Sickle Cell Trait and Renal Function in Hispanics in the United States: The Northern Manhattan Study

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Sickle cell anemia (SCA) is a common hematological disorder among individuals of African descent in the United States; the disorder results in the production of abnormal hemoglobin. It is caused by homozygosity for a genetic mutation in HBB; rs334. While the presence of a single mutation (sickle cell trait, SCT) has long been considered a benign trait, recent research suggests that SCT is associated with renal dysfunction, including a decrease in estimated glomerular filtration rate (eGFR) and increased risk of chronic kidney disease (CKD) in African Americans. It is currently unknown whether similar associations are observed in Hispanics. Therefore, our study aimed to determine if SCT is associated with mean eGFR and CKD in a sample of 340 Dominican Hispanics from the Northern Manhattan Study. Using regression analyses, we tested rs334 for association with eGFR and CKD, adjusting for age and sex. eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation and CKD was defined as eGFR < 60 mL/min/1.73 m^2. Within our sample, there were 16 individuals with SCT (SCT carriers). We found that SCT carriers had a mean eGFR that was 12.12 mL/min/1.73m^2 lower than non-carriers (P=.002). Additionally, SCT carriers had 2.72 times higher odds of CKD compared with non-carriers (P=.09). Taken together, these novel results show that Hispanics with SCT, as found among African Americans with SCT, may also be at increased risk for kidney disease. *Ethn Dis*. 2017; 27(1):11-14; doi:10.18865/ed.27.1.11.

Keywords: Chronic Kidney Disease (CKD); Hispanics; Sickle Cell Trait

Introduction

In the United States, sickle cell disease is the most prevalent genetic hematologic disorder and primarily affects people of African descent. New York state has the highest sickle-cell population, followed by Florida and Texas.[1] Classic sickle cell anemia (SCA) is caused by homozygosity for the rs334 mutation in the β-hemoglobin gene (*HBB*), resulting in the production of abnormal hemoglobin.[2] Carriers of a single altered copy of *HBB* have sickle cell trait (SCT), which has generally been viewed as a benign condition with symptoms only presenting under extreme circumstances, such as high altitudes combined with exercise.[3] SCT is common with an estimated 300 million carriers worldwide.[3] In the United States, it is estimated that SCT occurs in approximately 73 out of every 1,000 births in Blacks and about 7 out of every 1,000 births in Hispanics.[4] While it is well-established that chronic kidney disease (CKD) and decreased glomerular filtration rate are common in patients with SCA,[2] results from a recent study conducted in a cohort of self-identified African Americans suggest that SCT may also be associated with a higher risk of kidney disease.[5] However, it is unknown

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whether similar associations are present in Hispanics, the fastest growing minority population in the United States. Therefore, we aimed to determine if eGFR and CKD were associated with SCT in Hispanic individuals from the Dominican Republic.

Methods

Study Population

Participants for this study were derived from the Northern Manhattan Study (NOMAS). Details of NOMAS have been published previously.[6] Briefly, NOMAS is a population-based cohort study based in Northern Manhattan. A total of 3,298 participants were enrolled from 1993-2001 and identified via random digit dialing. Eligibility criteria included being:1) stroke-free at time of enrollment; 2) aged ≥40 years old; and 3) a resident of a household with a telephone in Northern Manhattan for ≥3 months. All participants provided written informed consent to participate. The study was approved by the Institutional Review Boards of Columbia University and the University of Miami.

Outcome and Covariate Assessment

The outcome measures for this study were eGFR and CKD. eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation using serum creatinine measurements.[7] CKD was defined as eGFR < 60 mL/min/1.73 m^2. Covariate measures included diabetes and hypertension. Diabetes was defined as having either a self-reported diagnosis of diabetes or fasting glucose level ≥ 126 mg/dL. Hypertension was defined as having a self-reported diagnosis of hypertension, systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or receiving medication for high blood pressure.

Genotyping Methods

Genotype data for rs334 was obtained on 779 NOMAS participants, including 341 Dominican Hispanics, using customized Taqman® genotyping following a previously published protocol.[5]

Statistical Methods

Prior to analyses, eGFR was winsorized using SAS v. 9.3 to ensure a normal distribution. Means ± standard deviations (SD) as well as frequencies were calculated to compare characteristics between SCT carriers and non-carriers. Means were compared with t-tests and proportions by Fisher's exact tests using two-sided P. Linear regression analyses were performed to test the association between rs334 and mean eGFR. Logistic regression was performed for CKD analyses. Our primary model included rs334 genotype, coded additively, age and sex. Secondary analyses included the presence of diabetes and hypertension. These analyses were implemented in PLINK.[8] A Bonferroni correction was made to account for false positives and $P<.025$ was considered significant (.05/2 tests). Analyses were restricted to participants with rs334 genotype and eGFR measurements (n=340).

Table 1. Association of Sickle Cell Trait (SCT) with estimated glomerular filtration rate (eGFR) and chronic kidney disease (CKD) in NOMAS Dominicans

eGFR			Unadjusted		Model 1[a]		Model 2[b]	
	n	μ (SD)	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
SCT carriers	16	59.36 (15.01)	-16.09 (-24.68 to -7.50)	<.0001	-12.12 (-19.92 to -4.32)	.002	-12.72 (-20.50 to -4.94)	.001
Non-carriers	324	75.45 (17.12)	--	--	--	--	--	--
CKD								
	n/total[c]	%	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
SCT carriers	7/16	43.75	3.49 (1.25-9.76)	.02	2.72 (.86-8.62)	.09	2.80 (.87-9.01)	.08
Non-carriers	59/324	18.21	--	--	--	--	--	--

a. Adjusted for age and sex.
b. Adjusted for age, sex, diabetes and hypertension.
c. Number of participants with CKD/total number of participants.

Results

A total of 340 self-identified Hispanics from the Dominican Republic living in northern Manhattan, NY were included in our analyses (mean age 67 ± 8y; 66% female). Within our sample, 16 individuals were found to be SCT carriers (having one copy of the rs334 alternate allele) and none with SCD. SCT carriers were slightly older and more likely to have diabetes compared with non-carriers. SCT carriers and non-carriers did not differ with respect to sex or presence of hypertension.

Our study found that Hispanic SCT carriers had a lower mean eGFR and a higher prevalence of CKD compared with non-carriers (Table 1). After adjusting for age and sex, SCT carriers had a mean eGFR that was 12.12 mL/min/1.73m^2 lower compared with non-carriers *(P*=.002) (Table 1). Additionally, our results suggest that SCT carriers may have slightly higher odds of CKD compared with non-carriers, although this finding did not reach statistical significance (OR=2.72; *P*=.09) (Table 1). Inclusion of diabetes and hypertension in the model did not significantly alter results.

Discussion

Our study, the first to our knowledge to investigate SCT in Hispanics, found that Dominican Hispanics with SCT are at increased risk for kidney disease. In our sample, the prevalence of SCT was 4.7%, which is within the range of previously reported prevalence estimates in other Hispanics groups.[9-10] We further showed that Dominicans with SCT have significantly lower mean eGFR compared with Dominicans without SCT. These findings expand upon a previous study, which found similar results among African Americans.[5] Hispanics form the largest minority group in the United States and are known to have a higher incidence rate, compared with non-Hispanic Whites, for end-stage renal disease (ESRD), the most severe form of CKD.[11-12] Identification of Hispanic individuals at increased risk for kidney disease is necessary to ensure appropriate preventive efforts and early detection methods are put into place.

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For Hispanic individuals born in the United States, sickle cell disease screening is performed as part of neonatal screening programs.[3] However, many Hispanic individuals have not been screened as part of this program (eg, those born outside the United States). Two facts may reduce the frequency of SCT testing in this group. First, the term "Hispanic" is often viewed as an ethnic designation rather than a racial designation. However, in the 2011 US National Survey of Latinos, more than half of Hispanics (51%) choose "some other race" or "Hispanic/Latino" when asked to identify a racial identity.[13] Secondly, the proportion of African ancestry varies greatly among Hispanics, even among individuals with the same country of origin.[14] Our study suggests that although the frequency of SCT is lower in Hispanics (specifically Dominicans) compared with African Americans, screening for this trait may help identify individuals at greater risk of kidney disease prior to its onset. Yet, when considering the findings of our study, a limitation to consider is our limited sample size. However, our study was the first to examine the association between SCT and renal disease in a US Hispanic cohort.

Conclusion

In conclusion, as found among African Americans, SCT is associated with a decline in eGFR and may be associated with an increased risk of CKD among Dominican Hispanics living in the United States.

Acknowledgments and Compliance with Ethical Standards

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Conflict of Interest

No conflicts of interest to report.

Author Contributions

Research concept and design: Della-Morte, Blanton; Data analysis and interpretation: Dueker, Della-Morte, Rundek, Sacco, Blanton; Manuscript draft: Dueker, Rundek, Sacco, Blanton; Statistical expertise: Dueker; Acquisition of funding: Rundek, Sacco; Administrative: Sacco; Supervision: Della-Morte, Rundek, Blanton

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