Some clinical and haematological effects of G6PD deficiency among individuals with sickle cell disorders in Kumasi, Ghana

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Abstract

Background: As to whether the presence of Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency ameliorates or worsens sickle cell disease (SCD) is still not clear. Aim and Objectives: This study was therefore aimed at investigating whether the presence of G6PD deficiency among SCD subjects (HbSS and HbSC) would have any significant impact on the severity of crisis and haematological indices. Subjects and Methods: A structured questionnaire was used to obtain information on the clinical state of the subjects. The qualitative methaemoglobin reduction method was used to screen for G6PD deficiency, followed by the measurement of some haematological indices. Results: The data showed that the different genotypes of SCD subjects had similar clinical features, voiding of darkened urine, frequency of crises and blood transfusion, p > 0.05. Statistically, the presence of G6PD-deficiency among the HbSS and HbSC patients had no significant impact on their haematological indices (p > 0.05), except the glutathione stability, (p < 0.05). However, a statistically significant difference occurred between the haematological indices of the SS and SC patients (p < 0.05), with improved values in the SC subjects. The presence of the G6PD in the SCD population was quite low (6.49 %) compared with other similar studies (8 - 30 %) among the general population. These findings strongly support some reports that SCD subjects with G6PD-deficiency do not show a compromised function due to the combined defects.

Keywords: Clinical, Haematological, G6PD deficiency, Sickle cell disease, Haemoglobinopathy.

INTRODUCTION

Sickle cell disorders are the name for several related but different inherited disorders associated with the sickling of red cells leading to haemolytic anaemia. The most common types of the disorders include SCD (HbSS), haemoglobin SC disease and sickle beta-thalassaemia. The different kinds of the disease and its traits are mainly found in people whose families come from Africa, the Caribbean, the Eastern Mediterranean, Middle East and Asia. [1] Approximately, 3 percent of children born in West Africa suffer from sickle cell disorders (Hb SS or Hb SC), and there are probably 1,000,000 sufferers in tropical Africa; so the problem is very enormous. [2]

The SCD is usually the most severe type of the disorders where the majority of the haemoglobin inherited is sickle. Sickle red cells are easily damaged and have a lifespan of only about 20 days, compared with the 120 days of normal red cells. [3] The sickling is precipitated by infection, dehydration, cold, acidosis or hypoxia. [4] In haemoglobin C trait, haemoglobin C forms about 30-40 per cent of the haemoglobin and the condition is not associated with clinical abnormalities in heterozygous HbAC. [5] Homozygous haemoglobin-C disease (HbCC) has been characterized as a mild haemolytic anaemia with splenomegaly, but double heterozygosity of HbA and HbC frequently occurs and death from HbSC disease is not uncommon, especially in pregnancy. [6] The highest incidence of SC genotype in Ghana is in the Northern part of the country and the neighbouring Burkina Faso (18 per cent); the incidence falls in the south to 12 per cent. [2]

Like the sickle cell disorders, G6PD deficiency is a genetic disorder which primarily causes the reduction of G6PD activity in the red cells with resultant haemolytic crises when exposed to a potential oxidant. Males are most likely affected by G6PD deficiency, but chance inactivation of the normal X-chromosome has led to equally severe G6PD deficiency in females. [7] The deficiency is the most common X-linked genetically
determined enzyme abnormality affecting nearly all populations of the world, with high frequencies in areas where malaria is, or was, endemic.\(^{(10)}\) The highest prevalence rates (with gene frequencies from 5-25%) of the deficiency are found in tropical Africa, the Middle East, tropical and subtropical Asia, some areas of the Mediterranean, and Papua New Guinea.\(^{(9)}\) Over 400 G6PD variants have been identified and many of them have no haematological consequences.\(^{(10)}\) Some of these may have almost complete loss of activity, others have some varying degrees of diminished activity, and others may have increased activity.\(^{(11)}\) The Mediterranean and the African (A) variants are by far the most clinically significant. Enzyme activity is scarcely detectable in the Mediterranean type but close to normal in the African variant.\(^{(12, 13)}\)

In the G6PD deficiency, the red cells capacity to protect itself from oxidative stress is reduced. This is because the affected individuals produce lower than normal amounts of NADPH, which results in an impaired capacity to generate reduced glutathione (GSH). The GSH keeps sulphhydryl groups on haemoglobin and other proteins in a reduced state by preventing the formation of disulfide bonds.\(^{(1)}\) This function is critically important to prevent haemoglobin precipitation and haemolysis. The failure of this mechanism may result in rigidity due to cross-linking of spectrin that decreases membrane flexibility, causing 'leakiness' of the red cell membrane.\(^{(14)}\) Oxidative damage can also affect the haem portion of haemoglobin, creating methaemoglobin (MetHb) which is incapable of carrying oxygen. It is formed by oxidation of the iron in haemoglobin from a ferrous (Fe\(^{2+}\)) to a ferric (Fe\(^{3+}\)) state in methaemoglobin.\(^{(15)}\) So the oxidation of the haemoglobin molecule, producing methaemoglobin and precipitation of globin chains as Heinz bodies may be localized on the inside of the membrane. Consequently, these bodies are removed from circulating red cells by the spleen.\(^{(15)}\)

Based on the above information, it can be hypothesized that the presence of G6PD deficiency could increase the severity of crises in individuals with sickle cell disorders as reported in other studies.\(^{(16)}\) Some studies in Burkina Faso,\(^{(17)}\) in Senegal,\(^{(18)}\) in Turkey,\(^{(19)}\) in Ghana\(^{(20)}\) and in Kenya\(^{(21)}\) had confirmed the association of high prevalence of G6PD deficiency among SCD patients as compared to the general population. However, studies carried out among the Saudi population\(^{(22)}\) had shown that there is no such relationship. There is therefore the need for further studies to include other parameters not used by the previous investigators, like glutathione levels and some clinical features so as to ascertain the likelihood of G6PD deficiency among individuals with sickle cell disorders impacting significantly on the clinical and haematological indicators of these patients.

**SUBJECTS AND METHODS**

The study involved 310 SCD subjects, over a period of 18 months (October, 2011- March 2013). The subjects were attending the Sickle Cell Clinic at Komfo Anokye Teaching Hospital (KATH), Kumasi-Ghana, and were between the ages of two and eighteen years. Ethical approval was granted by the Committee for Human Research, Publication and Ethics at KATH. Informed consent was also solicited from the patients or their caregivers. The patients were in steady state with no history of blood transfusion in the last three months. A questionnaire was administered to each patient or caregiver. The response of each participant was recorded by the interviewer. A section of the questionnaire which sought information on clinical conditions of the patients was handled by the clinician.

Venous blood samples were taken from the patients into EDTA containers for later analysis. The haematological indices (Haemoglobin-Hb, packed cell volume-PCV, red blood cell counts -RBC, Erythrocyte Sedimentation Rate-ESR, Reticulocyte Counts-RC and G6PD deficiency, using the methaemoglobin reduction method were determined in accordance with the standard methods, described by Cheesbrough (2000).\(^{(22)}\) The erythrocyte glutathione concentration (Glutathione level-Gl and Glutathione stability-GS) was also measured using the 5, 5'-Dithiobis 2-nitrobenzoic acid (DTNB) test as stipulated by other studies.\(^{(23)}\)

**RESULTS**

**Questionnaire response**

Of the 310 SCD subjects interviewed, 56.13% were males and 43.87% were females with an overall average age of 10.4 ± 5.0 years (±S.D.). Two hundred and six (206) patients were HbSS (66.5%) whilst the rest were HbSC (33.5%). From Table 1, the passing of darkened urine among the different genotypes; SS normal, SS deficient in G6PD activity; SC normal and SC deficient in G6PD activity, in the past was approximately 50.0% for each different group, whereas those experiencing darkened urine at the time of the study were between 0.0 -23.0%.

The different genotypes of SCD subjects had similar frequencies (p-value > 0.05) of crises, frequency of transfusion and other clinical features as indicated in Tables 2, 3 and 4. Approximately, one out of every three subjects in the different groups had experienced at least three crises for the pass one year. This ratio also holds for the number of persons who had been transfused before. About 55% of the subjects had none of the common clinical features associated with the SCD.

**Glucose-6-Phosphate Dehydrogenase activity, Glutathione level and Haematological indices**

Out of the total number of patients involved in the study, 89.35% were G6PD-normal, 4.20% G6PD-carriers and 6.45% were G6PD-deficient. The prevalence of the enzyme deficiency was very low in the females (0.97%) but higher in the males (5.48%). Statistically, there was no significant difference (p > 0.05) in the determined haematological indices (Table 5) between the patients who showed the presence and absence of G6PD activity, except the glutathione stability, (p< 0.05). In addition, there was a statistically significant difference (p < 0.05) between the SS and SC patients.

**DISCUSSION**

The prevalence (6.45%) of the G6PD deficiency among the SCD population was lower than what had been estimated in previous studies for the general Ghanaian populace. These estimates include 8.4%,\(^{(23)}\) 12.2%\(^{(24)}\) and 26.5%\(^{(25)}\) with the following respective assay methods; DNA analysis, NADPH fluorescent spot and methylene blue reduction test. These results were also contrary to other studies in Senegal which revealed that the prevalence of G6PD deficiency was higher in SCD patients (27.0 %) and that of the control population (7.8%). Additionally, G6PD deficiency was found in 7.0 % of sickle-cell anaemic patients;\(^{(26)}\) however, other studies did not confirm this association.\(^{(27, 28)}\) These observations could be due to differences in assessment methods (DNA analysis detecting the presence of the mutant allele and NADPH fluorescent spot being unreliable for distinguishing between both heterozygous females and homozygous males) for the detection of G6PD deficiency.\(^{(9, 29)}\) Even though a similar assay (methylene blue reduction test was used, our study showed a comparatively lower value (6.45%). It has been reported that within a given country there can be tremendous variation in the prevalence of G6PD deficiency.\(^{(30)}\) In addition, if the heterozygous females (4.2%) and the homozygous males (6.5 %) are put together, then the total estimate obtained in this study would be 10.7 %.
Table 1: Presence of darkened urine among the SCD subjects

<table>
<thead>
<tr>
<th>Past and present urine observation</th>
<th>Sickle Cell subjects</th>
<th>Past-Yes</th>
<th>Present-Yes</th>
<th>p-value</th>
<th>Past-No</th>
<th>Present-No</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS with normal G6PD activity n = 197 (%)</td>
<td>SS with deficient G6PD activity n = 9 (%)</td>
<td>92 (46.7)</td>
<td>14 (7.1)</td>
<td>0.585</td>
<td>105 (53.3)</td>
<td>183 (92.9)</td>
<td>0.148</td>
</tr>
<tr>
<td>SC with normal G6PD activity n = 93 (%)</td>
<td>SC with deficient G6PD activity n = 11 (%)</td>
<td>4 (44.4)</td>
<td>2 (22.2)</td>
<td>6 (54.5)</td>
<td>5 (55.6)</td>
<td>7 (77.8)</td>
<td>0.446</td>
</tr>
</tbody>
</table>

The p-value represents collective comparison of the different observations made between the various genotypes.

Table 2: Frequency of crisis among the SCD subjects for the previous year

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Sickle Cell subjects</th>
<th>SS with normal G6PD activity n = 197 (%)</th>
<th>SS with deficient G6PD activity n = 9 (%)</th>
<th>SC with normal G6PD activity n = 93 (%)</th>
<th>SC with deficient G6PD activity n = 11 (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td></td>
<td>80 (40.6)</td>
<td>3 (33.3)</td>
<td>43 (46.2)</td>
<td>3 (27.3)</td>
<td>0.665</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td></td>
<td>2 (23.4)</td>
<td>1 (11.1)</td>
<td>3 (3.2)</td>
<td>0 (0.0)</td>
<td>0.505</td>
</tr>
<tr>
<td>Anaemia</td>
<td></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (2.2)</td>
<td>1 (9.1)</td>
<td>0.324</td>
</tr>
<tr>
<td>Acute chest Syndrome</td>
<td></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Hand-and Foot Syndrome</td>
<td></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (9.1)</td>
<td>0.324</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td>115 (58.4)</td>
<td>5 (55.6)</td>
<td>45 (48.4)</td>
<td>6 (54.5)</td>
<td>0.946</td>
</tr>
</tbody>
</table>

The p-values represent collective comparison of the various frequencies between the different subject genotypes.

Table 3: Clinical features exhibited by the subjects

<table>
<thead>
<tr>
<th>Frequency of crisis</th>
<th>Sickle Cell subjects</th>
<th>SS with normal G6PD activity n = 197 (%)</th>
<th>SS with deficient G6PD activity n = 9 (%)</th>
<th>SC with normal G6PD activity n = 93 (%)</th>
<th>SC with deficient G6PD activity n = 11 (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td>133 (67.5)</td>
<td>6 (66.7)</td>
<td>64 (68.8)</td>
<td>8 (72.7)</td>
<td>0.717</td>
</tr>
<tr>
<td>Once</td>
<td></td>
<td>42 (21.3)</td>
<td>3 (33.3)</td>
<td>19 (20.4)</td>
<td>2 (18.2)</td>
<td>0.865</td>
</tr>
<tr>
<td>Twice</td>
<td></td>
<td>9 (4.9)</td>
<td>0 (0.0)</td>
<td>2 (2.2)</td>
<td>0 (0.0)</td>
<td>0.865</td>
</tr>
<tr>
<td>Thrice</td>
<td></td>
<td>5 (11.2)</td>
<td>0 (0.0)</td>
<td>4 (4.3)</td>
<td>1 (9.1)</td>
<td>0.865</td>
</tr>
<tr>
<td>&gt; Three times</td>
<td></td>
<td>8 (4.0)</td>
<td>0 (0.0)</td>
<td>4 (4.4)</td>
<td>0 (0.0)</td>
<td>0.865</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td>13 (6.6)</td>
<td>0 (0.0)</td>
<td>7 (7.5)</td>
<td>2 (18.2)</td>
<td>0.865</td>
</tr>
</tbody>
</table>

The p-values represent collective comparison of the various clinical features between the different genotypes.

Table 4: Frequency of transfusion among the subjects

<table>
<thead>
<tr>
<th>Frequency of crisis</th>
<th>Sickle Cell subjects</th>
<th>SS with normal G6PD activity n = 197 (%)</th>
<th>SS with deficient G6PD activity n = 9 (%)</th>
<th>SC with normal G6PD activity n = 93 (%)</th>
<th>SC with deficient G6PD activity n = 11 (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td>133 (67.5)</td>
<td>6 (66.7)</td>
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<td>Once</td>
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<td>0.865</td>
</tr>
<tr>
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<td></td>
<td>9 (4.9)</td>
<td>0 (0.0)</td>
<td>2 (2.2)</td>
<td>0 (0.0)</td>
<td>0.865</td>
</tr>
<tr>
<td>Thrice</td>
<td></td>
<td>5 (11.2)</td>
<td>0 (0.0)</td>
<td>4 (4.3)</td>
<td>1 (9.1)</td>
<td>0.865</td>
</tr>
<tr>
<td>&gt; Three times</td>
<td></td>
<td>8 (4.0)</td>
<td>0 (0.0)</td>
<td>4 (4.4)</td>
<td>0 (0.0)</td>
<td>0.865</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td>13 (6.6)</td>
<td>0 (0.0)</td>
<td>7 (7.5)</td>
<td>2 (18.2)</td>
<td>0.865</td>
</tr>
</tbody>
</table>
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Table 5: Mean values of haematological parameters measured in normal-G6PD and deficient-G6PD sickle cell subjects

<table>
<thead>
<tr>
<th>Sickle cell status</th>
<th>G6PD Deficiency</th>
<th>Hb (g/dl)</th>
<th>PCV (%)</th>
<th>RBC (x 10^6/l)</th>
<th>ESR (mm/HR)</th>
<th>RC (%)</th>
<th>GL (mg/dl RBC)</th>
<th>GS (%) reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbSS</td>
<td>Present (n = 9)</td>
<td>Mean ± SD</td>
<td>8.7± 1.1</td>
<td>26.9± 3.3</td>
<td>3.0± 0.4</td>
<td>22.2± 4.1</td>
<td>19.6± 3.5</td>
<td>55.2± 10.9</td>
</tr>
<tr>
<td></td>
<td>Absent (n = 197)</td>
<td>Mean ± SD</td>
<td>8.2± 1.7</td>
<td>25.0± 5.0</td>
<td>2.8± 0.7</td>
<td>23.9± 17.8</td>
<td>17.5± 1.8</td>
<td>61.6± 12.3</td>
</tr>
<tr>
<td>HbSC</td>
<td>Present (n = 11)</td>
<td>Mean ± SD</td>
<td>9.0± 1.2</td>
<td>27.9± 3.8</td>
<td>3.1± 0.4</td>
<td>21.5± 5.4</td>
<td>15.9± 2.2</td>
<td>55.6± 8.2</td>
</tr>
<tr>
<td></td>
<td>Absent (n = 93)</td>
<td>Mean ± SD</td>
<td>9.4± 2.1</td>
<td>29.0± 6.5</td>
<td>3.1± 0.7</td>
<td>18.8± 12.6</td>
<td>16.5± 0.6</td>
<td>56.0± 7.5</td>
</tr>
</tbody>
</table>

All values in the same column with different superscripts are significantly different at (p < 0.05)

Hb(Haemoglobin), PCV(Packed Cell Volume), RBC-(Red blood cell counts), ESR- (Erythrocyte Sedimentation Rate), RC-(Reticulocyte Counts), GL-(Glutathione level) and GS-(Glutathione stability)

The presence of G6PD deficiency among the different genotypes of SCD subjects did not show any significant impact on the frequency of crises, frequency of transfusion and other clinical features (p > 0.05). This is very evident from the study as approximately one out of every three patients of each sickle cell genotype had experienced at least three crises for the past one year. The same ratio was recorded for the frequency of transfusion among the groups. Even though the sample size of G6PD-deficient patients was small, our observation somehow confirms the report that patients with G6PD-deficiency do not compromise on their combined defects. [30, 31] In a similar study, Diop and his colleagues (2005) found that there was no difference in the two groups of SCD patients concerning the number of vaso-occlusive crisis, number of transfusion, frequency of infectious episodes, number of chronic complications, and disturbances on patient’s activity and total index of severity. [17]

We included the use of passage of darkened urine to differentially diagnose the presence of the G6PD-deficiency, but from the study there was apparently no such difference between the various groups. This may be due to the fact that other factors apart from the G6PD could have been responsible for the urine colour. On the passage of darkened urine (Table 1), there was a difference in the frequencies between what was recollected to have occurred previously and the observation at the time of study. While about 50% recollected voiding darkened urine in the past, only 7-10% observed darkened urine at the time of study. The recollection on the previous occurrence covered a relatively longer period, and many observed voidings, as compared to just a one-time observation made for the present.

The 55% of the SCD subjects with no clinical features may have been mainly due to the bias in the recruitment into the study. It was only patients in steady state who were selected, and it is possible that the set of patients selected were subjects who seldom had sickle-related clinical conditions. Another reason could be attributed to the comprehensive care offered at the Sickle Cell Clinic, as a result of which good management practices had been adopted by the subjects and their caregivers.

From Table 5, the level of haematological indices in the different groups of patients (SS and SC) was similar, except the glutathione stability. The levels of Hb, RBC and PCV found in the different groups reflect their clinical conditions, and it must be emphasized that all the patients were in steady state at the time of the study. There was characteristically high reticulocyte counts and slightly raised ESR values (which are considered typical of anaemic conditions in tropical countries). [32] Statistically, there was no significant difference (p >0.05) between the different genotypes of the patients who showed the presence and absence of G6PD activity, except the glutathione stability (p< 0.05), for the determined haematological indices (Table 5). The results were in line with Beutler’s work (1990) in which there was no such relationship between the SCD and the enzyme deficiency. [33] Conversely, there was a statistically significant difference (p < 0.05) between the SS and SC patients. This significant difference implies that the presence of the SS genotype in some of the patients, as compared to the SC genotype has a significant impact on the determined haematological indices, consequently confirming the fact that individuals with SS disorder experienced more serious haematological problems than their counterparts SC patients. [31]

In the normal G6PD SCD subjects, the incubation of red cells with the oxidizing drug, acetylphenylhydrazine, reduced the glutathione level by an average of less than 15.0% which was within the normal reference range of glutathione stability test (>20%), as reported by Shelth et al. (1981). [34] This means that the oxidant drug has little effect on the GSH concentration, since its oxidation is reversed by glutathione reductase, which in turn, relies on normal G6PD activity for a supply of NADPH. But the reduction of glutathione level in deficient G6PD SCD subjects was approximately 60.0%, making the glutathione stability significantly lowered. Here, the mutant G6PD causes a decrease in NADPH which impaired the generation of reduced glutathione from oxidized glutathione. A positive glutathione stability test is usually characterized by a marked reduction (>50%) in the glutathione levels of erythrocytes after incubation with the oxidant, acetylphenylhydrazaline, while in normal red cells the level is slightly decreased (<20%). It has been suggested that this test be used as one of the models to screen for possible haemolytic effect in deficient G6PD patients. [34] Biochemically, phenylhydrazine and other related compounds combined with oxyHb to form metHb, leading to irreversible formation of hemichrome, causing the formation of Heinz bodies that induce haemolysis. [35] In the presence of normal G6PD activity, the metHb can be reduced, preventing the irreversible formation of the Heinz bodies. In this study, even though the presence of G6PD deficiency did not have any significant impact on the severity of SCD, it is important that patients should be aware of their G6PD genotype in order to avoid oxidative drugs that might provoke oxidative stress leading to haemolytic anaemia.

Thus, this study has also shown that the presence of G6PD deficiency did not affect the SCD subjects, even though their erythrocytes could be vulnerable to limited reversible injury by exogenous and endogenous oxidants. The situation may be due to the fact that the African (A) variant is the most prevalent among the Ghanaian populace. This variant has a reduced activity in matured red cells, but a normal activity in young red cells. The matured red cells are more susceptible to haemolysis, particularly under oxidative stress. The breakdown of the old cells increases the rate of erythropoiesis, which in turn, may lead to reticulocytosis, as the body releases more young red cells (have the normal stock of enzyme) to make up for the lost cells. Other contributing factors could be the regular routine medical check-ups and strict adherence to daily medication by the patients at...
the clinic. Another possibility is that the patients under study may not have been exposed to any oxidizing condition at the time of the investigation.

CONCLUSION

This study has shown that the presence of the combined defects (G6PD-deficient SCD subjects) in the SCD population was quite low, 6.49%, as compared to other similar studies. And more importantly, the occurrence of the G6PD deficiency among individuals with the different genotypes of sickle cell disorders did not worsen their diseased condition. This was reflected in the observation that there was no significant statistical difference in the severity of crises, clinical conditions and the haematological indices among the various groups of patients.

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Author's contribution

CKF- performed the experiments and wrote the manuscript. FAY-contributed in developing the concept of the experiment. KN-designed and directed the study, as well as the overall editing and approval of the paper. All authors reviewed the paper.

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All authors declared no conflict of interest.

REFERENCES