Hyperfiltration is Associated with the Development of Microalbuminuria in Patients with Sickle Cell Anemia

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To the editor:

We hypothesized that glomerular hyperfiltration, observed in about half of adults with sickle cell anemia (SCA) (1), may contribute to the initial stages of glomerular injury, similar to diabetic (2) and hypertensive nephropathy (3). We estimated the glomerular filtration rate (eGFR) in 356 adult patients with SCA (Hb SS: n=346, Hb $S\beta^0$ n=10) receiving routine medical care at the University of Illinois at Chicago between 2008 and 2014 using the Chronic Kidney Disease Epidemiology Collaboration formula: eGFR in mL/min/1.73 m^2=175×(serum creatinine)$^{-1.154}$×(age)$^{-0.203}$×(0.742 if female)×(1.212 if African American). Hyperfiltration was defined as eGFR ≥130 mL/min/1.73 m^2 for females and ≥140 mL/min/1.73 m^2 for males, similar to previous reports in SCA (1). The prevalence of hyperfiltration decreased with age (Figure 1A) and, in 196 patients with urine albumin measured, the prevalence of albuminuria (>30mg/g creatinine) increased with age (Figure 1B), as previously shown in other studies.

Eighty-eight SCA patients did not have chronic kidney disease (CKD) at baseline evaluation as evidenced by eGFR >60 mL/min/1.73 m^2 and urine albumin <30 mg/g creatinine. To investigate the relationship of hyperfiltration to the development of albuminuria, we focused on 45 of these patients who had subsequent urine albumin measurements over 68 months. Urine albumin concentrations were measured by random, spot urine collections during a clinic visit and development of urine albumin ≥30mg/g creatinine was confirmed by two consecutive determinations. Forty-three patients had Hb SS and two had Hb $S\beta^0$thalassemia. The median age was 27 years with a range of 18–59 years. Twenty-nine were female and 24 were on hydroxyurea (HU) therapy. Thirty

patients had hyperfiltration, and this likely represents persistence of hyperfiltration into adulthood since most children have hyperfiltration. The median length of follow up was 26 months (range 6–68) with a median number of three urine albumin assessments (range 2–8). Thirteen patients developed microalbuminuria (urine albumin 30–299 mg/g creatinine) with a median time to development of 21 months (range 11–57). No patient developed macroalbuminuria (urine albumin ≥300mg/g creatinine). Rates of developing microalbuminuria were not different based on HU status or body-mass index (BMI) at baseline. The eGFR remained >90 mL/min/1.73 m^2 in all subjects. Consistent with the role of hyperfiltration contributing to the early stages of CKD, we observed higher rates for developing microalbuminuria in patients with higher filtration categories (3 of 15 in patients without hyperfiltration, 6 of 23 with hyperfiltration but eGFR <160mL/min/1.73 m^2, 4 of 7 with eGFR >160mL/min/1.73 m^2). Using Cox proportional hazard modeling, the unadjusted HR was 2.4 (95% CI: 1.1–5.3, *P*=0.036) while the age-adjusted HR was 2.7 (95% CI: 1.1–5.8, *P*=0.032) and the age and HU-adjusted HR was 2.6 (95% CI: 1.1–6.4, *P*=0.031) (Figure 1C).

Nephrin, a major component of the slit diaphragm that maintains normal podocyte foot process architecture, is a sensitive urinary biomarker for glomerular injury and is detected before albuminuria develops in animal models (4). Kidney injury molecule-1 (KIM-1) is a transmembrane proximal tubular protein with increased expression after tubular injury (5). We used ELISA to measure urine concentrations of nephrin (Exocell, Philadelphia, PA, USA) and KIM-1 (R&D Systems, Minneapolis, MD, USA) in 32 adult SCA patients, six from the follow-up cohort just described and 26 additional consecutive

outpatients with eGFR >60mL/min/1.73 m^2, between March and May 2013. Urine nephrin concentration correlated significantly with eGFR (r=0.36, *P*=0.044) but urine KIM-1 concentration did not (r=0.11, *P*=0.6). Urine nephrin concentration also correlated strikingly with urine albumin concentration (r=0.92, *P*<0.0001) (Figure 1D). Our findings are consistent with the possibility that a high eGFR causes damage to the glomerulus reflected by its correlation with a urine biomarker of glomerular injury but not with a urine biomarker of tubular injury and by the increased risk for developing microalbuminuria in SCA patients with hyperfiltration.

Limitations to this study include that we did not directly measure the GFR, although the CKD-EPI based eGFR is reported to have good correlation with measured GFR in patients with SCA (6). Another potential limitation is that nephrin is expressed in the pancreas and may be circulating in the plasma and filtered through the glomerulus with albumin which will need to be evaluated in future studies. Furthermore, our study may have been underpowered to detect associations between hydroxyurea therapy or BMI and the development of microalbuminuria.

In conclusion, a higher degree of persistent hyperfiltration in adults may be an important risk factor for the development of CKD in addition to other factors such as joint polymorphisms in *MYH9* and *APOL1*. Future research is needed to understand mechanisms of how hyperfiltration may damage the glomerulus and to identify interventions to protect the kidney in this context.

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Conflict-of-interest disclosure

The authors declare no competing financial interests.

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Figure Legends:

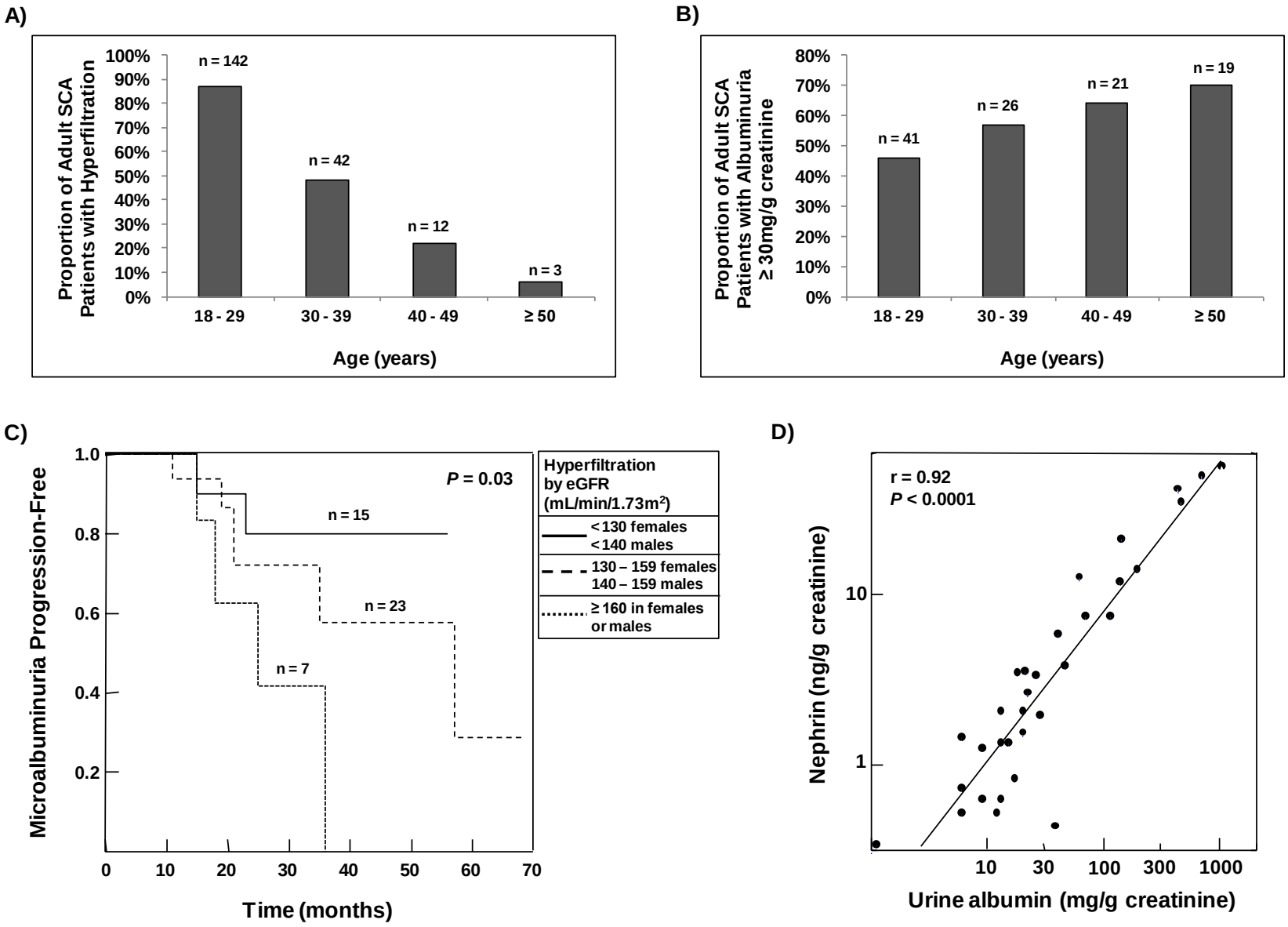
Figure 1A: Prevalence of hyperfiltration by age. The persistence of hyperfiltration (defined as an eGFR ≥ 130 mL/min/1.73m^2 in women and ≥ 140 mL/min/1.73m^2 in men) decreases with increasing age in 356 adult patients with sickle cell anemia (SCA).

Figure 1B: Increasing prevalence of albuminuria ≥ 30mg/g creatinine by age in 196 patients with SCA.

Figure 1C: Increasing hyperfiltration category is associated with a higher risk for progressing to microalbuminuria. Hyperfiltration was associated with an incremental risk for progressing to microalbuminuria in follow up of 45 SCA patients without CKD (age-adjusted HR 2.5, 95% CI: 1.1–6.0).

Figure 1D: Relationship of urine nephrin and urine albumin concentrations in 32 consecutive adult SCA patients with an eGFR > 60 mL/min/1.73m^2.

Figure 1


A)
Proportion of Adult SCA Patients with Hyperfiltration
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
n = 142
n = 42
n = 12
n = 3
18 - 29
30 - 39
40 - 49
≥ 50
Age (years)
B)
Proportion of Adult SCA Patients with Albuminuria ≥ 30mg/g creatinine
80%
70%
60%
50%
40%
30%
20%
10%
0%
n = 41
n = 26
n = 21
n = 19
18 - 29
30 - 39
40 - 49
≥ 50
Age (years)
C)
Microalbuminuria Progression-Free
1.0
0.8
0.6
0.4
0.2
P = 0.03
n = 15
n = 23
n = 7
0
10
20
30
40
50
60
70
Time (months)
Hyperfiltration by eGFR (mL/min/1.73m²)
< 130 females
< 140 males
130 – 159 females
140 – 159 males
≥ 160 in females
or males
D)
r = 0.92
P < 0.0001
Nephrin (ng/g creatinine)
10
1
10
30
100
300
1000
Urine albumin (mg/g creatinine)