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# High prevalence of individuals with low concentration of fetal hemoglobin in F-cells in sickle cell anemia in Tanzania

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## To the Editor

Sickle cell anemia (SCA) has a high prevalence in Sub-Saharan Africa, with up to 11,000 births of SCA individuals occurring in Tanzania annually [1]. Fetal hemoglobin (HbF) is one of the most important factors influencing the disease severity. In adults, HbF expression is restricted to a subset of red blood cells (RBCs) called F-cells. Although high HbF is associated with mild disease, there are reports of severe disease occurring in individuals with high HbF levels. One of the factors that accounts for this is thought to be the distribution of HbF within F-cells [2] rather than the overall percentage of HbF. This is because the uneven distribution of HbF in F-cells may result in inadequate number of F-cells with sufficient concentrations of HbF to inhibit sickle hemoglobin (HbS) polymerization [2,3]. It is therefore hypothesized that a more important measure of disease modification is the concentration of HbF per F-cell (HbF/F-cell) rather than the overall percentage of HbF and F-cells. The level of HbF/F-cell of 10 pg has been suggested as a cut-off, with levels equal or above this associated with milder forms of disease [2]. To date, there is no information on

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**Authors Contributions**

F.U. designed the research, collected data, participated in data analysis, and wrote the manuscript; S.E.C., M.L., and S.N.M. reviewed the results, contributed to data analysis, and commented on draft manuscripts; B.P.M. analyzed the data, interpreted results, and participated in writing the manuscript; J.M. designed the research, contributed to data analysis, and participated in writing the manuscripts. All authors have read and approved the final manuscript

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the distribution of F-cells and HbF/F-cell in SCA individuals in Tanzania. Therefore, we conducted a study to describe the epidemiology of F-cells and calculated mean HbF/F-cell for individuals and described associations with selected hematological parameters of individuals with SCA.

We studied 107 SCA, median age (19 [IQR: 15–23]) and 32 non-SCA (30 [IQR: 26– 35]) individuals. HbF quantification was determined by high performance liquid chromatography (HPLC) (Bio-Rad Variant I, USA) using the Beta-Thalassemia short program and reported as a percentage of total hemoglobin. F-cell quantification was performed using flow cytometry (FACSCalibur-Beckton Dickinson, USA). Compared to non-SCA, SCA individuals had significantly higher HbF (median 8.9 [IQR: 6.9–11.6] vs. 0.4 [IQR: 0.2–1.1], $P < 0.001$) and F-cells (38.8 [IQR: 30.3–47.8] vs. 4.6 [IQR: 2.9–6.9], $P < 0.001$). F-cells were correlated with HbF levels in SCA ($\rho = 0.87$, 95% CI: 0.82–0.91, $P < 0.001$) more so in males than females ($P < 0.001$). F-cells were independently associated with mean cell hemoglobin (MCH) and hemoglobin, where a unit increase in F-cells raised MCH by 1.64 pg ($P < 0.001$) and hemoglobin by 1.80 g/dL ($P = 0.039$). F-cells were higher in females [5.69% (95% CI: 0.35–11.03, $P = 0.039$)] than in males.

About 96.3% of SCA individuals had low HbF/F-cell (HbF/F-cell <10 pg). The median HbF/F-cell for those with low levels was 6.47 (IQR: 5.65–7.02), compared to 14.3 (IQR: 11.6–22.44). Hemoglobin was significantly lower in individuals with low HbF/F-cell (median 7.9 g/dL (IQR: 3.5–11.4), vs. 10.0 g/dL (IQR: 8.1–12.1), $P = 0.02$), Table I.

This is the first study in Tanzania to describe the spectrum of F-cells and HbF/F-cells in SCA and evaluate its correlatIon with hematological factors.

This study reports a wide variation in the level of F-cells in SCA population, which as expected is higher compared to those without SCA. When compared to other SCA populations, the F-cell proportion is lower than that reported in African Americans (2–80%) [4] but higher than that reported in Democratic Republic of Congo (DRC), where the median was 2.19% (IQR 0.0–30.3) [5]. This is an important finding as the assumption has been that SCA populations which are in close geographical location such as Tanzania and DRC would have similarity in disease phenotype. One important modifier of this finding is thought to be the genetic factors.

In this study, we also report a wider variation and higher level of F-cells in females than in males. However, the correlation between HbF and F-cells in male was stronger compared to that of females. These findings suggest that there may be disease modifiers that are linked to the X-chromosome [6].

This study has shown that only 3.7% of SCA patients had average amount of HbF/F-cell concentration ≥ 10 pg. The four SCA patients with high HbF/F-cell concentration were of particular interest because their hematological parameters differed considerably from the rest of the SCA study participants. These findings coincide with the postulation by Steinberg et al. [2] that those SCA individuals with high levels of HbF/F-cell would most likely have less severe disease. However, a larger study is needed to evaluate the effect of high HbF/F-cell concentration (≥10 pg) on disease-outcomes. The independent association between HbF/F-

cell and hemoglobin and RBCs from this study warrants further investigation in other settings to validate these findings.

This study was limited by sample size (only 139 SCA individuals); this may be one of the factors that contributed to lack of sufficient power to detect the association between hematological variables and HbF/F-cells. Furthermore, this study employed an indirect method of evaluating the amount of HbF/F-cell by calculating the product of MCH and HbF divided by F-cell levels. This assumes that each F-cell contains the same amount of HbF. Therefore, we recommend future study using direct methods to obtain accurate measurements of HbF/F-cell.

In summary, the findings from this study include the description of the spectrum of concentration of HbF/F cell in SCA in Tanzania. About 96.3% of SCA individuals had low level of HbF/F-cell and that hemoglobin was independently associated with HbF/F-cell. We recommend further studies to explore the gender-based differences in correlation between HbF and F-cells as well as a larger study to evaluate the effect of high HbF/F-cell concentration (≥10 pg) on disease-outcomes and its role as a predictor of the likelihood of severe disease in SCA.

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## Table I

Comparison of Selected Haematological Parameters in Individuals With SCA With Low and High pg HbF/F-Cell ($n$ = 107)

| | High (HbF/F-cell ≥ 10 pg), median (min, max) ($n$ = 4) | Low (HbF/F-cell < 10 pg), median (min, max) ($n$ = 103) | *P* |
|---|---|---|---|
| HbF, % | 12.55 (5.1–19.1) | 8.9 (0.5–19.8) | 0.221 |
| F-cell, % | 16.9 (8.32–50.81) | 38.53 (5.19–77.37) | 0.091 |
| HbF/F-cell, pg | 14.3 (11.6–22.44) | 6.47 (5.65–7.02) | <0.001 |
| MCH, pg | 28.1 (21.2–31.3) | 27.9 (19.1–35) | 0.889 |
| MCHC, g/Dl | 34.7 (33.5–35.7) | 34.3 (30.3–37.6) | 0.705 |
| Hemoglobin, g/dL | 10 (8.1–12.1) | 7.9 (3.5–11.4) | 0.020 |
| RBC, $\times 10^6/\mu L$ | 3.66 (2.79–4.99) | 2.88 (1.41–4.82) | 0.053 |
| MCV, fL | 82.2 (61.5–87.8) | 81.3 (55.6–103.2) | 0.928 |
| Reticulocytes, % | 7.795 (3.92–8.46) | 9.31 (2.52–25.31) | 0.079 |
| WBC, $\times 10^3/\mu L$ | 8.62 (7.14–11.34) | 11.13 (5.39–20.57) | 0.073 |
| Platelets, $\times 10^3/\mu L$ | 418 (208–553) | 382 (78–1061) | 0.799 |

HbF indicates fetal hemoglobin; RBC, red blood cells; MCV, mean cell volume; MCH, mean cell hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; WBC, white blood cells.