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# Impact of sickle cell trait on glycated hemoglobin levels in Abidjan

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**Glycated hemoglobin (HbA1c) is a marker for glycemic control and diagnosis in diabetic patients. Sickle cell trait (SCT), characterized by the presence of hemoglobin S (HbS), may interfere with HbA1c formation. This study aimed to determine the impact of sickle cell trait (AS) on HbA1c levels. This cross-sectional analytical study included 94 patients and 76 control subjects over a 12-month period. HbA1c was measured using a chromatographic method, and additional biological parameters were assessed after obtaining informed consent. Statistical analyses included the Student's t-test, Spearman's rank correlation, Chi-square ($\chi^2$) test, and ANOVA, all applied at a 5% significance level. The mean age of the control and sickle cell trait groups was 35.17 ± 11.35 years and 34.22 ± 11.54 years, respectively. Most participants were female, with a sex ratio of 0.46 in controls and 0.56 in patients. The prevalence of anemia was significantly higher in the sickle cell trait group than in the controls (26.6 vs. 10.5%, P=0.008). HbA1c levels were lower in subjects with sickle cell trait (AS) (4.99 ± 0.65) than in controls (5.56 ± 0.30) among those with normal blood glucose, independent of BMI and hemoglobin levels. Similarly, in individuals with moderate hyperglycemia, HbA1c values followed a similar trend (5.7 ± 0.67 in AA vs. 5.68 ± 0.59 in AS), showing a significant difference (p< 0.0001). HbA1c may underestimate average blood glucose levels in heterozygous Black patients with sickle cell trait, suggesting the need for alternative tests, such as fructosamine levels.**

**Key words:** Abidjan, glycated hemoglobin (HbA1c), sickle cell disease.

## INTRODUCTION

Glycated hemoglobin (HbA1c) is a highly reliable marker for monitoring and diagnosing diabetes mellitus (Gariani et al., 2009). Although easy to measure and interpret, it may be influenced by several factors, including hemoglobinopathies (International Diabetes Federation, 2015; Sumner et al., 2015). This difficulty in using HbA1c in the presence of hemoglobinopathy has been confirmed by several studies (Little and Roberts, 2009; American Diabetes Association, 2014). Sickle cell disease is the most common hemoglobinopathy in the world, according

to the World Health Organization (2006). It is prevalent in sub-Saharan Africa, where the heterozygous form (sickle cell trait) reaches 15 to 30% of the population (World Health Organization, 2006). In Côte d'Ivoire, its prevalence is estimated to be between 12 and 14% of the population (Kakou-Danho et al., 2020). According to Behan et al. (2015), the presence of hemoglobin S leads to a reduction in hemoglobin glycation, which may, in turn, influence the interpretation of HbA1c. Studies carried out in the United States have suggested different levels of HbA1c in subjects with sickle cell trait (Lara, 2017). However, we have previously studied the correlation between glycated hemoglobin and glycemia in diabetes mellitus in two large communities in Abidjan (Monde et al., 2020). Likewise, Bédié et al. (2023) also studied the variation in glycated hemoglobin in diabetic ketoacidosis in intensive care. Moreover, few studies have been carried out on variations in glycated hemoglobin in sickle cell patients. The aim of this study was, therefore, to determine the impact of sickle cell trait on glycated hemoglobin in Abidjan.

## METHODOLOGY

### Patients and method

This was a cross-sectional analytical study of 170 non-diabetic subjects, calculated according to the Schwartz formula (Schwartz, 1996). The sample was divided into 94 patients with sickle cell trait (HbAS) and 76 controls without hemoglobinopathy (normal electrophoretic profile of hemoglobin or HbAA). The study lasted 12 months. Patients and controls were recruited from the hematology departments of the Treichville and Cocody university hospitals. Subjects between 15 and 80 years of age who had agreed to have their blood sample taken and had given informed consent (or through a parent) were selected for glycemia, glycated hemoglobin, and hemoglobin electrophoresis and hemoglobin determination. Subjects with other hemoglobinopathies, renal failure, hemoglobin levels ≤ 10 g/dl (Hoelzel et al., 2004), hyperbilirubinemia, hypertriglyceridemia, as well as alcoholics and pregnant women, were not selected.

### Sampling and analysis

Venous blood samples were taken from the elbow of subjects who had fasted for 12 h the previous day. The blood was collected in three tubes: a grey tube containing potassium oxalate (anticoagulant) and sodium fluoride (anti-glycolytic), a purple tube containing ethylene diamine tetra-acetic acid (EDTA) for hemoglobin electrophoresis and determination of hemoglobin levels, and a red tube for urea and creatinine determination.

### Biological analyses

Hemoglobin electrophoresis was performed on an agarose gel using the Hydrasys 2 Scan focusing system by Sebia (2022). Blood glucose levels were determined using the classical glucose oxidase peroxidase (GOD-POD) enzymatic method (Yapo et al., 1990), with the Cobas C311 (2022) by Roche Diagnostic (multiparameter automated system). The reference values (in g/L) ranged from 0.60 to 1.10 for normal glycemia and above 1.10 but below 1.25 for moderate fasting hyperglycemia (Yapo et al., 1990). HbA1c was measured using a boronate fluorescence quenching chromatography (BQFT) method with a Quo-labA1C test kit 310-3051.0055 analyzer. The result was presented as a percentage, with a reference range of 4 to 5.7% (Hirst et al., 2017). The hemogram was performed to determine hemoglobin levels using the principle of impedancemetry, analyzed by the URIT-3000Plus automatic analyzer. Anemia was defined as an Hb level (g/dl) of less than 11 in women and less than 12 in men (World Health Organization, 2024). This study was approved by the University Hospital Center of Treichville Scientific Committee (Approval number: 30/CHU-T/DG/DMS/050221). The Student's t-test, Spearman's rank correlation, ANOVA, and Chi-square test were used for statistical analysis of the data, at the 5% significance level.

## RESULTS

The mean ages of the control and patient groups were 35.17 ± 11.35 and 34.22 ± 11.54 years, respectively. Females predominated, with a sex ratio of 0.46 in controls and 0.56 in heterozygous sickle cell patients. Moderate fasting hyperglycemia was observed in 8.5% of sickle cell trait carriers and in 2.6% of controls.

Table 1 shows the significant variations in HbA1c levels as a function of hemoglobin electrophoretic profile, demonstrating in particular that heterozygous sickle cell patients (Hb AS) have significantly lower HbA1c levels than control subjects with normal hemoglobin (Hb AA), with a highly significant p-value of < 0.0001.

Table 2 shows the distribution of hemoglobin levels according to the electrophoretic profile. For controls and patients with sickle cell trait, the proportion of anemia was significantly higher in HbAS patients (26.6%) than in AA controls (10.5%) (P = 0.008). However, the majority of subjects in both groups had normal hemoglobin levels, although the proportion was slightly lower in the patient group (73.4%) than in the controls (89.5%).

Table 3 shows the distribution of HbA1c levels according to electrophoretic profile and hemoglobin level. For subjects with an Hb AA profile (control), those with anemia had a mean HbA1c level of 5.51 ± 0.35, while those with normal hemoglobin levels had a slightly higher HbA1c level of 5.6 ± 0.41, with a statistically significant difference (p<0.0001). On the other hand, in sickle cell trait carriers (Hb AS), anemic patients showed a mean HbA1c level of 5.02 ± 0.64, while those with a normal profile showed a slightly higher level, at 5.04 ± 0.7.

Table 4 shows the distribution of HbA1c levels

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**Table 1.** Variation in glycated hemoglobin (HbA1c) levels according to electrophoretic profile.

| Variable | Hb 1Ac (%) | |
|---|---|---|
| | Mean ± SD | P |
| Controls (Hb AA)* | 5.57 ± 0.39 | 0.0001 |
| Patients (Hb AS)* | 5.03 ± 0.67 | |

HbAA: Haemoglobin A1A2 normal electrophoretic profile of haemoglobin; HbAS: hemoglobin AS or sickle cell trait; HbA1c: glycated hemoglobin.

**Table 2.** Distribution of hemoglobin levels according to electrophoretic profile.

| Variable | | Electrophoretic profile of hemoglobin | | P |
|---|---|---|---|---|
| | | Hb AA | Hb AS | |
| Hemoglobin level | Anemia* | 8<br>10.5% | 25<br>26.6% | 0.008 |
| | Normal | 68<br>89.5% | 69<br>73.4% | |

HbAA: Haemoglobin A1A2 normal electrophoretic profile of haemoglobin; HbAS: Hemoglobin AS or sickle cell trait. HbA1c: Glycated hemoglobin; Anemia was defined as a Hemoglobin level (g/dl) of less than 11 in women (normal value: 12-14 g/dl) and less than 12 in men (normal value: 13-15 g/dl).
Source: World Health Organization (2024).

**Table 3.** Distribution of HbA1c levels according to electrophoretic profile and haemoglobin level.

| Hemoglobin profile | Hemoglobin level | HbA1c (%) | |
|---|---|---|---|
| | | Mean ± SD | P |
| Control (HbAA); n=76 | Anemia* (n=8) | 5.51 ± 0.35 | 0.0001 |
| | Normal (n= 68) | 5.6 ± 0.41 | |
| Patients (HbAS)*; n=94 | Anemia (n=25) | 5.02 ± 0.64 | |
| | Normal(n=69) | 5.04 ± 0.7 | |

HbAA: Haemoglobin A1A2 normal electrophoretic profile of haemoglobin; HbAS: hemoglobin AS or sickle cell trait; HbA1c: glycated hemoglobin.

**Table 4.** Distribution of HbA1c levels according to hemoglobin electrophoretic profile and blood glucose.

| Hemoglobin profile | Basal blood glucose (g/l) | HbA1c (%) | |
|---|---|---|---|
| | | Mean ± SD | P |
| Controls (Hb AA)* n=76 | Normal blood glucose [0.60 - 1.10] 74 (97%) | 5.56 ± 0.30 | 0.0001 |
| | Moderate fasting hyperglycemia [1.10 -1.25] 2 (3%) | 5.7 ± 0.67 | |
| Patients (Hb AS)* n=94 | Normal blood glucose [0.60- 1.10] 8 (9%) | 4.99 ± 0.65 | |
| | Moderate fasting hyperglycemia [1.10 -1.25] 86 (91%) | 5.68 ± 0.59 | |

HbAA: Haemoglobin A1A2 normal electrophoretic profile of haemoglobin; HbAS: hemoglobin AS or sickle cell trait; HbA1c: glycated hemoglobin.

according to hemoglobin electrophoretic profile and blood glucose level. In the normal blood glucose group (0.60 - 1.10 g/L), controls had a mean HbA1c of 5.56 ± 0.30%, whereas sickle cell trait carriers had a significantly lower

mean HbA1c of 4.99 ± 0.65% (p = 0.0001). Similarly, in the group with moderate hyperglycemia (1.10 - 1.25 g/L), the mean HbA1c of the controls was 5.7 ± 0.67%, compared with 5.68 ± 0.59% for the patients. Although the difference was less marked than in the normal glycemia group, it remained statistically significant.

## DISCUSSION

### Age and sex

This study serves as a landmark analysis of HbA1c levels in patients with sickle cell disease in Abidjan, focusing on a young population. The mean age of controls and sickle cell trait carriers was 35.17 ± 11.35 years and 34.22 ± 11.54 years, respectively. The majority of participants were female, with a sex ratio of 0.46 in controls and 0.56 in patients. There was no statistically significant difference in age or sex between controls and cases. This distribution parallels that found by Tavares et al. (2017), who reported a population with 54% women and an average age of 34.6 ± 21 years. In contrast, Bleyer et al. (2010), in their study on the impact of sickle cell disease on glycated hemoglobin in diabetic patients at North Carolina Baptist Hospital, observed an average age of 57.3 ± 13.3 and 54.9 ± 13.5 years in subjects with and without sickle cell trait. This discrepancy may be due to the fact that Bleyer's study population consisted of type 2 diabetics, a form of diabetes typically manifesting around middle age, often after 40 years.

### Biological parameters

Most control subjects did not present with glucose intolerance. Therefore, the risk of falsely elevated HbA1c in controls was likely reduced. All patients had normal creatinine levels, and most had normal urea levels, which minimizes the potential influence of hyperuremia and/or hypercreatinemia on HbA1c measurements. This finding is consistent with other studies on HbA1c measurement in the United States and Brazil (Lacy et al., 2017; Tavares et al., 2017). Moderate anemia was observed in both groups (subjects with Hb ≤ 9 g/dL were excluded), and the proportion of anemic subjects was significantly higher in the sickle cell group (26.6%). This could be explained by the presence of hemoglobin S, which, along with intrinsic factors, reduces cell deformability, leading to mild hemolysis (Monique, 2022; Tavares et al., 2017). Sickle cell trait carriers had a significantly lower mean HbA1c level (5.03 ± 0.67) than control subjects (5.57 ± 0.39) (p < 0.0001). A similar finding was noted in Lacy et al. (2017) retrospective cohort study involving 7,938 participants from two community-based cohorts (CARDIA study), which demonstrated lower HbA1c levels in subjects with sickle cell trait at any level of fasting or postprandial glucose compared to normals. However, the difference in HbA1c levels in this study (0.5%) was greater than Lacy's finding (0.3%), likely because the subjects were younger and lacked major risk factors, reducing their likelihood of elevated HbA1c.

These results, however, differ from those of Bleyer et al. (2010) and Tavares et al. (2017), who used high-performance liquid chromatography (HPLC) and found no HbA1c difference between AS heterozygous patients and controls. These authors attributed HbA1c variability to analytical method differences, suggesting that methods free from analytical interference be used to reliably interpret HbA1c in patients with hemoglobin variants, specifically HbS (NSG guidelines) (Lenters-Westra and English, 2018). The discrepancies between our findings and previous studies may be due to different analytical techniques. However, boronate affinity chromatography, the method used in this study, is NSG-standardized (Lenters-Westra and English, 2018) and offers good reliability, with a specificity of 0.998 compared to IFCC standards, showing comparable performance to HPLC (Hoelzel et al., 2004). Hirst et al. (2017) also found that Afinion2 and Quo-Lab (automated HbA1c assays) exhibited excellent analytical performance.

### HbA1c variability with sickle cell trait, hemoglobin level, and blood glucose

Regardless of hemoglobin or blood glucose levels, HbA1c was significantly lower in sickle cell trait carriers than in normal subjects, in line with Lacy et al. (2017), who found significantly lower HbA1c levels in sickle cell trait carriers at the same fasting or postprandial glucose levels, indicating the difference was not due to analytical interference (Lacy et al., 2017). This suggests that HbS does not affect the accuracy of methods such as boronate affinity and HPLC (Little et al., 2014). In addition to analytical interferences and blood glucose, some studies suggest factors like the glycation rate and glycation sites on hemoglobin globin chains may affect HbA1c measurements (Wang et al., 2014). For instance, Kabytaev et al. (2016) reported that HbS chains have a higher glycation rate than HbA chains (9.37 ± 3.28 vs. 7.39 ± 2.42), potentially explaining the lower HbA1c levels in sickle cell trait carriers. However, unlike these previous studies that analyzed Hb AS and Hb AC participants together, this study focuses solely on the sickle cell trait.

### Clinical implications

The results of this study have important clinical implications for the management of diabetes in patients with sickle cell trait. Artificially lower HbA1c levels due to the presence of hemoglobin S may lead to an

underestimation of mean glucose levels in Black patients with sickle cell trait, as highlighted by Lacy et al. (2017), who postulated that individuals with sickle cell trait have lower HbA1c levels across a range of glycemic states. This discrepancy could hinder adequate glycemic control and increase the risk of long-term complications associated with diabetes, such as cardiovascular disease, neuropathy, and retinopathy (Bleyer et al., 2010).

In addition, Tavares et al. (2017) noted that exclusive reliance on HbA1c for diabetes management in populations with hemoglobinopathies might lead to misdiagnosis and inappropriate treatment strategies. The potentially higher prevalence of anemia in patients with sickle cell trait (26.6% in this study) may further complicate the interpretation of HbA1c levels, as anemia may influence glycation levels (Monique, 2022). Therefore, clinicians need to be cautious when applying standard HbA1c cut-offs to these patients. To address these challenges, it is important that healthcare providers incorporate other markers of glycemic control into routine assessments. Continuous glucose and fructosamine monitoring systems could provide more reliable information about a patient's glycemic status (Wang et al., 2014; Little et al., 2015). These methods allow real-time monitoring of blood glucose levels, improving diabetes management and potentially reducing the risk of diabetes-related complications in this vulnerable population. In addition, raising awareness among healthcare professionals and patients of the limitations of HbA1c in the context of hemoglobinopathies is essential to improve diabetes management. This awareness can enable patients with sickle cell trait to proactively manage their diabetes.

## Conclusion

This study demonstrates that the presence of hemoglobin S may artificially lower HbA1c levels, potentially underestimating the average past glucose levels in Black patients with sickle cell trait. Clinically, this underestimation could lead to less rigorous glycemic control and an increased risk of complications, raising diabetes-related morbidity and mortality in these patients. This underscores the need for additional, more precise tests such as fructosamine.

## STUDY LIMITATIONS

The limitations of this study include the small sample size and young population profile, which limit the generalizability of the results. The use of a single method to measure HbA1c (boronate affinity chromatography) could introduce analytical bias. Additionally, the cross-sectional design prevents tracking the evolution of HbA1c levels over time.

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## CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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