Arterial Stiffness and Peripheral and Central Blood Pressure in Patients With Sickle Cell Disease

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Blood pressure (BP) in patients with sickle cell disease (SCD) has been reported to be lower than in persons in the general population. Data on arterial stiffness, which is an important risk factor for the progression of BP, are inconclusive for this patient population. Forty-five adult patients with SCD and 40 controls matched for sex, age, and body mass index were studied. Brachial systolic BP (SBP) and diastolic BP (DBP) were significantly lower in the patient group (SBP 115.1±13.8 mm Hg vs 121.9±11.3 mm Hg and DBP 68.5±8.0 mm Hg vs 80.6±9.1 mm Hg, $P<.05$, respectively). Augmentation index (AIx), however, was significantly higher in SCD patients compared with healthy controls (24.9±9.6 for patients vs 12.4±10.8 for controls, $P<.001$), while carotid femoral pulse wave velocity was comparable between the two groups. The study shows that mechanisms other than arterial elasticity are involved in the low BP phenotype of patients with SCD. *J Clin Hypertens (Greenwich).* 2015;17:726–731. © 2015 Wiley Periodicals, Inc.

Sickle cell disease (SCD) is an autosomal recessive inherited blood disorder that arises from the point mutation of the β-globin gene resulting in the substitution of valine with glutamine at the sixth position of the beta chain, which leads to the expression of hemoglobin S (HbSS). The high frequency of the sickle cell hemoglobin (*HbS*) gene in malaria-endemic regions is caused by a heterozygote advantage against fatal malaria.[1] The actual anemia of the disease is caused by hemolysis and the destruction of red blood cells because of their shape. Persistent intravascular hemolysis over decades leads to chronic vasculopathy.[2] Many HbSS patients develop pulmonary hypertension. Nonetheless, patients with SCD have lower systemic blood pressure (BP) than those without the disease.[3–5]

The physiologic background of this observation is still unknown, while some proposed mechanisms include sodium and water wasting as a result of medullary defect, systemic vasodilation compensating for microcirculatory flow disturbances, increased production of prostaglandins and nitric oxide (NO), and reduced vascular reactivity.[6–9]

One of the main components of the BP phenotype is arterial stiffness. Whether it precedes BP rise or comes after long-time exposure to high BP is not known.[10,11] Arterial stiffness is associated with high BP, but more often with high pulse pressure (PP), which is affected by aortic stiffness and the balance between aortic flow and lumen diameter in the proximal aorta as well as by wave reflection.[11] To what extent the BP pattern in SCD is caused by alterations in arterial elasticity is largely unknown.

The aim of the present study is to report BP levels in patients with SCD and healthy matched controls and to investigate the effect of arterial stiffness and renal function on BP levels in this patient population. We also sought to investigate whether aortic pressures follow the pattern of peripheral BP.

PATIENTS AND METHODS

A total of 45 adult patients with SS-type SCD aged between 26 and 65 years (mean age, 43 years) followed in our center between October 2012 to March 2013 and in a steady state of disease for at least 6 months (no acute illness and no vaso-occlusive or acute chest syndrome episode) were enrolled in the study. Patients with S-β-thalassemia genotype, diabetes mellitus or other endocrine disease, arterial hypertension, and glomerular filtration rate (GFR) <59 mL/min/1.73 m^2 were excluded. Forty healthy individuals matched for sex, age, and body mass index (BMI) were also recruited as controls.

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the institutional review board of Aristotle University of Thessaloniki. All participants gave their written informed consent.

Clinical data were collected using a standardized form that included sociodemographic characteristics, medical history, and current medication.

Study Protocol

All clinical and biochemical measurements were performed from 7:30 AM to 11:30 AM after an overnight fast. The waist circumference was measured in the standing position at the level of the umbilicus, and the

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Manuscript received: January 18, 2015; **revised:** March 9, 2015; **accepted:** March 19, 2015
DOI: 10.1111/jch.12572

waist-to-hip ratio was calculated by dividing waist circumference by hip circumference.

Fasting parameters, including levels of fasting plasma glucose, fasting insulin, triglycerides (TGs), low-density lipoprotein (LDL), high-density lipoprotein, and total cholesterol, and basic biochemistry parameters were measured in each patient using standardized procedures.

25 OH D_3, ferritin, cortisol, parathyroid hormone (PTH), thyroid-stimulating hormone (TSH), osteocalcin calcium, and phosphate were also measured.

Homeostatic model assessment for insulin resistance (HOMA-IR) and β-cell function (HOMA-β) were calculated according to known formulas.

Oral Glucose Tolerance Test. A 75-g oral glucose tolerance test was performed with plasma glucose and insulin sampling performed at 0, 30, 60, 90, and 120 minutes.

Pulse Wave Velocity. Aortic (carotid-to-femoral [cf]) pulse wave velocity (PWV) was calculated from measurements of common carotid and femoral artery waveforms using an automatic applanation tonometry-based device, the SphygmoCor Vx system (AtCor, Itasca, IL), as described. Briefly, electrocardiogram-gated pulse waveforms were obtained sequentially over the common carotid and femoral arteries. PWV was calculated as the distance between recording sites measured over the surface of the body, divided by the time interval between the feet of the pressure waves. All of the measurements were performed by the same observer, who was blinded to the patient's clinical data. Central artery waveforms derived from the radial artery waveform and pressure by using a transfer function validated previously during catheterization studies.[12] The point at which the central aortic pressure becomes augmented by wave reflection is recognized by a computer program, and the degree of increase is expressed as the aortic augmentation, which is quantified either in absolute term or as a percentage of aortic pulse pressure (aortic augmentation index [AIx]).

Glomerular Filtration Rate. We calculated eGFR according to the four-variable Modification of Diet in Renal Disease (MDRD) equation and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[13]

BP Measurements. BP measurements were performed in the morning with the patients in the seated position following a 5-minute quiet resting period. BP was measured in both arms with a mercury sphygmomanometer using an appropriately sized cuff. Values for systolic BP (SBP) and diastolic BP (DBP) were defined by Korotkoff phase I and V, respectively. The average of the second and third measurements on both the right and left arms was used in the analysis.

Statistical Analysis

Normality of distribution was tested by Kolmogorov-Smirnov test. Parametric data were expressed as mean±standard deviation and nonparametric as median (range).

Independent samples *t* test or Mann-Whitney test was performed to evaluate differences in measured parameters between the patient population and the control group. We tested differences in our measurements of interest between the patient population and the control group using when variables were parametric and Mann-Whitney test if otherwise.

Pearson's correlation coefficient *r* was used to test the relation of AIx, PWV, HOMA-IR, and Belfiore with the under-study parameters, while Spearman test was used to find correlations with the HOMA-β index.

To test which parameters affect arterial stiffness and central BP in our patient population, we used forward stepwise-regression analysis and created models using AIx, PWV, central SBP, and central DBP as dependent variables. The existence of SCD was marked as 0 for controls and 1 for patients with SCD.

We tested for the magnitude of multicollinearity in our models using the variance inflation factor (VIF). A VIF >2 for a variable was considered high.

$P<.05$ was considered statistically significant. The analysis was performed using Predictive Analytics Software (PASW version 18.0; Chicago, IL).

RESULTS

BP, Arterial Stiffness, and GFR in the Two Groups

Patients were matched with controls in regards to age (43.3±9.8 years and 39.8±11.5 years, $P>.05$), BMI (24.1±3.6 kg/m^2 and 24.4±3.2 kg/m^2, $P>.05$), and sex (15/30 and 17/23 for female/male, respectively; $P>.05$).

Brachial SBP and DBP were significantly lower in the patient group compared with the control group (SBP 115.1±13.8 mm Hg vs 121.9±11.3 mm Hg and DBP 68.5±8.0 mm Hg vs 80.6±9.1 mm Hg, $P<.05$, respectively). Brachial mean arterial pressure (MAP) was also significantly lower in the SCD group (Table IB, Figure 1 and Figure 2). Similar results were observed for central DBP (70.0±8.3 mm Hg vs 79.8±9.4 mm Hg, $P<.001$, for patients and controls, respectively). Central MAP was also lower in the patient group (Figure 3).

On the contrary, brachial and central PP were higher in the patient group compared with normal controls (46.9±10.2 mm Hg vs 41.0±9.9 mm Hg and 35.4±15.5 mm Hg vs 28.5±6.1 mm Hg, respectively). Heart rate did not differ between the two groups (Table IB).

AIx, however, was significantly higher in SCD patients compared with controls (24.9%±9.6% for patients vs 12.4%±10.8% for controls, $P<.001$), while PWV was comparable between the two groups (Table IB). PWV difference between groups remained not significant even after brachial DBP adjustment taking into consideration possible different distending pressures that may affect stiffness measurements (Figure 4). In terms of renal function, eGFR was significantly higher in patients with

TABLE I. Biochemistry and Blood Parameters (A); Blood Pressure, Arterial Stiffness, and Glomerular Filtration Rate (B); Bone Homeostasis and Hormones (C); and Glucose Homeostasis (D)

Variable	SCD	Controls	*P* Value
(A)			
Cholesterol total	146.1±42.6	197.5±36.7	<.001
Triglycerides	113.6±57.6	82.0±38.0	.006
LDL	82.8±35.1	131.8±32.1	<.001
HDL	39.1±10.5	50.0±13.4	<.001
Ferritin	170.3 (1439.9)	30.7 (175.8)	<.001
Ferrum	95.2±36.3	94±44.4	NS
Creatinine	0.60±0.15	0.75±0.14	<.001
Urea	22±8.2	26.6±8.4	.02
Sodium	139.5±3.7	136.0±1.4	<.001
Potassium	4.4±0.4	4.1±0.4	<.001
Hemoglobin, g/dL	10.8±1.1	13.1±1.4	<.001
Hematocrit, %	29.7±3.5	38.5±3.2	<.001
MCV, fL	72.9±6.9	85.2±3.5	<.001
MCHC, g/dL	36.5±1.2	34.4±1.1	<.001
(B)			
Branchial SBP	115.1±13.8	121.9±11.3	.02
Branchial DBP	68.5±8.0	80.6±9.1	<.001
Branchial MAP	91.8±10.1	101.3±9.0	<.001
Branchial PP	46.9±10.2	41.0±9.9	.025
Heart rate	76.4±10.5	73.8±10.7	NS
Central SBP	105.4±17.7	108.4±10.0	NS
Central DBP	70.0±8.3	79.8±9.4	<.001
Central MAP	87.7±11.5	94.1±9.2	.009
Central PP	35.4±15.5	28.5±6.1	.01
AIx	24.9±9.6	12.4±10.8	<.001
PWV, m/s	7.2±1.4	7.1±0.8	NS
MDRD, mL/min/1.73 m^2	138.0±37.3	110.6±20.0	<.001
(C)			
25 (OH) D3	13.1±8.4	32.4±14.2	<.001
PTH	32.7±20.4	31.0±14.9	NS
Calcium	9.0±0.6	9.0±0.4	NS
Phosphate	3.5±0.5	3.6±0.6	NS
Osteocalcin	14.1±5.7	3.6±0.6	<.001
TSH	2.1±1.4	1.7±0.7	NS
Cortisol	316±145.5	379.9±244.2	NS
(D)			
Fasting glucose, mg/dL	81.4±12.5	78.9±7.9	NS
Fasting insulin, μU/mL	5.1±2.7	11.3±6.6	<.001
HOMA-IR, %	18.6±10.2	41.8±25.7	<.001
QUICKI	0.38 (0.5)	0.35 (0.11)	<.001
HOMA-β, %	101.1 (1983.6)	274.1 (4351.1)	<.001

Abbreviations: AIx, augmentation index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA-β, homeostatic model assessment for β-cell function; HOMA-IR, homeostatic model assessment for insulin resistance; MAP, mean arterial pressure; LDL, low-density lipoprotein; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MDRD, Modification of Diet in Renal Disease; PP, pulse pressure; PTH, parathyroid hormone; PWV, pulse wave velocity; SBP, systolic blood pressure; SCD, TSH, thyroid-stimulating hormone; QUICKI, All blood pressures are measured in mm Hg.

SCD compared with controls (138.0±37.3 mL/min/1.73 m^2 vs 110.6±20.0 mL/min/1.73 m^2 for patients and controls, respectively).

Table IC and ID show bone homeostasis hormones and glucose homeostasis parameters, respectively, for the two groups.

Simple Correlations of the Under-Study Parameters in the SCD Group

Table II shows simple correlations of the under-study parameters.

AIx significantly and positively correlated with aortic SBP, aortic PP, and age. PWV significantly and positively correlated with all aortic and brachial BP measurements, but also with age, waist circumference, total cholesterol, TGs, and LDL.

Regression Analyses

Stepwise forward linear regression analyses were used to identify determinants of arterial stiffness, eGFR, and central BP.

cf-PWV was significantly determined by age (β=0.063, *P*=.001; R^2=0.35, *P*=.001) (adjustments for aortic SBP, HOMA-IR, eGFR, heart rate, BMI, waist, total cholesterol, TGs, 25 OH D_3, ferritin, cortisol, PTH, TSH, calcium, phosphate, and SCD).

AIx was significantly determined by the existence of SCD (β=9.8, *P*=.02), age (β=0.72, *P*=.003), and waist (β=−0.4, *P*=.04; R^2=0.51, *P*=.001) (adjustments for aortic SBP, HOMA-IR, estimated glomerular filtration rate (eGFR), heart rate, BMI, total cholesterol, TGs, 25 OH D_3, ferritin, cortisol, PTH, TSH, calcium, and phosphate).

eGFR was determined by ferritin (β=0.045, *P*=.006) and was negatively associated with central DBP (β=−0.96, *P*=.04) and age (β=−0.8, *P*=.049; R^2=0.42, *P*<.001) (adjustments for sex, aortic SBP, PWV, BMI, total cholesterol, TGs, 25 OH D_3, calcium, HOMA-IR, and SCD).

Age was the sole most significant determinant of central SBP (β=0.63, *P*<.001; R^2=0.38, *P*<.001) (adjustments for aortic DBP, HOMA-IR, eGFR, heart rate, BMI, total cholesterol, TGs, 25 OH D_3, ferritin, cortisol, PTH, TSH, calcium, phosphate, and SCD).

Central DBP was determined by waist circumference (β=0.03, *P*=.017) and central PP (β=0.045, *P*=.03; R^2=0.34, *P*=.001) (adjustments for aortic SBP, HOMA-IR, eGFR, heart rate, BMI, total cholesterol, TGs, 25 OH D_3, ferritin, cortisol, PTH, TSH, calcium, phosphate, and SCD).

DISCUSSION

The main finding of the present study was that despite their lower peripheral and central BP levels, patients with SCD had higher peripheral and central PP levels than age- and sex-matched controls.

In addition, SCD along with age and waist circumference significantly determined AIx in the study

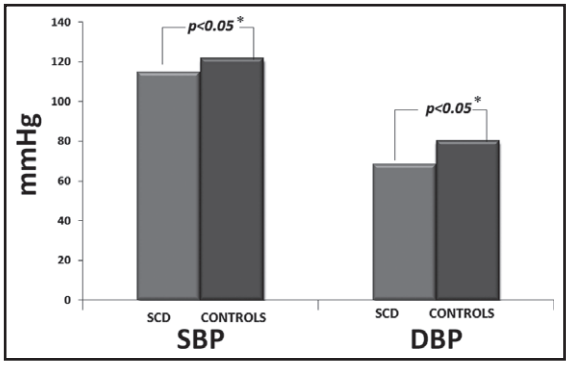

FIGURE 1. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the sickle cell disease (SCD) group and the control group. *Indicates statistical significance.

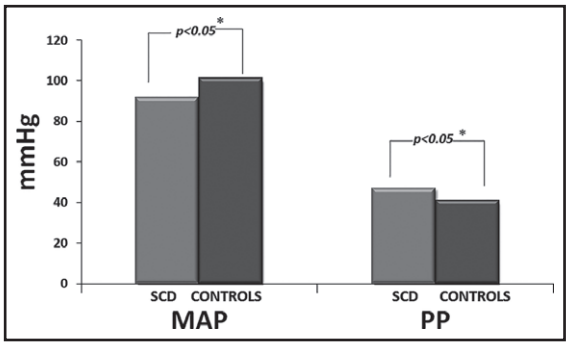

FIGURE 2. Mean arterial pressure (MAP) and pulse pressure (PP) in the sickle cell disease (SCD) group and the control group. *Indicates statistical significance

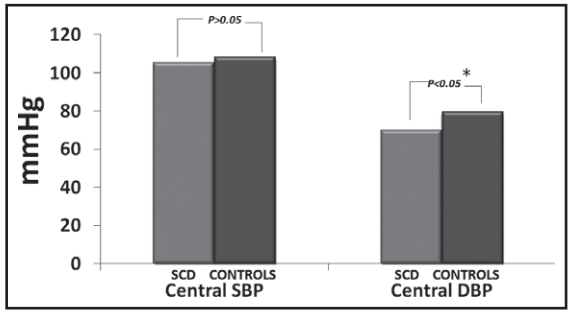

FIGURE 3. Mean central systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the sickle cell disease (SCD) group and the control group. *Indicates statistical significance.

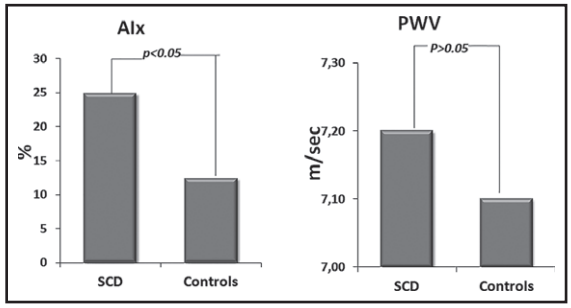

FIGURE 4. Indexes of arterial stiffness in the sickle cell disease (SCD) group and the control group. AIx indicates augmentation index, PWV, pulse wave velocity.

population. Finally, eGFR was higher in SCD patients and significantly positively affected by ferritin and negatively associated with age and central DBP in the study population.

The first to describe BP levels in SCD were Johnson and colleagues, who in 1981 showed that SCD patients had lower BPs than controls. The authors attribute this paradox phenomenon to the renal tubular defect responsible for the increased sodium and water excretion in these patients.[3] Several studies conducted thereafter nearly all confirmed this observation.

Pegelow and colleagues[4] showed that in a cohort of 3317 SCD patients, BP in patients was lower than values reported by age-, ssex-, and race-matched patients in the National Health and Nutrition Examination Surveys I and II. However, they show that in SCD patients, this relative systemic hypertension that still falls within the population norms predicts early mortality.

Moreover, Johnson and colleagues[14] support this concept with their multivariate analysis showing that SBP percentiles together with oxygen desaturation while asleep and age were independent predictors of left ventricular mass.

Morover, Gordeuk and colleagues showed that in SCD patients, SBP 120 mm Hg to 139 mm Hg and DBP 70 mm Hg to 89 mm Hg defines a category of relative systemic hypertension and is associated with increased risk for pulmonary hypertension and renal dysfunction. As a result of this low normal BP, higher BP levels that are within the normal range for the general population may be indicative of underlying renal disease or other comorbid medical conditions.

Therefore, they propose a new threshold for BP ≤120/70 mm Hg in patients with SCD.[15]

Although the exact mechanism of the lower BP is unknown, contributing factors could include salt-losing sickle cell nephropathy[16]; lower peripheral resistance; alteration of circulating levels of catecholamine, renin, aldosterone and prostaglandin; or changes in the sensitivity of receptors to these agents.[17,18] It is also possible that low BP is a compensation mechanism that is developed to overcome the detrimental effects of vaso-occlusive disease.

Another hypothesis for the resistance of hypertension in SCD is the activation of the NO system. One study showed that higher urinary excretion of NO metabolites was higher in SCD patients than in nonanemic control patients,[19] and another study showed a decreased response of peripheral vessels to blockade of the NO system, both suggestive of chronic NO activation.[20,21]

Later studies showed that hemolysis consumes NO and induces oxidative stress and thus induces

TABLE II. Simple Correlations of Arterial Stiffness Indices With the Under-Study Parameters in Patients With Sickle Cell Anemia

	AIx		PWV		Aortic SBP		Aortic DBP		Aortic PP		MDRD	
Variables	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value
Aortic SBP	**0.34**	**.027**	**0.57**	**<.001**	**1**	**NS**					−0.14	NS
Aortic DBP	0.011	NS	**0.32**	**.04**	**0.47**	**.002**	**1**	**NS**			**−0.37**	**.03**
Aortic PP	**0.38**	**.01**	**0.48**	**.001**	**0.89**	**<.001**	0.02	NS	**1**	**NS**	0.02	NS
BMI	0.13	NS	0.15	NS	0.024	NS	0.26	NS	**0.48**	**.001**	**−0.38**	**.02**
Age	**0.34**	**.027**	**0.67**	**<.001**	**0.51**	**.001**	0.30	NS	**0.43**	**.005**	**−0.39**	**.02**
Branchial SBP	0.22	NS	**0.60**	**<.001**	**0.70**	**<.001**	**0.60**	**<.001**	**0.47**	**.02**	**−0.32**	**.05**
Branchial DBP	−0.01	NS	**0.34**	**.03**	**0.36**	**.02**	**0.91**	**<.001**	−0.06	NS	−0.31	NS
HR	−0.07	NS	−0.07	NS	−0.17	NS	−0.065	NS	−0.15	NS	−0.21	NS
Waist	−0.06	NS	**0.42**	**.007**	0.18	NS	0.54	.001	−0.06	NS	−0.31	NS

Abbreviations: AIx, augmentation index; BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; MDRD, Modification of Diet in Renal Disease; NS, not significant; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.

endothelial dysfunction, cancelling NO abundance as a mechanism for the reduced BP.[22,23]

A different plausible explanation for the adverse cardiovascular events of low normal BP in SCD is that they might eventually have true hypertension since data in children indicate a high percentage of masked hypertension in this patient population. Two studies have demonstrated this altered BP pattern that not only misclassifies these patients as being normotensive, but also may lead to detrimental side effects such as microalbuminuria, left ventricular hypertrophy, and stroke, as well as other consequences of untreated high BP.[24,25]

When evaluating BP in SCD, we should consider that, as a group, patients with anemia have lower than expected SBP and DBP.[3,4] However, it has been reported that BP in SCD is higher than expected given the severity of anemia, further building the case of the existence of relative hypertension in this patient population.[5]

In addition, one of the parameters that may confound the relationship between SCD patients and controls in relation to their BP status may be the smaller stature of SCD patients; however, in our population, BMI and waistline were comparable between the two groups.

Arterial stiffness and BP are highly interrelated conditions.[10] Two studies investigated the topic of arterial stiffness in SCD patients with conflicting results.[26,27]

In the first study, Lemogoum and colleagues[27] showed that cf-PWV and carotid-brachial PWV, as well as aortic AIx, was lower in SCD patients compared with controls and they were both negatively associated with hemoglobin SS type. In contrast, Belizna and colleagues[26] showed that 49 patients with SCD had higher carotid stiffness than 47 matched controls and suggest an association between arterial stiffness with stroke. The latter is in accordance with the results of the present study indicating that low levels of BP in patients with SCD may not be a consequence of higher arterial elasticity rather than other mechanisms that remain to be completely clarified.

SCD patients in our study, despite both their lower brachial and central SBP and DBP, demonstrated higher brachial, central PP, and AIx, all indicative of increased arterial stiffness; however, PWV was comparable in the two groups,which does not allow definite conclusions.

Another issue in SCD that the present study addresses is renal disease. It was as early as 1955 that Etteldorf and colleagues[28] found GFR in children with SCD to be abnormally high while it normalized during adolescence and further declined with age.

In 1992, Falk and colleagues[29] demonstrated that 25% of patients with SCD have proteinuria. It has been proposed that this nephropathy may be the consequence of a toxin such as iron administered during blood transfusions. The fundamental lesion is focal segmental glomerulosclerosis in the setting of glomerular hypertrophy.

Haymann and colleagues[30] suggested that red blood cell (RBC) sickling-induced vaso-occlusion is not causative in glomerular hyperfiltration since it does not cosegregate with vaso-occlusive clinical complications of SCD. Instead, in addition to younger age, markers of chronic hemolysis such as lower hemoglobin levels, greater hemoglobin F levels, and higher reticulocyte count are independent risk factors for glomerular hyperfiltration in SCD.

Hemolysis causes hyperfiltration through the induction of anemia, which causes increased renal plasma flow as a consequence of increased cardiac output.

Additionally, higher hemolysis rate leads to increased tissue iron deposition, which may be a cause of hyperfiltration.[30]

In our study, patients had higher GFR than controls, and hyperfiltration (MDRD-GFR >130 mL/min per 1.73 m^2 in women and >140 in men) was found in 51%.

Our multivariate analysis showed that ferritin significantly affected GFR, along with a negative association with age and aortic DBP. Our population consisted of relatively young individuals with a mean age of 40 years; therefore, our results can only be extrapolated to this age group.

Previous studies have found similar results, associating hyperfiltration with young age and chronic kidney disease that leads to end-stage chronic kidney disease in older patients.[30]

STUDY LIMITATIONS

Our study has some limitations. First, the fact that BP was measured in the office and not ambulatory gives only a snapshot of what happens with BP given that SCD patients present desaturations in their sleep and possibly obstructive sleep apnea. They are also a group with a high incidence of masked hypertension.

In addition, the cross-sectional design does not allow for conclusions regarding cardiovascular endpoints or target organ damage in our study group. Further, the fact that patients with a small age range were included in the study makes it difficult to extrapolate the results to the whole SCD population.

CONCLUSIONS

A more detailed examination of BP in patients with SCD is in order. This should include a 24-hour BP measurement especially in those who have signs of target organ damage in order to identify cases of masked hypertension. Since there are still no separate/specific criteria by the European Society of Hypertension or the Eighth Joint National Committee for defining BP in SCD patients as a special population, this issue should be carefully addressed by opinion makers. More studies are needed to further evaluate the benign (or not) character of low BP in patients with SCD.

Acknowledgment: We thank Dr Spyros Gerou, MD, head of the "Analysis" laboratory, for his kind contribution in the measurement of the biochemistry parameters.

Disclosures: The authors report no specific funding in relation to this research and no conflicts of interest to disclose.

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