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Prediabetes among individuals with sickle cell disease: a hospital-based cross-sectional study

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Abstract

Background: Studies have shown that comorbidity of sickle cell disease (SCD) and diabetes mellitus (DM) leads to adverse microvascular complications. Recent studies elsewhere have reported co-existence in some populations. The need to determine the relationship between SCD and DM is reasonable due to improved life expectancy among individuals with sickle cell disease and the increasing reports of high DM incidence and prevalence among this population.

Objective: This study aimed to determine whether SCD patients attending the Korle-Bu Teaching Hospital (KBTH) have a lower DM prevalence than non-SCD patients.

Methods: This hospital-based cross-sectional study involving 53 SCD participants and 60 non-SCD randomly selected participants was conducted at KBTH from February to June 2019. About 3 ml of venous blood samples were collected from all consenting patients, and fasting blood glucose (FBG) was estimated using the VITROS Chemistry Analyser. Point of care glucometer (OneTouch® Select™ Plus brand) was used to estimate random blood glucose (RBG) from SCD participants' capillary blood samples taken 2 hours after they ate. RBG levels were not estimated for non-SCD participants. WHO diabetes diagnostic criteria were used to determine the diabetes status of all participants.

Results: While no SCD participant had diabetes, 3.3% (n = 2) of non-SCD participants had diabetes. The mean age and body mass index (BMI) of the non-SCD participants (48 years, 27.0 kg/m^2) were higher than that of the SCD participants (36 years, 22.9 kg/m^2). Most SCD participants (52.8%, n = 28) had impaired glucose tolerance (prediabetes) (5%, n = 3). Male SCD participants were significantly less likely to have prediabetes than their female counterparts (OR = 0.109, 95% CI: 0.016 – 0.737, p = 0.023).

Conclusion: The prevalence of prediabetes among SCD individuals was high. This might be due to increasing BMI with age among the SCD cohort, suggesting the need for continuous monitoring of DM status among ageing SCD patients.

Keywords: Sickle cell disease, diabetes mellitus, prediabetes

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INTRODUCTION

Sickle cell disease (SCD) and diabetes mellitus (DM) are major public health concerns in the WHO African Region [1,2]. In SCD, there is a haemoglobin (Hb) disorder because of a single nucleotide polymorphism (SNP), which allows for certain complications: anaemia, hand-foot syndrome, pulmonary infarction, joint necrosis, and organ damage [3,4]. Compared to the general population, individuals with SCD have an increased risk of kidney disease, stroke, pulmonary hypertension, and retinopathy [5]. With DM, which is classified into type 1 DM (T1DM), type 2 DM (T2DM), and gestational DM, increased concentrations of glucose in the bloodstream pose direct consequences for affected individuals: hyperglycaemic hyperosmolar syndrome (HHS) and diabetic ketoacidosis (DKA) [6].

Similar to SCD, DM poses other related consequences, including macrovascular complications such as stroke and coronary heart disease [6] and microvascular complications

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that could occur in the retina, kidney, and periphery of the nervous system [1]. Therefore, a concurrent case of SCD and DM may yield a double morbidity and mortality burden on such individuals. However, there have been contradicting reports on the relationship between these two conditions (SCD and DM) of public health concern. First, a US-based epidemiologic study revealed an increase (15.7% to 16.5%) in T2DM prevalence among 7,070 SCD study participants over six years [7]. Also, when assessing the success of voxelotor (a drug that inhibits HbS polymerisation and reduces red blood cell sickling) in a clinical trial, Alshurafa and Yassin [8] considered the case of a 49-year-old man with SCD and DM. Though not specific with the DM type in their case, they reported that their patient had a chronic kidney disease (stage IV), was hypertensive, and needed frequent blood transfusions [8]. In another study in Qatar, Soliman et al. [9] observed that about 6.7% (n = 5/75) of their sickle cell participants developed T2DM over five years. Interestingly, they reported that SCD participants requiring blood transfusions developed DM earlier than those who did not, further suggesting a possible development of DM due to iron overload in SCD patients [9]. Indeed, multiple and frequent transfusions might cause hemosiderosis (iron accumulation in tissues), which can damage the pancreas and lead to diabetes mellitus [10].

Over the years, the presumed benign sickle cell trait (SCT) and T2DM co-existence have been reported. Diaw et al. [11] reported that the co-existence of SCT and T2DM may have additive effects on the development of microvascular complications. They observed increased oxidative stress, abnormal rheology, and vascular dysfunction in individuals with SCT and T2DM [11]. In their case series, Brown et al. [12] reported a concurrent case of SCT and, perhaps, T2DM, where the patient had a history of multiple transient ischemic attacks, hypertension, and cerebrovascular accident. These reports suggest a possible concurrent case of SCD and DM, which could have additive effects on the development of microvascular complications. However, others have reported lower prevalence rates of DM among SCD populations. For instance, a study in Bahrain showed a lower prevalence of either T1DM or T2DM among patients with SCD (8.3%) compared to the general population (15.4%) [13].

In the US, Liem et al. [14] reported no case of DM among their SCT cohort but 0.8% DM prevalence in the non-SCT population. Prusty and colleagues [15] in India observed a 1.46% (n = 2/137). DM prevalence rate among their SCD group against a DM prevalence rate of 8.76% (n = 12/137) among the control group. Interestingly, they observed that while one of their SCD participants had T1DM, the other was a case of T2DM [15]. In West Africa, Akpan and Akpanyung [16] reported a prevalence of 6.25% of HbAS genotype among people with diabetes compared to 27.60% among non-diabetics[16]. Interestingly, these studies showing a low prevalence of SCD patients among either T1DM or T2DM among SCD patients did not consider the "unreliable" glycated haemoglobin (HbA1c) test, which suggests a protective role of SCD against DM [17,18]. Though protective mechanisms are not entirely conclusive, studies have suggested that a lowered rate of obesity in the SCD population and a lowered life expectancy due to increased illness frequency reduce the risk of overt DM developing over time [13,15]. Others also suggest that abnormal Hb is a better buffer for absorbing increasing blood glucose concentrations [19]. This prevents hyperglycemia-induced tissue damage, as in the case of DM [19]. Furthermore, changes associated with sickled red blood cells (RBCs) create an unfavourable environment for the antibodies targeted against the β-cells of the pancreas, and microRNAs present in the sickle cells block the mRNA translation of antibodies that may cause the autoimmune destruction of the pancreas; thereby protecting against T1DM [16].

Presently, few studies directly show the association between SCD and DM in areas where SCD prevalence and incidence are high. With conflicting opinions and scanty information on the association between the two conditions in the African population, many more studies are needed, especially in these areas, for better management and improved outcomes. The possibility of any association cannot be overlooked in low-resourced settings where both conditions are highly prevalent. Understanding the burden of DM in SCD populations in low-resource settings would be essential to consider management options and preventive measures in sickle cell populations. This study determined whether T2DM prevalence was lower among SCD patients compared with non-SCD controls.

MATERIALS AND METHODS

Study population and sites

This cross-sectional study was conducted at the Sickle Cell and Genetics Clinic and the Central Laboratory of KBTH from February to June 2019. The Sickle Cell and Genetics Clinic is the sickle unit of KBTH, where SCD patients report for medical attention. Sickle cell patients are expected to report to the Clinic once every three or six months for review. The Central Laboratory is the unit of KBTH where most laboratory testing is done at clinicians' request from the hospital's various departments. SCD patients of at least 18 years old (adult) who presented to the Clinic and consented to the study were randomly enrolled as participants. Control subjects were adult non-SCD patients who presented to KBTH for various reasons and conditions (Table 1) and consented to the study. Considering a confidence level of 95%, an allowable error margin of 5%, and a 2% DM prevalence in the Ghanaian adult population [20], a total of 113 participants were included. These consisted of 53 SCD participants and 60 non-SCD participants.

Sample collection and processing

Study participants were recruited by simple random sampling at the two study sites, and a well-structured

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questionnaire was used to collect data on all participants' socio-demographic characteristics. For both groups (SCD and non-SCD), participants were recruited based on the criterion that they had not been previously diagnosed with type 1 or 2 diabetes. Weight was measured in light clothing and without shoes with SECA 877 scales to the nearest 0.1 kg. Height was measured without shoes with a portable stadiometer (SECA 217) to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). All SCD participants were tested for fasting blood glucose (FBG) using the VITROS Chemistry Analyzer [VITROS 5.1 /FS by J & J Ortho Clinical Diagnostics, USA] and random blood glucose using OneTouch® Select™ Plus glucometer. Random blood glucose (RBG) levels were checked 2 hours after participants ate. The Hb genotypes of SCD participants were confirmed at the Clinic using Capillary2 Flex Piercing (Serbia, France). Non-SCD participants were tested for FBG only. Newly diagnosed diabetics were referred to the attending clinician and laboratory for consultation and further testing for confirmation.

Participants' DM statuses were classified according to the WHO diagnostic criteria: no diabetes (normal), diabetes, impaired glucose tolerance (IGT), or impaired fasting glucose (IFG) [21]. HbA1c test was not used to confirm a DM diagnosis or otherwise, as this is affected by haemoglobinopathies.

Data analysis

The data obtained were analysed using statistical tools in IBM SPSS Statistics for Windows, Statistical Package for Social Sciences version 25.0 (IBM Corp., Armonk, N.Y., USASPSS Inc.). Descriptive statistics such as frequencies and percentages were computed for categorical variables. Continuous variables were summarised as means with standard deviations and were compared using the Student's t-test. Categorical variables were compared using the z-test for proportions. A p-value less than 0.05 was interpreted as significant. The factors associated with prediabetes status among the SCD participants were evaluated using logistic regression analysis, adjusting for the traditional independent variables. The Hosmer-and-Lemeshow test was used to verify how well the data fit the logistic regression model. A p-value of more than 0.05 signified that the regression model was a good fit for the data.

RESULTS

Socio-demographic and clinical characteristics of study participants

This study recruited 53 SCD and 60 non-SCD patients as participants. While most of the non-SCD participants attended KBTH for a general medical check-up (n = 31, 51.7%), and some presented with metabolic conditions such as chronic kidney disease (CKD), acute left ventricular failure (LVF), hypertension and hyperlipidemia (n = 8, 13.3%), there were single cases of breast cancer and cataract (n = 1, 1.7%) (Table 1). More than half of the SCD participants had the Hb SS genotype (n = 32, 60.4%), with the least represented genotype being Hb Sβ Thalassemia (n = 1, 1.9%) (Table 2). In both groups (SCD and non-SCD), there were more females than males (66.1% and 63.3% vs. 33.9% and 36.7%, respectively). The mean age of the SCD participants was 36.2 (± 14.5) years, significantly lower than that of their non-SCD control counterparts [(48.2 ± 15.6) years, $p < 0.001$]. The mean BMI among the SCD participants was 22.9 kg/m^2, significantly lower than that of the control group, 27.0 kg/m^2 $p < 0.001$ (Table 3).

Diabetes status of study participants

According to the WHO diagnostic criteria, no SCD participant had diabetes. However, most had impaired glucose tolerance (prediabetes) (n = 28, 52.8%). Among the control group, 3.3% (n = 2) had diabetes mellitus, and 5% (n = 3) had impaired fasting glucose status (prediabetes). With only their RBG levels estimated, this study did not determine the impaired glucose tolerance status of the non-SCD participants (Table 3). From our Pearson Chi-Square analysis, we observed that the frequencies of DM were notsignificantly different between SCD and non-SCD participants ($\chi 2 = 1.798$, df = 1, $p = 0.180$); however, the frequencies of prediabetes between the two groups were

Table 1. Clinical characteristics and symptoms of non-SCD participants

Characteristic/Symptom	non-SCD patients (*n* = 60) Frequency (%)
General medical check-up	31 (51.7)
Metabolic syndrome (CKD, acute LVF, hypertension, hyperlipidemia)	8 (13.3)
Maternity issues (pregnancy, uterine fibroids)	5 (8.3)
Inflammatory conditions (acute gastritis, peritonitis, rheumatoid arthritis, testicular swelling, bilateral pedal oedema)	5 (8.3)
Viral infection (hepatitis B & C, herpes simplex)	4 (6.7)
Pre-cancerous conditions (BPH, thyroglossal cyst)	3 (5.0)
Other infections (typhoid fever, UTI)	2 (3.3)
Cancerous conditions (breast cancer)	1 (1.7)
Cataract	1 (1.7)

n, total number of study participants; CKD, chronic kidney disease; LVF, left ventricular failure; BPH, benign prostatic hyperplasia; UTI, urinary tract infection

Table 2. Sickle genotypes among SCD participants

Genotype	SCD patients (*n* = 53) Frequency (%)
SS	32 (60.4)
SC	18 (33.9)
SF	2 (3.8)
Sβ Thalassemia	1 (1.9)

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Table 3. Socio-demographic characteristics and diabetes mellitus status of study participants

	Participants (*n* = 113)		
Characteristic	SCD (*n* = 53)	non-SCD (*n* = 60)	*P*-value
Sex			–
Male	18 (33.9)	22 (36.7)	0.841
Female	35 (66.1)	38 (63.3)	0.756
Age (years)	36.2 ± 14.5	48.2 ± 15.6	< 0.001*
BMI (kg/m^2)	22.9 ± 4.1	27.0 ± 5.4	< 0.001*
FBG (mmol/L)	3.52 ± 0.30	4.95 ± 2.59	< 0.001*
Diabetes status	0 (0.0)	2 (3.3)	0.180
Prediabetes[a]	28 (52.8)	3 (5.0)	< 0.001*

n, total number of study participants; BMI, body mass index; FBG, fasting blood glucose
*P-value is significant at 5%
a Prediabetes status is specifically impaired glucose tolerance for sickle cell participants and impaired fasting glucose for non-sickle cell participants

Table 4. Clinical characteristics of the diabetic non-SCD participants

Patient	Sex	Age (years)	BMI (kg/m^2)	FBG (mmol/L)	Clinical Condition
1	F	44	20.6	16.1	Acute left ventricular failure
2	F	51	24.4	19.9	Chronic kidney disease

F, female; BMI, body mass index; FBG, fasting blood glucose

Table 5. Factors associated with prediabetes status among SCD participants

	Unadjusted		Adjusted[b]	
Factor[a]	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Sex				
Female	1.00	-	1.00	-
Male	0.295 (0.089-0.977)	0.046*	0.109 (0.016-0.737)	0.023*

n, number of participants; OR, odds ratio; CI, confidence interval
*P-value significant at 5%
a Only risk factor with significant association is shown
b Regression model was adjusted for age groups, sex, sickle genotypes, and BMI

significantly different ($\chi2 = 32.340$, df = 1, $p < 0.001$). The mean FBG level among the control group (4.95 mmol/L) was significantly higher than that of the SCD group (3.52 mmol/L, $p < 0.001$) (Table 3). Further, we observed that the two non-SCD participants who were diagnosed as diabetic were females of at least 40 years old and had underlying metabolic conditions (CKD and acute LVF) (Table 4).

Risk factors of prediabetes among SCD participants

Logistic regression analysis was used to analyse the factors associated with having prediabetes among the SCD participants. The complete regression model, containing independent variables such as age, sex, BMI, and sickle genotypes, was statistically significant ($\chi2 = 30.219$, df = 11, $p = 0.001$). The results of the Hosmer-and-Lemeshow test ($\chi2 = 6.778$, df = 8, $p = 0.561$) indicated that the regression model was a good fit for the data. In the adjusted model, we observed that SCD male participants were significantly less likely to have prediabetes than their female counterparts (OR = 0.109, 95% CI: 0.016 – 0.737, $p = 0.023$) (Table 5), signifying that sex is a significant predictor of prediabetes among SCD participants.

DISCUSSION

This hospital-based cross-sectional study aimed to determine whether SCD populations were less likely to develop type 2 DM than those without SCD. Overall, no SCD participant had diabetes. However, we observed that many of the SCD participants had prediabetes. Again, male SCD participants were less likely to have prediabetes than their female counterparts. In determining their DM status, no SCD participant had DM according to the WHO criteria; however, a 3.3% DM prevalence was observed among the

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non-SCD participants. To our knowledge, there is currently no known prevalence of DM among SCD populations in Ghana, yet there have been wide variations of DM prevalence among SCD patients across the globe. The no DM prevalence among the SCD participants in our study suggests that SCD may confer protection against DM development, similar to findings reported in the Middle East [13], India [15], the U.S. [14], and Nigeria [16]. Previous studies have suggested that a low prevalence of DM among SCD populations may be due to a lowered life expectancy of SCD individuals, reducing the risk for overt DM development over time [22]. Others have also suggested that SCD individuals who are underweight due to frequent illnesses have a lower predisposition to DM [23]. Nonetheless, concurring with Mohammed et al. [13], the relatively lowered obesity rates in the SCD population may contribute to this study's low prevalence of DM. Contrary to their non-SCD counterparts (48 years and 27.0 kg/m^2), the mean age and BMI among the SCD participants were 36 years and 22.9 kg/m^2, respectively. Age and BMI are major non-genetic risk factors for type 2 diabetes in SCD and the general population [24]. In this study, the average age of both groups did not fall within the high-risk age group of diabetes. This seems to suggest age did not adversely influence our findings. Lower BMI has been reported in SCD patients compared to the general population. This may account for the observed difference in BMI between the SCD patients and the controls. This is consistent with our findings. Even further, while various studies have reported SCD protection broadly against DM (including both T1DM and T2DM) [13,15], we expect protection, if any, to be more against T2DM as age and BMI are primarily implicated in T2DM than the other DM types [24].

However, similar to the findings by Zhang et al. [24], we observed that the percentage of overweight increased with age among the SCD participants. This finding suggests that any likely protection of SCD against DM may be lost with older age and increasing BMI. Perhaps as SCD patients live longer, this presumed protection may wane. It was, therefore, not surprising to observe that most of the SCD participants (52.8%, n = 28) had prediabetes, specifically, impaired glucose tolerance. The prediabetes prevalence among our SCD participants is higher than that reported by a similar study in Bahrain (11.0%), which had a high DM prevalence among SCD and non-SCD populations. Furthermore, our study revealed that the male participants with SCD were significantly less likely to have prediabetes compared to the female participants with SCD. Our finding is consistent with literature indicating a commoner occurrence of impaired glucose tolerance (IGT) among women [25]. This may explain why we observed a higher prevalence of prediabetes among our SCD population than that reported by Mohammed et al. [13]; our study reported a higher proportion of females (66.1%) than theirs (47.9%). IGT is an intermediate hyperglycaemic state resulting from peripheral insulin resistance and progressive dysfunction of the pancreatic beta cells, and importantly, it is a modifiable risk factor for DM [25,26]. The increase in the prevalence of overweight and obesity among older age groups of the SCD population in this study may be due to improved SCD management through the use of effective medications such as hydroxyurea, SCD prognostics [27], wide availability of high-calorie diets [24], targeted reduction in malaria infections, and dietary counselling at the Sickle Cell Clinic, KBTH, and this might have contributed to their increased risk of prediabetes in this study. Interestingly, studies in the U.S. suggest that the prevalence of type 2 DM among SCD individuals may be increasing over the years [7]. Therefore, we propose the need for continuous monitoring of the DM status of patients with SCD, considering a possible T2DM development over time.

Though we did not determine IGT status among the non-SCD group for a thorough comparison with their SCD counterparts, we cannot overlook the fact that significant advances in the management of SCD over the years may have increased the life expectancy of SCD individuals; hence, a few developing chronic metabolic conditions such as DM, dyslipidemia and hypertension over time [28]. We observed that the two non-SCD participants with higher-than-normal FBG levels presented to the hospital with underlying metabolic conditions. Specifically, while one presented with an acute LVF or heart failure, the other was a case of CKD. While we do not know whether the then undiagnosed DM in our participants led to these metabolic conditions or whether the heart and renal diseases caused their diabetic situation, we cannot overlook the relationship between diabetes and these two (heart and renal disease). Indeed, long-term complications of DM include the development of microvascular complications such as nephropathy [1], which appears to be more directly related to the hyperglycaemic state in DM [29]. Further, the macrovascular disease of DM, closely related to insulin resistance [29], includes coronary heart disease [6]. In this study, we did not determine non-DM factors that might have led to CKD and acute LVF in our diabetic participants. Thus, we can only speculate that these conditions led to diabetes in our non-SCD participants. In CKD, high urea levels impair insulin secretion, leading to secondary diabetes [30]. On the other hand, heart failure can lead to DM due to multifactorial processes such as reduced sensitivity to insulin and a hyperglycaemic state due to reduced physical activity or congestion and hypoperfusion of the pancreas due to blood volume and pressure output changes [31].

Our study was limited by a seemingly small sample size and cross-sectional study design, which prevented us from detecting the progression from borderline prediabetes to diabetes among our cohorts. However, our study used both FBG and RBG test parameters to accurately diagnose whether the SCD participants were diabetic or not, and the diabetic status of our non-SCD participants was confirmed by additional tests at the Central Laboratory (KBTH). Additionally, the use of a control group limits the effect of

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a seemingly small sample size. Despite not determining their likelihood for other cardiovascular diseases, as the first study to be conducted in Ghana (where both SCD and DM are highly prevalent), we show the low prevalence of DM among patients with SCD, adding to existing literature that suggests that SCD may be protective towards the development of DM.

Conclusion

There is a high prevalence of prediabetes among SCD participants owing to increasing BMI with age. However, the relatively low BMI among the SCD participants might have contributed to their low DM prevalence compared to the non-SCD participants. While sickle cell disease may protect against type 2 diabetes mellitus, the same cannot be said for prediabetes in this population. As the management of SCD improves and becomes more personalised, DM prevalence is expected to increase among patients with SCD. Therefore, SCD patients should be educated on DM to prepare them for its occurrence. Further, additional studies determining the risk of SCD patients for other cardiovascular diseases, such as hypertension and hyperlipidemia, need to be conducted as co-occurrence could lead to a devastating prognosis.

DECLARATIONS

Ethical consideration

Ethical clearance was obtained from the Ethics and Protocol Review Committee of the School of Biomedical and Allied Health Sciences of the University of Ghana [Protocol Identification Number: SBAHS – MLS./10571490/SA/2018-2019]. Administrative approval was sought from the Sickle Cell and Genetics Clinic and the Central Laboratory Department at KBTH. Informed consent was sought and obtained from all study participants.

Consent to publish

All authors agreed on the content of the final paper.

Funding

None

Competing Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Author contributions

DNA, EA and SA conceived the idea. SA and EA participated in the laboratory analysis, data analysis and interpretation. All authors were actively involved in the manuscript drafting and approved the final version of this article.

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Availability of data

Data is available upon request to the corresponding author.

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