Original article

Clinical profile, dietary zinc content, and lifestyle habits of adult male and female hbss and hbsc patients

Anuoluwapo Abisola Alaka[1], Olubunmi Olayemi Alaka[2], Ayobola Abolape Iyanda[3]

Abstract:

Objective: Males and females have been reported to show significant variation with respect to clinical profile of sickle cell disease (SCD) (e.g. cardiovascular, musculoskeletal and chronic end-organ complications). Clinical features of SCD are also influenced by lifestyle and dietary habits. Thus, the study was conducted to examine whether the distributions of other manifestations (e.g. priapism, pain frequency, leg ulcers rates) and habits (lifestyle, dietary) of SCD patients in Osun state, Nigeria are influenced by gender or genotype. ***Material and methods:*** *Q*uestionnaires were administered to obtain information on age, gender, concoction/herbal preparations, and fruit/vegetable consumption, as well as zinc contents of 24-hour meal recall, physical exercise, lifestyle parameters and clinical profile of SCD. Descriptive (relative frequency) and inferential (Chi-square ($\chi 2$) test of independence) statistics were employed. Statistical significant was set at $p<0.05$. ***Results and discussion:*** HbSS rather than HbSC showed higher distributions of pain frequency and more frequent hospitalization rates at p= .001 and p=.001 respectively. There was no significant relationship between hemoglobin genotype and the following variables: leg ulcers, priapism, fruit intake, herb/concoction consumption, 24-hour dietary zinc content. Moreover, all the variables were not influenced by gender not only among HbSS but also HbSC patients. ***Conclusion:*** There are indications from data obtained that clinical profile of SCD such as priapism, leg ulcers, high hospitalization rates and pain episodes are present among HbSS and HbSC SCD patients in Osun state Nigeria. Although only pain episodes and hospitalization rates were significantly higher among HbSS than HbSC, for either variable though there was no gender bias in its distribution. Similarly the distributions of other variables (such as exercise, dietary, etc) for each of SCD (HbSS, HbSC) categories were not influenced by gender.

Keywords: leg ulcer, priapism; dietary zinc content; physical exercise; alcohol intake; genderhemoglobinopathies.

Bangladesh Journal of Medical Science Vol. 23 No. 01 January'24 Page : 74-82
DOI: https://doi.org/10.3329/bjms.v23i1.70681

Introduction:

Sickle cell disease (SCD) comprises a range of sickle cell syndrome. It occurs as a result of a genetic mutation in which there is substitution of one amino acid for another. In the homozygous SCD i.e. sickle cell anemia (SCA), glutamic acid is substituted for valine at the 6th position of the β-globin chain.[1,2] Patients with this disorder present with varied spectrum of medical crises or clinical events such as acute bone pain, pulmonary crises, vaso-occlusive crises[1], leg ulcer and priapism. In Nigeria like many countries in sub-Saharan Africa, there is high burden of SCD. That the burden of the disease is high in Nigeria is evident by available data which shows that as many as one-third of global

1. Anuoluwapo Abisola Alaka, Department of Chemical Pathology, College of Health Sciences, Ladoke Akintola University of Technology, Ogbomoso, Nigeria.
2. Olubunmi Olayemi Alaka, Department of Medical Microbiology and Parasitology, Obafemi Awolowo University Teaching Hospital, Ile-Ife.
3. Ayobola Abolape Iyanda, Department of Chemical Pathology, College of Health Sciences, Ladoke Akintola University of Technology, Ogbomoso, Nigeria.

Correspondence: Ayobola Abolape Iyanda, Department of Chemical Pathology, College of Health Sciences, Ladoke Akintola University of Technology, Ogbomoso, Nigeria. E-mail lapeiyanda@yahoo.com

SCD births take place in Nigeria,[3] aside the fact that between one-half to nine-tenths of SCA patients die during childhood especially before the age of 5 years,[3] which extrapolates to 150,000-300,000 child deaths yearly. Even those that avoid childhood deaths suffer substantial morbidity compared with non-SCD children.[4,5]

Due to the fact that Sickle cell disease (SCD) is made up of a range of hemoglobinopathies, patients suffering from this disease display substantially variable clinical manifestations. Although there are different types of sickle cell syndromes, sickle cell anemia (SCA) that is characterized by the homozygous hemoglobinopathy- hemoglobin S (HbS) is the most critical type and commonest especially in Nigeria, the heterozygous form i.e. SC hemoglobinopathy (HbSC) has been identified as the milder form.[6] While the differences in severity of SCD has been linked with variations in morphological defects of RBC of HBSS and HBSC patients, the possible impacts of exogenous factors such as dietary zinc content, use of herbal preparation (concoction), and some lifestyle choices (e.g. alcohol consumption and physical exercise) have not been exhaustively investigated. There is the possibility of such an impact because dietary or supplemented zinc has been reported to modulate several markers of SCD severity such as infection, growth retardation, etc.[7] Although there is no sufficient data directly linking zinc with priapism or pain frequency, the role of this important mineral in wound-healing process (leg ulcer) is well documented.[8] Meanwhile the positive role of concoction/herbal remedies has been postulated[9] but there is no sufficient data on the impact of exercise on clinical presentations of two genotypes of SCD [HBSS, HBSC] especially as it relates with gender.

Males and females have been known to show great degree of variation in relation to both laboratory data presentations as well as clinical profile of SCD. Udezue and Girshab[10] reported that males were admitted more often to the stabilization unit for pain control. Additionally, they observed that males were often over-represented among those whose pain persisted for over 47 hours. The reason for such differences has been addressed through various studies especially with respect to a myriad of factors already associated with SCD, but the influences of other factors such as lifestyle and dietary habits have not be investigated as concerning how they affect clinical manifestation of SCD in both male and female patients. Thus, the study was conducted to examine whether the distributions of clinical profile of SCD is affected by genotypes or gender.

Materials and methods:

Study Design and Sampling Technique:

It is a cross-sectional study in which comparison was made between two genotypes [HBSS, HBSC] of SCD as well as between the two genders for the same genotype. Multi-stage random sampling technique was employed.

Study Location and Participants

Consented participants were recruited at primary, secondary, tertiary tiers of health care (government-owned) as well as private hospitals across Osun state. Namely Haematology and Out-Patient Clinics of tertiary hospitals such as Obafemi Awolowo University Teaching Hospital Complex (OAUTHC) Ile-Ife, Wesley Guild Hospital Ilesha, Osun State University Teaching Hospital Osogbo (UTH) were sites of SCD patients recruitment. Meanwhile other hospitals under the Osun State Hospitals Management Board (OSHMB) in Osun state, Nigeria represented the primary and secondary health-care centers. Additionally, private health-care centers served as SCD patient recruitment centers.

Sample Size Determination/Selection of Study Participants

Sample size was determined to be 30 for each type of SCD [HbSS, HbSC]. It was calculated using the Cochrane formula: $n = z^2pq/d^2$. [11]

Female and male sickle cell disease patients (HbSS, HbSC) were recruited for the study. All participants were adults aged 18 or above. They were identified based on results of haemoglobin electrophoresis using cellulose acetate paper. Excluded from the study were patients that had been transfused with whole blood or blood products within the preceding 12 weeks before the commencement of the study, pregnant women, and individuals with any other chronic disease, aside SCD. More importantly, those whose haemoglobin genotype could not be confirmed using cellulose acetate haemoglobin electrophoresis were excluded.

Questionnaire

Pre-tested questionnaires were administered to all participants to collect information on age, gender, exposure to/intake of concoction/herbal preparations, and use of any medication, as well as signs and

symptoms of diseases. Moreover, information was obtained from each participant on habits as it relates with fruit and vegetable consumption, degree and frequency of physical exercise, and lifestyle parameters. To measure pain frequency, a time scale was used to stratify the patients. The scale was used to divide the patients into categories based on pain episode incidents: never (absence of pain), every day, every week, every month, biannually and every year. Additionally, information was obtained from each participant on the presence or absence of leg ulcer during the course of the disease as well as occasion of priapism in male subjects of each genotype of SCD.

Classification of Zinc Content in 24-Hour Meal Recall

Dietary zinc content was obtained using the classification described by Temiye *et al.*[12] The zinc contents of 24-hour meal recall and the last meal consumed before blood collection was classified based on the concentration of zinc in food items consumed by the participants. Thus, each food item was classified as containing high, moderate, or low zinc.[13,14]

Meals which contain items such as plantain, red beef, sea foods, egg, milk, cocoa products, and fish were classified as high zinc content, while beans, cereals made out of maize and rice products contain moderate zinc. Cassava products were classified as having traces or low zinc content.[13,14] For the purpose of this study, a subject who had more than 2 high zinc containing items with any 3 moderate zinc containing items or all high zinc containing items was classified as having high zinc diet. A subject who had one high zinc containing item and less than 3 moderate zinc containing items or had all moderate zinc containing items was classified as having moderate zinc, while a subject who had one moderate zinc or one high zinc containing item with low zinc containing item, or only low zinc containing items, was classified as having low zinc.

Statistical Analysis

Statistical analysis was performed on data generated using Statistical Package for Social Sciences (SPSS) version 20.0 (IBM Corporation, Armonk, NY, USA). Relative frequency distributions were generated for all categorical variables namely gender of participants, leg ulcer, pain frequency, priapism (for male only), fruit/vegetable consumption habits, zinc dietary contents, concoction intake, lifestyle choices (cigarette, alcohol consumption), and degree of physical exercise. Chi-square ($\chi 2$) test was applied to determine relationship between SCD genotypes and dependent variables (i.e. clinical profile, dietary zinc content, habit, etc) and extended to how this related to gender. Differences between values were considered statistical significant where probability was less than 0.05 ($p<0.05$).

Ethical Clearance:

Ethical approval for the study was obtained from the Osun State Ministry of Health, Osogbo, Osun state. Informed consent of each participant was sought and obtained. Information obtained from participants was kept in strict confidentiality.

Results:

The relative frequencies of clinical profile, lifestyle (except alcohol intake and smoking) and dietary habits of adult HbSS and HbSC participants based on gender are shown in **Figures 1-3 and Table 1**. Results revealed that none of the participants indicated alcohol intake, neither were there SCD patients that had smoked cigarette nor cannabis. Chi-square test of independence was performed to assess the relationship between several variables (clinical profile, lifestyle, dietary habits) and hemoglobin genotypes- HbSS, HbSC. There were significant differences between hemoglobin genotype and the following variables- 1. pain frequency X^2 (4, N=66) = 18.41, p = .001; 2. latest hospitalization X^2 (**3**, N=66) = 16.77, p = .001. In each case HbSS rather than HbSC showed higher distributions of pain frequency and more frequent hospitalization rates. Meanwhile, others such as leg ulcers X^2 (1, N=66) = 1.243, p = .428; priapism X^2 (**1**, N=33) = 0.775, p = .513; fruit intake X^2 (**2**, N=66) = 5.02, p = .081, herb/concoction consumption X^2 (1, N=66) = 0.140, p = .458; and 24-hour dietary zinc content X^2 (2, N=66) = 5.647, p = .060 did not show significant relationship with hemoglobin genotypes.

Additionally, Chi-square test of independence was performed to assess the relationship between several variables (clinical profile, lifestyle, dietary habits) and gender (male, female) among HbSC as well as HbSS. For HbSC, there was no significant association between gender and the following variables- pain frequency X^2 (4, N=32) = 3.377, p = .497; latest hospitalization X^2 (3, N=32) = 0.234, p = .972. As well as others such as leg ulcers X^2 (**1**, N=32) = 0.001, p = 1.000; fruit intake X^2 (**2**, N=32) = 2.182, p = .336, herb/concoction consumption X^2 (1, N=32) = 0.155, p = 1.000; 24-hour dietary zinc content X^2 (2,

N=32) =1.292, p = .524; and physical exercise X^2 (2, N=32) =4.571, p = .073. Similarly for HbSS, there was no significant association between gender and the following variables- pain frequency X^2 (4, N=34) = 1.354, p = .716; and latest hospitalization X^2 (**3**, N=34) = 1.074, p = .585, as well as others such as leg ulcers X^2 (1, N=34) =2.110, p = .335; fruit intake X^2 (**2**, N=34) = 0.552, p = .759; herb/concoction consumption X^2 (1, N=34) = 0.134, p = 1.000; 24-hour dietary zinc content X^2 (2, N=32) =1.668, p = .434; and physical exercise X^2 (2, N=32) =0.001, p = 1.000.

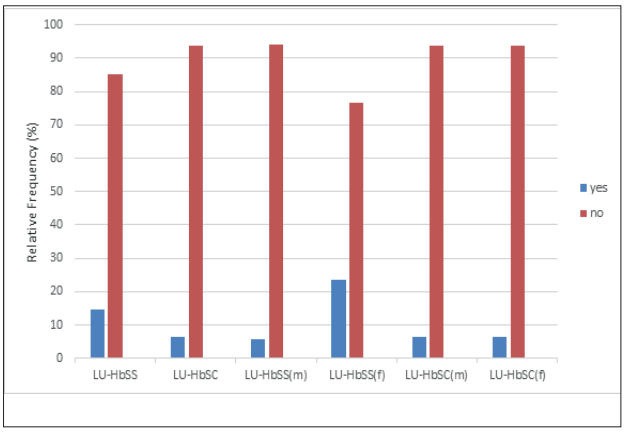

Figure 1: Relative frequency (%) of leg ulcers among adult sickle cell disease patients based on gender

Abbreviation: LU-HbSS (leg ulcers among HbSS patients); LU-HbSC (leg ulcers among HbSC patients); LU-HbSS(m) (leg ulcers among male HbSS patients); LU-HbSS(f) (leg ulcers among female HbSS patients); LU-HbSC(m) (leg ulcers among male HbSC patients); LU-HbSC(f) (leg ulcers among female HbSC patients).

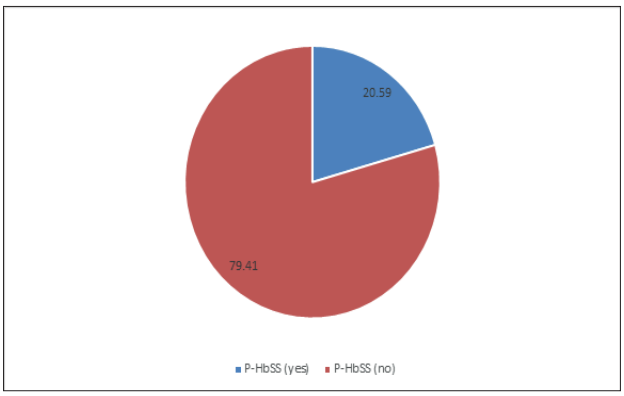

Figure 2: Relative frequency (%) of priapism among adult male HbSS (sickle cell patients) patients

Abbreviations: P-HbSS (yes) means presence of priapism among HbSS male patients; P-HbSS (no) means absence of priapism among HbSS male patients

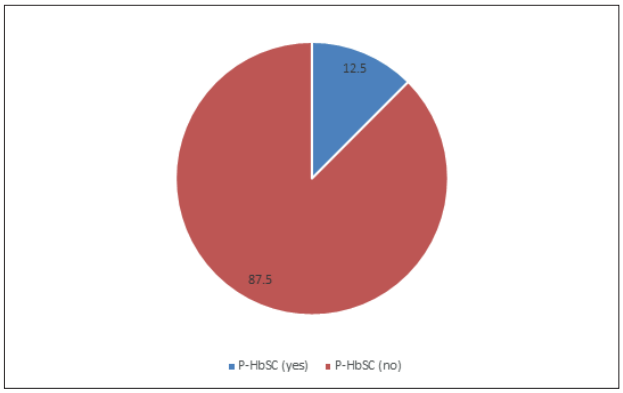

Figure 3: Relative frequency (%) of priapism among adult male HbSC (sickle cell patients) patients

Abbreviations: P-HbSC (yes) means presence of priapism among HbSC male patients; P-HbSC (no) means absence of priapism among HbSC male patients

Discussion:

Available data suggests that gender plays a role in rates of SCD complications among patients with hemoglobinopathies.[15] Yet the present study showed that based on gender, pain frequency and leg ulcers of HbSS and HbSC were comparable. Especially as there was a lack of association between each of the variables [pain frequency-HbSS (p = .716), HbSC (p = .497), leg ulcers- HbSS (p = .335); HbSC (p = 1.000)] and gender. The study is in agreement with earlier observations made by Abd Elmonein *et al.*[16], among Saudi Arabian population. According to them there was no significant difference between males and females with respect to overall clinical presentations of SCD. Even though, acute pain crisis, acute chest infection and stroke were more common among female patients while the most frequent presentations among males were infection and anemia. Additionally, they reported that only 0.97% of SCD males presented with priapism and that all of those with priapic activity were aged above the pre-teenage years of life. The result of the study is quite different from the observation of Abd Elmonein *et al.*[16] Although, except with much higher rate of priapism in HbSS [41.2%] than HbSC [25%], the result is similar to what obtains among male Jamaican SCD population. Priapism is

Table 1: Relative frequency (%) of pain incidents, latest hospitalization episodes, 24-hour dietary zinc recall, fruit intake, and concoction intake among HbSS and HbSC sickle cell disease patients

Variables	HbSC		HbSS	
	Male	Female	Male	Female
Pain frequency				
Daily	6.25	6.25		
Weekly	3.13	0	5.88	8.82
Monthly	15.63	18.75	41.18	35.29
Biannually	0	6.25	0	2.94
Yearly	25.00	18.75	2.94	2.94
Never	0	0		
Latest hospitalization				
< 1 year	9.38	9.38	11.76	17.65
1-3 years	12.50	12.50	32.35	23.53
4-6 years	9.38	12.50	5.88	8.83
Never	18.75	15.63		
24- hour dietary zinc recall				
High	18.75	28.13	35.29	29.41
Moderate	25.00	15.63	8.82	5.88
Low	6.25	6.25	5.88	14.71
Fruit intake				
Daily	18.75	9.38	23.53	17.65
Weekly	0	3.13	5.88	8.83
Occasionally	31.25	37.50	20.59	23.53
Herbal preparation/concoction intake				
Yes	15.63	12.50	14.71	17.65
No	34.38	37.50	35.29	32.35
Exercise (mild/moderate)				
Yes	31.25	12.50	17.65	17.65
No	18.75	37.50	32.35	32.35

alleged to be as high as 40% among post-pubertal males in Jamaica[17,18] Whether this wide variation reported by many researchers was due to differences in individuals' disposition to genetic aberrations of SCD remains to be determined. Meanwhile, it has been alleged that the presence of the Arab-India beta globin haplotype leads only to milder phenotypes.[19]

Priapism of SCD occurs from many altered physiologic processes associated with the disease, many of which are related with NO levels, i.e. there is intrinsic relationship between priapic activity and NO. Cell- free plasma hemoglobin from intra-vascular hemolysis consumes NO 100-fold more rapidly, thereby decreasing NO bioavailability in patients with SCD.[20] Meanwhile low bioavailability of NO has been linked with constellation of medical complications (also known as hemolysis-endothelial dysfunction syndrome). Severe hemolysis seems to be accompanied by leg ulcers and priapism [painful persistent penile erection] in many individuals afflicted with SCD. Although it seems counterintuitive that priapism will result from impaired NO bioavailability since NO is required to cause normal penile erection. Yet an association between impaired NO bioavailability and priapism has been suggested not only from available human data relating with SCD but also in many experimental animal models of SCD, especially in sickle cell transgenic mouse.[21] Additionally, it has been proposed that decreased NO levels down regulates expression of the counterbalancing phosphodiesterase 5 [PDE5], leading to impairment in the process that should dampen surges in cyclic GMP level in the penile blood vessels.

Aside hemoglobin, increased arginase release has been linked with low NO- induced priapism in SCD patients. Although results of some studies contest the supposed role of NO in the priapic phenomenon of SCD, yet mice genetically deficient in NO synthesis have developed priapic activity. Such new data seem to suggest that hemolysis-linked dysregulation of adenosine signaling in the penis contributes to priapism in sickle cell mice.[22] Genetically altered mice, (i.e. from transgenicity and knockout process) demonstrated a disordered pathway that caused of priapism. Mice genetically deficient in endothelial NO synthase manifested spontaneous priapic activity. And for mice that were particularly deficient in

both endothelial and neuronal NO synthase, greater occurrence of priapic action were detected.

Chronic leg ulcer, a complication of SCD is a wound on the skin that occurs between the foot and the knee showing no signs of healing after 3 months of proper treatment.[23] Male= 6.25%; female= 6.25% of HbSC and male= 5.88%; female= 23.53% of HbSS reported incidence of leg ulcers. Apart from the relative frequency, Chi square results of p= .335 (HbSS) and p= 1.000 (HbSC) suggests that gender has no impact on occurrence of leg ulcers among SCD patients in Osun state. This incapacitating complication of SCD, hemoglobin S polymerization, and erythrocyte sickled shape (that result in eventual entrapment of sickle-shaped RBCs in microcirculatory system) are intrinsically linked.[24] More often, alteration in microcirculation, progresses to microvascular vaso-occlusion, tissue damage and painful episodes. Occurrence of this especially in the lower leg, results in venous hypertension, varicose eczema, oedema, along with deposition of scar tissue and iron pigments in the skin. All of which cumulates to breakdown of the skin, delay healing or chronic leg ulcer. Although leg ulcer is a universal complication of SCD as also observed in the study, its incidence varies widely. Incidence rates being 2.5% to 25% (USA); 75% (Jamaica); 10% Ghana/Nigeria- 10%.[24] Meanwhile the rate of re-occurrence of leg ulcers can be as high as 70% in some communities.[24] The lower frequency of leg ulcers in HbSC (6.25%) than HbSS (14.71%) as well as higher frequency of hospitalization (p= .001) and pain (p= .001) among HbSS than HbSC further support the fact that HbSC is the milder form of the disease. In contrast to the present observation, Shah *et al*.[25] and Panigrahi *et al*.[26] recorded no occurrence of leg ulcers in both HbSS and HbSC patients. Meanwhile, Oluwagbenga *et al*.[27] reported 12% of chronic leg ulcers among SCA Nigerian adults. Unlike the study of Oluwagbenga *et al*.[27] which was carried out among SCA Nigerian adults, Shah *et al*.[25] surveyed SCD Indian children. The wide array of frequencies reported for different studies may not be unconnected to differences in genotypes, age range and sample sizes of study participants adopted by various researchers. The more females than males that presented with leg ulcers is not in agreement with the study of Minniti *et al*.[28] and contrary to the common assumption that some clinical presentations of SCD are more prevalent in males than females.[16]

Just like the present study in which 0% identified as smokers, used cannabis or drank alcohol, Gerardin *et al*. [29] also reported that the use of alcohol, tobacco and cannabis by the French subjects included in their SCD study was very low. Also it seems to be compatible with assumption of Habibi *et al*.[30] that stated that the absence of tobacco and alcohol consumption is part of the basic hygieno-dietary rules among patients with SCD. Although Howard *et al.*[31] identified that sometimes cannabis is used by some chronic pain patients to relieve discomfort, including patients with SCD. Meanwhile, none of the study participants reported cannabis use. The rate of alcohol consumption was 0% for both genotypes, therefore association between clinical profile and alcohol intake in SCD condition could not be determined. Tendency to exercise did not differ between HbSC and HbSS as well as between male and female of each genotype of SCD (HbSS- p= 1.000, HbSC- p= .073). Just like lifestyle (smoking, alcohol intake), no SCD patients reported partaking in rigorous exercise. The lack of interest in rigorous exercise could not be determined although Matthews,[32] identified that SCD patients tend to avoid stressful behavior as well as labour-intensify activities which they believe may aggravate clinical presentations of the disease. In fact there is sufficient evidence in literature that aside factors such as hypoxia, acidosis, dehydration, infection, extreme fatigue, and trauma, physical exercise is another important agent capable of precipitating a sickle cell crisis.[33]

Emanuel et al.[34] had earlier reported difference in fruit and vegetable consumption among males and females. Yet results revealed that there was no difference in fruit consumption habits of HbSS when compared with HbSC (p= .081). Furthermore, gender did not play a significant role in fruit intake pattern among HbSS (p= .336) and HbSC (p= .759). That no significant difference was recognized in each case was not difficult to decipher, both males and females have equal access to these items in South western, Nigeria. Moreover, during clinic attendance, a lot of efforts are directed at educating patients about ways of preventing the onset of SCD complications, some of the ways in which this is achieved is by instructing patients on the role of nutrition, especially antioxidant rich foods in SCD management. This may explain why the results of the study differ from that of Emanuel et al.[34] That the impact of clinic attendance can be contested is evident from information already available in literature. It has been suggested that clinic attendance is higher among HBSS than HbSC.

It seems that fruits and vegetables were not the

major sources of dietary zinc even though many fruits and vegetables contain zinc and zinc possesses antioxidant property.[35] Results revealed that even though 28.13% of HbSC patients consumed fruits and vegetable on daily basis 46.88% were classified into 24-hour dietary zinc recall group. Similarly, for HbSS patients, daily fruit intake constituted 41.18% whereas 64.71% were classified into 24-hour dietary zinc recall group.

The investigation into the qualitative level of concoction consumed became imperative due to the emerging evidence that medicinal plant derived nutrients for SCD management is becoming common. Approximately 30.34% of male and 30.35% of female SCD patients indicated that they have at one time or another utilized herbal preparation/concoction for the treatment of SCD complications. There is growing interest in the use of natural products as an integrative approach to management of sickle cell disease as suggested by data obtained from the study. Certain plant extracts are known to possess antioxidant properties from bioactive components such as phytochemicals and flavanols.[36] For instance, the tropical plant *Moringa oleifera* is a good candidate. The ethanol extracts of *Moringa oleifera* showed antioxidant values between 77 and 4,458 µg/mL, and have been recognized to mitigate different components of SCD severity.[37,38,39] The importance of other plant leaves known to contain phytochemicals, such as *Cajanus cajan*, *Zanthoxylum zanthoxyloides*, and *Carica papaya* has been demonstrated as well. Experimentation carried out in an in vitro model by using 2% sodium metabisulfite to induce red cell sickling, revealed that these plants could aid in the resistance of hemolysis and reduce the number of sickled red blood cells.[38] According to Tang *et al*.[39] Data obtained in animal models did not show acute toxicity of the leaf.[39]

Additionally, that diet can modulate the course of a disease has been suggested by Kasuma et al.[40] They hypothesized that zinc containing *Minangkabau* food was useful in the treatment of periodontal disease, which probably can be linked to its role as cofactor of alkaline phosphatase. This is also supported by report of Nargis *et al*.[41] where it was postulated that Sharbat Misali (an Unani preparation of hematinics) enhanced hemoglobin level and its safety supported by data obtained from study of hepatic and renal function. Even when nutrients are present in supplemental form, alleviation of symptoms of diseases can still occur (Putri *et al*.)[42] The fact that SCD can be complicated by many other endemic diseases in Africa brings some urgency to our efforts in treating/managing sickle cell disease especially using nutritional and non-nutritional methods. For example, Prusty *et al*.[43] identified that multiple splenic infarcts may result from sickle cell complication of Dengue fever.

Conclusion:

There are indications from data obtained from the study that clinical profile of SCD such as priapism, leg ulcers, high hospitalization rates and pain episodes are common among HbSS and HbSC SCD patients in Osun state Nigeria. Although only pain episodes and hospitalization rates were significantly higher among HbSS than HbSC, for each of the variables there was no gender bias in their distributions. Similarly the distributions of variables (such as exercise, dietary, etc) for each of SCD (HbSS, HbSC) categories were not influenced by gender.

Source of fund: (if any): ***Self-funded***

Conflict of Interest: ***Nil***

Ethical clearance: Ethical approval for the study was obtained from the Osun State Ministry of Health, Osogbo, Osun State (OSHREC/PRS/569T/164)

Authors's contribution:

Idea owner of this study: Ayobola A **Iyanda; Anuoluwapo Alaka**

Data gathering: Anuoluwapo **Alaka**, Olubunmi Olayemi **Alaka**,

Study design: Ayobola Abolape **Iyanda,** Anuoluwapo **Alaka**

Writing and submitting manuscript: Anuoluwapo **Alaka**, Ayobola Abolape **Iyanda**

Editing and approval of final draft: Ayobola Abolape **Iyanda**

References:

1. Shittu KO, Egbeleke FA, Iyanda AA. Trace Element Levels and Socio-Demography of Pre-Teen Nigerians with Homozygous Sickle Cell Disorder. *Annual Research & Review in Biology* 2022;**37**(2):13-19. DOI: 10.9734/ARRB/2022/v37i230483
2. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, *et al*. (2018) Sickle cell disease. *Nat Rev Dis Primers* **4**: 18010. https://doi.org/10.1038/nrdp.2018.10 PMID: 29542687
3. Oron AP, Chao DL, Ezeanolue EE, Ezenwa LN, Piel FB, Ojogun OF, *et al.* Caring for Africa's sickle cell children: will we rise to the challenge?. *BMC Med* **18**, 92 (2020). https://doi.org/10.1186/s12916-020-01557-2
4. Macharia AW, Mochama G, Uyoga S, Ndila CM, Nyutu G, Makale J, *et al*. The clinical epidemiology of sickle cell anemia in Africa. *Am J Hematol* 2018. **93**; 363-70.
5. Marks LJ, Manube D, Kasitye P, Mupere E, Jin Z, LaRussa P, *et al*. Stroke prevalence in children with sickle cell disease in sub-Saharan Africa: a systematic review and meta-analysis. *Glob Pediatr Health* 2018; **5**: 2333794X18774970
6. Serjeant GR, Vichinsky E. Variability of homozygous sickle cell disease: The role of alpha and beta globin chain variation and other factors. *Blood Cells Mol Dis* 2018; **70**: 66–77. https://doi.org/10.1016/j.bcmd.2017.06.004 PMID: 28689691
7. Datta D, Namazzi R, Conroy A, Cusick SE, Hume HA, Tagoola A, et al. Zinc for infection prevention in sickle cell anemia: study protocol for a randomized placebo-controlled trial in Ugandan children with sickle cell anemia. *Trials* 20 Article number: 460 (2019).
8. Monfort JB, Senet P. Leg Ulcers in Sickle-Cell Disease: Treatment Update. *Adv Wound Care* (New Rochelle). 2020 Jun;**9**(6):348-356. doi: 10.1089/wound.2018.0918. Epub 2019 Apr 24. PMID: 32286203; PMCID: PMC7155924.
9. Ameh SJ, Tarfa FD, Ebeshi BU. Traditional herbal management of sickle cell anemia: lessons from Nigeria. *Anemia*. 2012;2012:607436. doi: 10.1155/2012/607436. Epub 2012 Nov 8. PMID: 23198140; PMCID: PMC3502758.
10. Udezue E, Girshab A M. Differences between males and females in adult sickle cell pain crisis in eastern Saudi Arabia. *Ann Saudi Med.* 2004 May-Jun; **24**(3): 179–182. doi: 10.5144/0256-4947.2004.179 PMCID: PMC6147926 PMID: 15307454
11. Cochran WG 1977. Sampling techniques. 3rd Ed. New York John Wiley & sons.
12. Ceglie G, Di Mauro M, Tarissi De Jacobis I, de Gennaro F, Quaranta M, Baronci C, et al. Gender-Related Differences in Sickle Cell Disease in a Pediatric Cohort: A Single-Center Retrospective Study. *Front Mol Biosci*. 2019 Dec 5;**6**:140. doi: 10.3389/fmolb.2019.00140. PMID: 31867340; PMCID: PMC6906547.
13. Temiye EO, Duke ES, Owolabi MA, Renner JK. Relationship between Painful crisis and serum zinc level in children with sickle cell. *Anaemia*. 2011;2011:698586. doi:10.1155/2011/698586 . PMID: 21490764; PMCID: PMC3065914.
14. Balch Aps. Minerals. In: Balch PA, Balch JF, editors. Prescription for Nutritional Healing. 3rd ed. New York: New York Press; 2000.
15. Norma MJT, Pearson CJ, Searle PGE. Tropical Food Crops in Their Environment. 2nd ed. Cambridge: Cambridge University Press; 1996.
16. Abd Elmoneim AA, Hawsawi ZM, Mahmoud BZ, Bukhari AA, Almulla AA, Sonbol AM, et al. Causes of hospitalization in sickle cell diseased children in Western region of Saudi Arabia. A single centre study. *Saudi Med J.* 2019; **40**(4): 401-404. Doi: 10.15537/smj.2019.4.24049
17. Emond AM, Holman R, Hayes RJ, Serjeant GR. Priapism and impotence in homozygous sickle cell disease. *Arch Intern Med*. 1980 Nov;**140**(11):1434-7. PMID: 6159833.
18. Serjeant GR. The natural history of sickle cell disease. *Cold Spring Harb Perspect Med.* 2013 Oct 1;3(10):a011783. doi: 10.1101/cshperspect.a011783. PMID: 23813607; PMCID: PMC3784812.
19. Yadav R, Lazarus M, Ghanghoria P, Singh MPSS, Gupta RB, Kumar S, *et al.* (2016) Sickle cell disease in Madhya Pradesh, Central India: A comparison of clinical profile of sickle cell homozygote vs. sickle-beta thalassaemia individuals. *Hematology*. 21; **9**:558-563, DOI: 10.1080/10245332.2016.1148893
20. Liu X, Miller MJ, Joshi MS, Sadowska-Krowicka H, Clark DA, Lancaster JR Jr. Diffusion-limited reaction of free nitric oxide with erythrocytes. *J Biol Chem*. 1998 Jul 24;**273**(30):18709-13. doi: 10.1074/jbc.273.30.18709. PMID: 9668042.
21. Bivalacqua TJ, Musicki B, Hsu LL, Gladwin MT, Burnett AL, Champion HC. Establishment of a transgenic sickle-cell mouse model to study the pathophysiology of priapism. J Sex Med. 2009 Sep;**6**(9):2494-504. doi: 10.1111/j.1743-6109.2009.01359.x. Epub 2009 Jun 11. PMID: 19523035; PMCID: PMC4011713.
22. Kato GJ. Priapism in sickle-cell disease: a hematologist's perspective. J Sex Med. 2012 Jan;**9**(1):70-8. doi: 10.1111/j.1743-6109.2011.02287.x. Epub 2011 May 6. *PMID*: 21554552; PMCID: PMC3253142.
23. Kahle B, Hermanns HJ, Gallenkemper G. Evidence-based treatment of chronic leg ulcers. Dtsch Arztebl Int. 2011 Apr;**108**(14):231-7. doi: 10.3238/arztebl.2011.0231. Epub 2011 Apr 8. *PMID*: 21547162; PMCID: PMC3087120.
24. Babalola OA, Ogunkeyede A, Odetunde AB, Fasola F, Oni AA, Babalola CP, et al. Haematological indices of sickle cell patients with chronic leg ulcers on

compression therapy. *Afr J Lab Med*. 2020; **9**(1): a1037 doi; 10.4102/ajlm.v9i1.1037

25. Shah V, Muley P, Choraria C, Rana P, Kanaria D, Markana A. Clinical and hematological profile of sickle cell disease affected children in rural tertiary level hospital. *J PediatrRes*.2017; **4**(03):204-208. doi:10.17511/ijpr.2017.03.01.
26. Panigrahi S, Patra PK, Khodiar PK. The screening and morbidity pattern of sickle cell anemia in chhattisgarh. Indian J Hematol Blood Transfus. 2015 Mar;31(1):104-9. doi: 10.1007/s12288-014-0407-z. Epub 2014 Jun 13. PMID: 25548454; PMCID: PMC4275531.
27. Oluwagbenga OO, Ndububa DA, Yusuf M, Bolarinwa RA, Ayoola OO. (2019) Clinical and Biochemical Manifestations of Severe Sickle Cell Anemia in Adult Patients in Steady State in Ile-Ife, Nigeria. *Sudan J Med Sci* 2019; **14**(1): pages 52–63. DOI 10.18502/sjms.v14i1.4381
28. Minniti CP, Eckman J, Sebastiani P, Steinberg MH, Ballas SK. Leg ulcers in sickle cell disease. *Am J Hematol.* 2010 Oct;**85**(10):831-3. doi: 10.1002/ajh.21838. PMID: 20872960; PMCID: PMC2953786.
29. Gerardin M, Rousselet M, Couec M-L, Masseau A, Guerlais M, Authier N, *et al*. (2021) Descriptive analysis of sickle cell patients living in France: The PHEDRE cross-sectional study. *PLoS ONE* **16**(3): e0248649. https://doi.org/10.1371/ journal.pone.0248649
30. Habibi A, Arlet J-B, Stankovic K, Gellen-Dautremer J, Ribeil J-A, Bartolucci P, *et al*. [French guidelines for the management of adult sickle cell disease: 2015 update]. *Rev Med Interne*. 2015 May 11; **36**(5 Suppl 1):5S3–84. https://doi.org/10.1016/S0248-8663(15)60002-9 PMID: 26007619
31. Howard J, Anie KA, Holdcroft A, Korn S, Davies SC. Cannabis use in sickle cell disease: a questionnaire study. *Br J Haematol*. 2005 Oct; **131**(1):123–8. https://doi.org/10.1111/j.1365-2141.2005.05723.x PMID: 16173972
32. Matthews C. The Role of Nutritional Care in Sickle Cell Disease: A Real Phenomenon. *Acta Scientific Nutritional Health* 3.2 (2019): 74-80.
33. Connes P, Machado R, Hue O, Reid H. Exercise limitation, exercise testing and exercise recommendations in sickle cell anemia. Clin Hemorheol Microcirc. 2011;**49**(1-4):151-63. doi: 10.3233/CH-2011-1465. PMID: 22214686.
34. Emanuel AS, McCully SN, Gallagher KM, Updegraff JA. Theory of Planned Behavior explains gender difference in fruit and vegetable consumption. Appetite. 2012 Dec;**59**(3):693-7. doi: 10.1016/j.appet.2012.08.007. Epub 2012 Aug 14. PMID: 22898607; PMCID: PMC3490048.
35. Iyanda AA. Abnormal presentation of serum micro-nutrients in wistar rats: consequence of virgin engine oil exposure. American Journal of Life Science Researches 2017; **5**(2): 62-69. http://www.diili.org/ojs-2.4.6/index.php/ajlsr/index
36. Khan SA, Damanhouri G, Ali A, Khan SA, Khan A, Bakillah A, Marouf S, Al Harbi G, Halawani SH, Makki A. Precipitating factors and targeted therapies in combating the perils of sickle cell disease--- A special nutritional consideration. Nutr Metab (Lond). 2016 Aug 8; **13**:50. doi: 10.1186/s12986-016-0109-7. PMID: 27508000; PMCID: PMC4977632.
37. Wright RJ, Lee KS, Hyacinth HI, Hibbert JM, Reid ME, Wheatley AO, Asemota HN. An Investigation of the Antioxidant Capacity in Extracts from Moringa oleifera Plants Grown in Jamaica. Plants (Basel). 2017 Oct 23;**6**(4):48. doi: 10.3390/plants6040048. PMID: 29065510; PMCID: PMC5750624.
38. Nurain IO, Bewaji CO, Johnson JS, Davenport RD, Zhang Y. Potential of Three Ethnomedicinal Plants as Antisickling Agents. Mol Pharm. 2017 Jan 3;**14**(1):172-182. doi: 10.1021/acs.molpharmaceut.6b00767. Epub 2016 Dec 5. PMID: 28043127; PMCID: PMC5963525.
39. Tang R, Tian RH, Cai JZ, Wu JH, Shen XL, Hu YJ. Acute and sub-chronic toxicity of Cajanus cajan leaf extracts. Pharm Biol. 2017 Dec;**55**(1):1740-1746. doi: 10.1080/13880209.2017.1309556. PMID: 28494681; PMCID: PMC6130582.
40. Kasuma N, Arma U, Risalina L, Liputo I, Fajrin FN. Zn as the Factor of Alkaline Phosphatase in Periodontal Patients consuming Minangkabau food in West Sumatra, Indonesia. *Bangladesh Journal of Medical Science*,2019;**18**(2):228–232. https://doi.org/10.3329/bjms.v18i2.40690
41. Nargis N, Mahmood AKA, Afrin SF, Sayeed MH, Hassan MZ. Unani preparation 'Sharbat Misali' is useful as an alternate medicine to safely treat anemia: A pilot study. *Bangladesh Journal of Medical Science* 2018;**17**(1):144–148. https://doi.org/10.3329/bjms.v17i1.35295
42. Putri WB, Akhmad SA, Desrini S. The role of zinc supplementation for diarrhoea in children: a critical review. Bangladesh Journal of Medical Science 2019 **18**(2);190–195. https://doi.org/10.3329/bjms.v18i2.40684
43. Prusty BSK, Rameneni KK, Ingle A, Reddy KM, Perveen S, Majed ABM. Dengue Fever Complicated by Sickle Cell Crisis with Multiple Splenic Infarcts. *International Journal of Human and Health Sciences (IJHHS*), [S.l.], v. 5, n. 4, p. 519-524, july 2021. ISSN 2523-692X. Available at: <https://ijhhsfimaweb.info/index.php/IJHHS/article/view/367>. Date accessed: 13 feb. 2023. doi:http://dx.doi.org/10.31344/ijhhs.v5i4.367.