for red blood cell transfusions and the number of hospitalizations [35, 36]. Aloni *et al.* judiciously excluded SCD patients on HU treatment from their study, to ensure the correct interpretation of albuminuria [7]. There is, therefore, compelling evidence to suggest that HU administration can modify renal parameters in SCD patients. Aygun *et al.* showed that HU treatment over a period of 3 years in children can decrease glomerular hyperfiltration without significantly affecting albuminuria [37]. Laurin *et al.* suggested that HU therapy in adult SCD patients was associated with a lower prevalence of albuminuria [38]. A recent pilot study suggested that the newly introduced HU therapy, administered for 6 consecutive months, significantly decreased urinary ACR without the need for concomitant treatment with renin-angiotensin system inhibitors [39]. In total, ACR decreased in the study population, but this decrease was driven primarily by the decrease in ACR in the subgroup of patients with microalbuminuria. Statistical analyses revealed a close relationship between improvements in markers of haemolysis, such as the percentage of dense red blood cells, and ACR decline. HU may have pleiotropic actions, improving both the properties and rheology of red blood cells, thereby attenuating deleterious effects on the renal vascular endothelium.

Conclusion

Our understanding of SCN and the occurrence of proteinuria in SCD patients has increased greatly over the last decade. However, the assessment of other robust biomarkers before the onset of microalbuminuria and/or GFR deterioration is desirable, to help clinicians to detect SCD patients at risk of renal damage early and to identify patients with a subsequent risk of renal disease progression. Preliminary results concerning the potential effects of HU and/or renin-angiotensin system inhibitors require confirmation in additional prospective, randomized controlled trials, to determine the appropriate contribution of these treatments to the optimal management of SCN.

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