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The Association of Sickle-Cell Disorders With Diabetic Retinopathy: A Large Database Study

Muhammad Z. Chauhan, MD, MS, Abdelrahman M. Elhusseiny, MD, MSc, Ahmed B. Sallam, MD, PhD

Purpose: To evaluate the association of sickle-cell disease (SCD) and sickle-cell trait (SCT) disease with diabetic retinopathy (DR) in patients with diabetes mellitus (DM).

Design: Population-based, retrospective cohort study utilizing data from the TriNetX Research Network, including 119 million patients across 80 health care organizations worldwide.

Participants: Diabetes mellitus patients (type 1 [T1DM] or 2 [T2DM]), with or without SCD and SCT, were included. Three cohorts were analyzed, including (1) DM patients without SCD, SCT, or sickle-cell/hemoglobin-C; (2) DM with SCD; and (3) DM with SCT.

Methods: All patients with DM were categorized into 3 cohorts based on the presence of SCD and SCT. Each cohort underwent 1:1 propensity score matching for demographics, blood glucose levels, hemoglobin A1C, and other relevant comorbidities.

Main Outcome Measures: Risk of DR in DM patients with and without SCD or SCT.

Results: There was no significant difference in the risk of any T1DR between those with and without SCD. However, for those with SCT, there was a notable twofold increased risk for T1-proliferative DR (PDR) (relative risk [RR]: 2.03; 95% confidence interval [CI]: 1.33−3.01). In contrast, there was an elevated risk for any T2DR in patients with SCD (RR: 1.50; 95% CI: 1.19−1.88), particularly due to higher PDR risks in T2DM patients (RR: 1.83; 95% CI: 1.29−2.60). The risk of mild to moderate T2DM non-PDR was also found to be higher in patients with SCT.

Conclusions: The risk of any DR was increased in T2DM patients with SCD or SCT, with increased risks for PDR in patients with SCT and T1DM. This indicates there may be a potential role of sickle-cell disorders in diabetic eye disease progression.

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Diabetes mellitus (DM), including both type 1 (T1DM) and type 2 (T2DM), represents an escalating global health challenge. It is characterized by chronic hyperglycemia due to defects in insulin secretion, insulin action, or both.[1] Diabetes mellitus has been implicated in a host of severe long-term complications, including cardiovascular disease, kidney failure, nerve damage, and microvascular complications such as diabetic retinopathy (DR) and cataract.[2–5] Diabetic retinopathy, in particular, is a major concern due to its substantial contribution to disease burden, frequently leading to significant visual impairment and even blindness in adults.[6–9]

Sickle-cell disease (SCD) and sickle-cell trait (SCT) disease are genetic hemoglobin (Hb) disorders characterized by the presence of sickle Hb.[10,11] Full SCD (Hb), the more severe form, is associated with repeated vaso-occlusive crises, chronic hemolytic anemia, and systemic inflammation.[12,13] On the other hand, SCT, usually milder, is characterized by the presence of both normal and HbS, with individuals generally asymptomatic under normal conditions.[14] Sickle-cell trait is widely found in regions affected by malaria, such as sub-Saharan Africa, India, the Middle East, and in specific populations in Europe and the Americas.[15] With rates of T2DM increasing, it has been suggested that a growing number of people will have both conditions concomitantly.[16] Sickle-cell disease and SCT have been associated with an increased risk of microvascular[17,18] and ocular complications,[19] but their effects on the development and progression of DR in DM patients remain understudied.[20]

The investigation into the relationship between SCD, SCT, and the development of DR in DM patients is important for several reasons. It may shed light on whether these sickle cell disorders exacerbate the progression of diabetic ocular complications, providing crucial information for the risk assessment and management of these complications. Additionally, it could help identify therapeutic targets and preventive strategies, potentially improving

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patients' outcomes. In this study, we sought to explore the association of SCD and SCT, and DR in a large, diverse cohort of patients with DM.

Methods

This is a population-based, retrospective cohort study. We utilized data from the TriNetX Research Network, a large database network of 119 million patients across 80 health care organizations worldwide. TriNetX is an international health research network that facilitates access to electronic health records—including diagnoses, procedures, medications, lab results, and genomic data—from numerous large-scale health care organizations. The data in this study were obtained from a subset of these health care organizations collectively known as the "Research" network and was performed in December 2023. This work used deidentified previously collected data. The study was determined to be exempt from the institutional review board approval at the University of Arkansas for Medical Sciences. The study complied with the tents of the Declaration of Helsinki.

We screened all patients' data in the TriNetX research network for the presence of DM using International Classification of Diseases (ICD)-10 codes (ICD codes: E08-E13). We included all patients who had a diagnosis of T1DM or T2DM, dividing them into 3 cohorts. The first cohort included patients with DM with no history of sickle-cell disorders (ICD: D57.xx). The second cohort was those with DM and a diagnosis of SCD (ICD: D57 or D57.1), excluding those with SCT or sickle-cell/Hb-C disease. The third cohort comprised patients with DM and a diagnosis of SCT (ICD: D57.3), excluding those with SCD or sickle-cell/Hb-C disease. We excluded, from all cohorts, patients with any history of retinal disorders in diseases classified elsewhere (H36.xx), which includes proliferative and nonproliferative sickle-cell retinopathy.

The index date for each patient within a cohort was the day on which the patient first met the selected criteria for the cohort. The index event encapsulated events that transpired within the last 20 years only. We excluded patients who experienced their index event $>$ 20 years back. We conducted 1:1 propensity score matching across cohorts based on demographic variables (age, sex, ethnicity, and race), blood glucose levels, HbS A1C, and the following confounding comorbidities with a 10-year lookback period: hypertension, chronic kidney disease, and hyperlipidemia. By employing propensity score matching, we achieved a balanced distribution of confounding factors between the groups, thereby enhancing their comparability.[21] In each cohort, we tracked patients to evaluate the likelihood of developing DR as the main outcome measure. As a secondary outcome, we also analyzed the grade of retinopathy: mild nonproliferative DR (NPDR) (ICD: E11.32 and E10.32), moderate NPDR (ICD: E11.33 and E10.33), severe NPDR (ICD: E11.34 and E10.34), and proliferative DR (PDR) (ICD: E11.35 and E10:35). We also examined the comparative risk of having to undergo panretinal photocoagulation (PRP) (Current Procedural Terminology: 67228), vitrectomy (Current Procedural Terminology: 67040, 67041, 67042, and 67113), and intravitreal injections (Current Procedural Terminology: 67028) between cohorts.

We presented the baseline characteristics by averages and standard deviations for continuous variables and counts and proportions for binary variables. In addition, for all comparison points, we supplied the outcomes from the propensity score matching, encompassing standardized mean differences for each covariate before and after the matching process and the relative risk (RR). The threshold for statistical significance for this study was $P < 0.05$ with 2-sided tests.

Results

SCD vs. No Sickle-Cell Disorders Among T1 and T2 Diabetics

Our first cohort comparison was those with DM, with and without SCD. There were 7 352 765 patients with DM with no history of sickle-cell disorders and 4285 patients with DM and a diagnosis of SCD. We found the overall risk in patients with SCD was 2.85% for any T1DR (1.81% PDR) and 4.28% for any T2DR (2.01% PDR) across the study period. For comparison, the risk in patients without SCD or SCT was found to be 3.42% for any T1DR (1.78% PDR) and 3.54% for any T2DR (0.36% PDR). After matching, there were 4208 patients in each group. Table 1 shows the results of the propensity score matching. Overall, we found the risk of T1DR or T2DR in patients with SCD was only slightly higher in those without SCD (RR: 1.39; 95% confidence interval [CI]: 1.12−1.72, $P = 0.002$). We found that the risk of any T1DR (NPDR and PDR) was comparable between groups (RR: 1.26; 95% CI: 0.69 to −2.30, $P = 0.445$). The risk of mild (RR: 0.78; 95% CI: 0.34−1.75), moderate (RR: 1.00; 95% CI: 0.42−2.40), and severe (RR: 1.00; 95% CI: 0.42−2.40) T1-NPDR was comparable between patients with and without SCD. The risk of T1-PDR was also comparable between groups (RR: 1.50; 95% CI: 0.68−3.33, $P = 0.317$).

Overall, the risk for any T2DR, encompassing both NPDR and PDR, was found to be higher in patients with SCD compared with those without a sickle-cell disorder (RR: 1.50; 95% CI: 1.19−1.88, $P < 0.001$). We found that this significant risk difference was primarily driven by patients with PDR pathology (RR: 1.83; 95% CI: 1.29−2.60, $P < 0.001$). The risk of mild T2-NPDR was slightly higher in the SCD group (RR: 1.35; 95% CI: 1.04−1.82, $P = 0.04$). For moderate and severe T2-NPDR, there was no observed elevated risk of between groups (RR: 1.36; 95% CI: 0.81−2.32 and RR: 1.45; 95% CI: 0.67−3.13, respectively) (Fig 1). We next examined the risk of undergoing several key procedures between cohorts. Among patients with T1DM we found no elevated risk of PRP (RR: 0.67; 95% CI: 0.30−1.48, $P = 0.313$), IV injections (RR: 0.54; 95% CI: 0.28−1.02, $P = 0.056$), or vitrectomy procedures (RR: 0.63; 95% CI: 0.29−1.37, $P = 0.235$) between those with and without SCD. In patients with T2DM, we also observed no significant difference among those receiving PRP (RR: 1.43; 95% CI: 0.72−2.83, $P = 0.302$), IV injections (RR: 0.89; 95% CI: 0.56−1.43, $P = 0.626$), or vitrectomy procedures (RR: 1.29; 95% CI: 0.64−2.58, $P = 0.479$).

SCT vs. No Sickle-Cell Disorders Among T1 and T2 Diabetics

We next determined the impact of an underlying diagnosis of SCT in DM patients across outcomes. The overall risk in

Table 1. Propensity Score Matching Results Between Patients With DM Plus SCD and DM Minus Sickle-Cell Disorders

Characteristics	Before Matching			After Matching		
	DM w/out SCD (n = 7 352 765)	*DM with SCD (n = 4285)*	*Std. Diff.*	*DM w/out SCD (n = 4208)*	*DM with SCD (n = 4208)*	*Std. Diff.*
Age, mean (SD)	59.3 (16.2)	53 (18)	0.368	52.3 (17.8)	53 (18)	0.039
Sex, No. (%)						
Male	3 464 981 (48.98)	1732 (41.16)	0.158	1739 (41.33)	1732 (41.16)	0.003
Female	3 449 571 (48.76)	2424 (57.61)	0.178	2417 (57.44)	2424 (57.61)	0.003
Ethnicity, No. (%)						
Non-Hispanic/LatinX	4 083 243 (57.72)	2756 (65.49)	0.160	2758 (65.54)	2756 (65.49)	0.001
Hispanic/LatinX	676 721 (9.56)	264 (6.27)	0.122	264 (6.27)	264 (6.27)	< 0.001
Race, No. (%)						
White	4 126 545 (58.33)	1111 (26.40)	0.682	1092 (25.95)	1111 (26.40)	0.010
Black or AA	1 116 860 (15.79)	2198 (52.23)	0.833	2207 (52.45)	2198 (52.23)	0.004
Asian	289 460 (4.09)	69 (1.64)	0.147	70 (1.66)	69 (1.64)	0.002
American Indian or Alaskan Native	33 731 (0.48)	14 (0.33)	0.023	19 (0.45)	14 (0.33)	0.019
Native Hawaiian or Pacific Islander	44 089 (0.62)	10 (0.24)	0.059	31 (0.73)	10 (0.24)	0.072
Laboratory values, mean (SD)						
Blood glucose	144 (71.4)	136 (73.6)	0.105	137 (72)	136 (73.6)	0.009
HbA1C	7.15 (1.92)	6.79 (1.9)	0.186	6.85 (1.9)	6.79 (1.9)	0.031
Comorbidities, No. (%)						
Chronic kidney disease	263 492 (3.73)	828 (19.68)	0.512	838 (19.84)	828 (19.68)	0.004
Hypertension	1 398 089 (19.76)	2307 (54.82)	0.777	2244 (53.33)	2307 (54.82)	0.030
Hyperlipidemia	703 657 (9.95)	1355 (32.20)	0.567	1316 (31.27)	1355 (32.20)	0.019

AA = African American; DM = diabetes mellitus; No. = number/frequency; SCD = sickle-cell disease; SD = standard deviation; Std. Diff. = standardized difference.
Those with "unknown" sex, ethnicity, and race were removed from analysis.

patients with SCT was 4.19% for any T1DR (2.79% PDR) and 5.73% for any T2DR (2.41% PDR). Table 2 shows the results before and after propensity score matching and included 12 895 patients before matching. After matching, there were 12 748 in both groups. The risk of any T1DR was found to be higher in patients with SCT compared with those without any sickle-cell disorder (RR: 1.70; 95% CI: 1.23−2.38, $P = 0.002$). The risk of mild (RR: 1.38; 95% CI: 0.79−2.42), moderate (RR: 1.50; 95% CI: 0.67−3.33), and severe (RR: 1.00; 95% CI: 0.42−2.40) T1-NPDR was comparable between patients with and without SCT. We found that the risk of T1-PDR was significantly higher in the SCT group compared with patients without a history of sickle-cell disorders (RR: 2.03; 95% CI: 1.33−3.01, $P = 0.0008$).

Overall, the risk for any T2DR was found to be higher in patients with SCT compared with those without any sickle-cell disorder (RR: 1.75; 95% CI: 1.55−1.97, $P < 0.0001$). We found an elevated risk of mild (RR: 1.56; 95% CI: 1.35−1.82) and moderate (RR: 1.82; 95% CI: 1.38−3.3) T2-NPDR, with no increased risk of severe (RR: 1.47; 95% CI: 0.97−2.25) T2-NPDR between patients with and

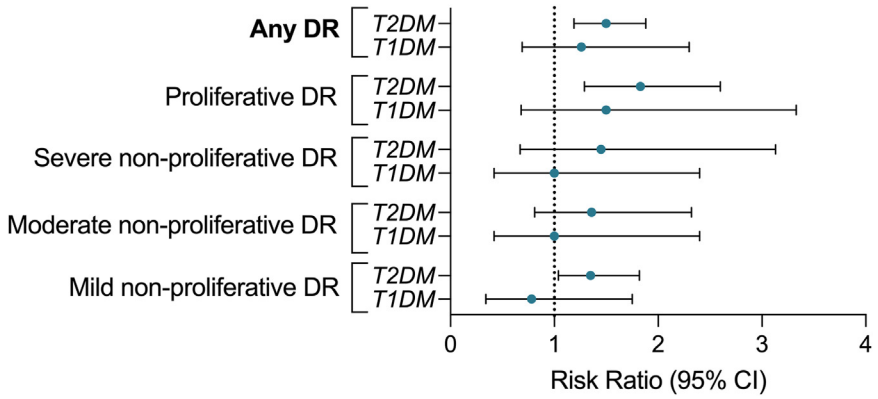

Figure 1. Comparisons of patients with diagnoses of diabetes mellitus (DM) plus sickle-cell disease vs. DM without sickle-cell disorders after propensity score matching. Significance is indicated by confidence interval lines that do not cross risk ratio of 1. DR = diabetic retinopathy; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Table 2. Propensity Score Matching Results Between Patients With DM Plus SCT and DM Minus Sickle-Cell Disorders

Characteristics	Before Matching			After Matching		
	DM w/out SCD (n = 7 352 765)	*DM with SCT (n = 12 895)*	*Std. Diff.*	*DM w/out SCD (n = 12 748)*	*DM with SCT (n = 12 748)*	*Std. Diff.*
Age, mean (SD)	59.3 (16.2)	50.2 (16.9)	0.551	50.2 (16.9)	50.2 (16.9)	0.005
Sex, No. (%)						
Male	3 464 981 (48.98)	3377 (26.49)	0.477	3380 (26.51)	3377 (26.49)	0.0005
Female	3 449 571 (48.76)	9182 (72.03)	0.489	9179 (72.00)	9182 (72.03)	0.0005
Ethnicity, No. (%)						
Non-Hispanic/LatinX	4 083 243 (57.72)	8872 (69.59)	0.249	8895 (69.78)	8872 (69.59)	0.004
Hispanic/LatinX	676 721 (9.56)	372 (2.91)	0.277	351 (2.75)	372 (2.91)	0.009
Race, No. (%)						
White	4 126 545 (58.33)	494 (3.88)	1.45	469 (3.68)	494 (3.87)	0.010
Black or AA	1 116 860 (15.79)	9860 (77.35)	1.56	9855 (77.31)	9860 (77.35)	0.001
Asian	289 460 (4.09)	69 (0.54)	0.28	86 (0.68)	69 (0.54)	0.017
American Indian or Alaskan Native	33 731 (0.48)	20 (0.16)	0.07	73 (0.57)	20 (0.16)	0.069
Native Hawaiian or Pacific Islander	44 089 (0.62)	10 (0.08)	0.09	65 (0.51)	10 (0.08)	0.079
Lab values, mean (SD)						
Blood glucose	144 (71.5)	135 (72.9)	0.132	136 (73.3)	135 (72.9)	0.018
HbA1C	7.15 (1.92)	7.04 (2.00)	0.057	6.92 (1.93)	7.04 (2.00)	0.059
Comorbidities, No. (%)						
Chronic kidney disease	262 049 (3.70)	2068 (16.22)	0.427	2038 (15.99)	2068 (16.22)	0.006
Hypertension	1 372 198 (19.39)	7154 (56.12)	0.818	7162 (56.18)	7154 (56.12)	0.001
Hyperlipidemia	687 949 (9.72)	3771 (29.58)	0.516	3759 (29.48)	3771 (29.58)	0.002

AA = African American; DM = diabetes mellitus; No. = number/frequency; SCD = sickle-cell disease; SCT = sickle-cell trait; SD = standard deviation; Std. Diff. = standardized difference.
Those with "unknown" sex, ethnicity, and race were removed from analysis.

without SCT. The risk of T2-PDR was significantly higher in patients with SCT compared with those with no sickle-cell disorder (RR: 1.97; 95% CI: 1.63−2.40, $P < 0.0001$) (Fig 2). Among patients with T1DM we found no increased risk of having PRP (RR: 0.86; 95% CI: 0.56−1.33, $P = 0.498$), IV injections (RR: 0.90; 95% CI: 0.65−1.25, $P = 0.549$), or vitrectomy procedures (RR: 1.05; 95% CI: 0.69−1.60, $P = 0.825$) in those with SCT compared with those with DM without any history of SCT. In focusing on patients with T2DM we found a significantly elevated risk of PRP (RR: 1.61; 95% CI: 1.11−2.32, $P = 0.001$), IV injections (RR: 2.00; 95% CI: 1.52−2.64, $P < 0.0001$), and vitrectomy procedures (RR: 2.16; 95% CI: 1.47−3.19, $P < 0.0001$).

Discussion

This large population-based study examined the association between sickle-cell disorders and the coexistence of DR. We found that in patients with SCD, there is an elevated risk of PDR in patients with T2DM. In patients with SCT, we found an increased risk of PDR in patients with T1DM and T2DM. These findings suggest the importance of accounting

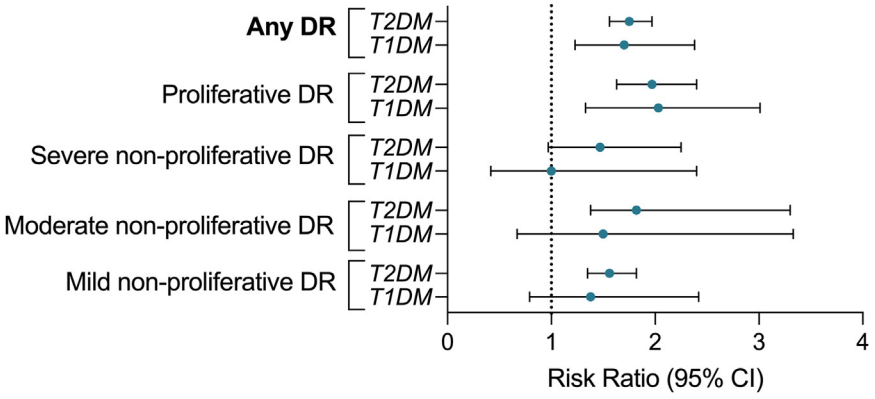

Figure 2. Comparisons of patients with diagnoses of diabetes mellitus (DM) plus sickle-cell trait vs. DM without sickle-cell disorders after propensity score matching. Significance is indicated by confidence interval (CI) lines that do not cross risk ratio of 1. DR = diabetic retinopathy; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

for sickle cell disorders in DM patients' screening and clinical management.[22–24]

While the role of SCD and SCT in microvascular complications has been previously reported, this study provides data on the association of these sickle-cell disorders with DR. Our findings align with the consensus that SCD and SCT may accelerate the development of microvascular complications in diabetes,[25–27] but extend this understanding to show specific impacts on DR stages and differential impact of SCD versus SCT in the setting of T1DM and T2DM. Our study shows that the impact of sickle-cell disorders appears more pronounced in patients with T2DM, especially for those with SCT, and most importantly, modulate PDR risk. Our findings corroborate the work by Skinner et al[28] (2018), who showed significantly increased risks of DR in patients with SCT and T2DM (n = 60) compared with T2DM alone (n = 52). A plausible explanation for this difference could lie in the chronic hyperglycemia that often characterizes T2DM, exacerbating the already compromised red blood cell function in these individuals leading to increased vascular damage. In the Skinner et al study, they also showed a heightened stiffness in arteries, elevated blood viscosity, increased thixotropic index, and higher concentrations of plasma advanced glycation end-products in patients with SCT and T2DM, which may provide a vascular link for these observed elevated risks. This heightened vascular damage, chronic inflammation, and oxidative stress, common in both DM and sickle cell disorders, may contribute to an accelerated onset and progression of DR.[29–31] Another study by Diaw et al[32] (2015) was the first to show the impact of T2DM in patients with SCT. They found increased blood viscosity and higher levels of oxidative stress in patients with T2DM and SCT. A recent study utilizing large data from the United Kingdom Biobank found that SCT was significantly associated with an elevated risk of DM-related complications.[33] Additionally, Vangipuarm et al, Jackson et al, and Nagpal et al,[22,24] reported cases where vascular disorders, predominantly DM and SCT, may have resulted in a synergetic effect on the development of retinopathy. However, there are contradictory findings in the literature among other populations; a single-center study of 446 West Indian diabetic patients found no association between SCT and DR presence or progression,[20] and a study of 200 patients from Saudi Arabia suggested a protective effect of SCT against the development and progression of DR.[34]

Another finding from our study was the differential impact of SCD and SCT on various stages of DR. While both conditions increased the risk of PDR, the overall impact appears more pronounced in patients with SCT. Bowers et al[35] uncovered that individuals with SCT require a higher optimal hematocrit to maximize oxygen delivery. This implies a greater concentration of red blood cells is needed for optimal physiological function, which, as a side effect, leads to increased blood viscosity. In the context of our study, where patients with SCT exhibited a heightened risk of PDR, particularly in T2DM, this higher blood viscosity could be a contributing factor. The elevated hematocrit and resultant increased viscosity in SCT could be exacerbating the vascular damage, chronic inflammation, and oxidative stress that are characteristic of diabetes, particularly under the conditions of chronic hyperglycemia seen in T2DM. A potential mechanism, suggested by the findings of Bowers et al, involves impaired blood flow dynamics due to increased viscosity. This impaired hemodynamics could lead to more pronounced microvascular insults in the retinal vasculature, contributing to the pathogenesis of DR.[35] The altered blood flow and shear stress could also amplify endothelial dysfunction and promote a prothrombotic state, thereby providing a plausible explanation for the increased incidence and severity of DR observed in our cohort of SCT patients with diabetes.

Our study has several strengths that enhance its validity and reliability. Firstly, utilizing a large, population-based cohort provides a diverse and representative sample, enhancing the generalizability of our findings. Moreover, applying propensity score matching allowed us to effectively control for potential confounding factors, including demographics and relevant systemic comorbidities. However, it is important to acknowledge the inherent limitations of a retrospective analysis. Despite our efforts to account for confounding variables, residual confounding is still possible due to unmeasured factors not included in our analysis. Additionally, misclassification bias may have occurred, as some cases of proliferative sickle retinopathy could have been misdiagnosed as PDR and vice versa. However, given the distinct phenotypical presentations of sickle retinopathy versus DR, we believe that any potential misclassification is likely to be minimal and unlikely to significantly impact our results. Caution also needs to be exercised when interpreting our findings in relation to the specific DR grading. Because of the clinical diagnosis of retinopathy grading, which may be made by clinicians without the use of fundus photography, inaccuracies can occur.[36] However, we expect this type of error to be nondifferential across all groups. Furthermore, although SCT and SCD status are now tested in United States through newborn screening, asymptomatic individuals with SCT may be unknown to the affected individuals and/or their health care team.[33] This may influence the accuracy of our findings. Lastly, it is crucial to consider the potential limitations associated with the generalizability of our findings. Variations in health care access and quality across different health care systems may influence the outcomes observed in our study. Therefore, caution should be exercised when extrapolating our results to populations with different health care contexts.

In conclusion, our study provides evidence that SCD and SCT may be associated with an increased risk of DR in DM patients, specifically PDR in those with T2DM. These findings underscore the importance of considering sickle cell disorders in DR screening and clinical management of DM patients. Furthermore, our study calls for deeper exploration into the underlying mechanisms connecting sickle-cell disorders with DR progression in DM patients, aiming to enhance patient outcomes.

Footnotes and Disclosures

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Harvey and Bernice Jones Eye Institute, University of Arkansas for Medical Sciences, Little Rock, Arkansas.

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The authors have no proprietary or commercial interest in any materials discussed in this article.

HUMAN SUBJECTS: No human subjects were included in this study.

No animal subjects were used in this study.

The study was determined to be exempt from the institutional review board approval at the University of Arkansas for Medical Sciences. The study complied with the tents of the Declaration of Helsinki.

Author Contributions:

Conception and design: Chauhan, Elhusseiny, Sallam

Data collection: Chauhan, Elhusseiny

Analysis and interpretation: Chauhan, Elhusseiny

Obtained funding: Sallam

Overall responsibility: Sallam

Abbreviations and Acronyms:
CI = confidence interval; **DM** = diabetes mellitus; **DR** = diabetic retinopathy; **Hb** = hemoglobin; **ICD** = International Classification of Diseases; **NPDR** = nonproliferative diabetic retinopathy; **PDR** = proliferative diabetic retinopathy; **RR** = relative risk; **PRPpanretinal** = photocoagulation; **SCD** = sickle cell disease; **SCT** = sickle-cell trait; **T1DM** = type 1 diabetes mellitus; **T2DM** = type 2 diabetes mellitus.

Keywords:
Diabetes mellitus, Diabetic retinopathy, Sickle cell disease, Sickle cell trait, Propensity score matching.

Correspondence:
Ahmed B. Sallam, MD, PhD. Department of Ophthalmology, Jones Eye Institute, University of Arkansas for Medical Sciences, 4301 W Markham Street # 523, Little Rock, AR 72205. E-mail: ahmedsallam11@yahoo.com.

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