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Haematological and Physical Changes in Steady State Sickle Cell Anaemia Subjects Post L-Arginine Supplementation

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Abstract

***Background*:** Sickle cell anaemia is responsible for one of the largest mortality rates in Africa, it is also associated with several complications including physical, systemic, endothelial, and haematological disorders.
***Objective*:** To evaluate changes in physical and haematological profile of steady state sickle cell anaemia subjects six weeks post oral administration of 1000mg L-arginine supplement.
***Methods*:** Eighty participants were recruited into the study. 40 steady state sickle cell patients from Ladoke Akintola University Teaching Hospital, Ogbomoso (LTH), haematology clinics and 40 healthy control subjects. Physical characteristic was recorded, blood samples of participants were also taken before and after six weeks administration of 1000mg oral L-arginine supplement. Full blood test was conducted pre and post administration. All data were analyzed using GraphPad prism version 8 with $p<0.05$ set as statistically significant value.
***Results*:** Age 18-25 years old and 26-33 years old were the majority age range representing 80% of the participants in this study while the remaining 20% were above 34 years old. Forty four were females and 36 were males. Steady state HbSS participants had significantly lower body weight and BMI (45.30.30±1.40kg and 20.91±0.69kg/m^2, respectively with p=0.001). Hb conc. significantly increased post-supplementation in HbSS group (7.93 to 11.72 g/dL), p=0.0001), Red blood cell (RBC) count decreased in HbSS post-supplementation (3.74 to 3.12 $\times 10^{12}$/L), and white cell count (WBC) increased significantly in HbSS post-supplementation (p = 0.0001).
***Conclusion*:** Oral dose of 1000mg L-Arginine supplement improved the physical condition and haematological profile of steady state sickle cell anaemia subject through increased NO availability to enhance erythropoiesis and improved immune response.

Keywords: Anaemia, Endothelial, Steady-State, Sickle Cell, Supplementation, Systemic.

Introduction

Sickle cell anaemia is a hereditary blood disorder defined by the production of sickle-shaped red blood cells, primarily affecting populations in sub-Saharan Africa, with Nigeria as a known endemic country or epicenter.[1] Sickle cell anaemia (SCA) is caused by mutations in the hemoglobin gene, leading to rigid and sickle cell shapes that obstruct blood flow, this is usually the cause of pain and tissue damage in such individuals.[2] SCA follow an autosomal recessive pattern of inheritance, this means that two gene copies are needed for disease manifestation in an individual, while carriers usually remain asymptomatic.[3] The high prevalence of SCA in Africa is said to be

associated with the impact of malaria outbreak, with several researches showing that individuals with the sickle cell trait have some protection against the disease, resulting in a higher gene frequency.[4,5] In Africa, over 150,000 annual births with sickle cell disease in sub-Saharan Africa have been reported and in Nigeria around 25% of the country's population are carriers of this gene.[6,7]

Sickle cell anaemia comes with a whole lot of systemic and vascular complications due to the fragile and rigid sickled cells leading to chronic anaemia and systemic complications, including notable growth retardation, pallor, and jaundice.[8,9] Physical changes include facial and skeletal alterations like frontal bossing, maxilla protrusion, and skeletal deformities due to repeated vaso-occlusive episodes, causing bone infarctions and avascular necrosis, leading to chronic pain and mobility issues.[10]

Body composition parameters, including waist circumference, weight, and body mass index (BMI), are critical for understanding the nutritional and metabolic status of individuals with sickle cell anaemia.[11] These metrics are often adversely affected by the chronic nature of the disease, leading to altered appetite, nutrient absorption, and energy utilization. Weight is notably decreased in SCA patients due to increased basal metabolic rate from chronic anaemia, recurrent infections, and nutrient malabsorption, resulting in undernutrition and growth issues, particularly in children.[12] Low BMI is associated with severe disease complications like lower haemoglobin levels and poorer immune response.[13] Waist circumference, reflecting central adiposity, is often lower due to reduced fat stores, though some patients on treatments may develop increased fat accumulation, raising concerns about metabolic risks and there might be no significant changes in SCA patients.[14]

Haemoglobin in sickle cell patients is predominantly the abnormal variant, haemoglobin S (HbS), which results from a single amino acid substitution (valine for glutamic acid) at the sixth position of the β-globin chain.[2] Under deoxygenated conditions, the Haemoglobin S tends to polymerize, causing the red cells to assume a sickled or crescent shape. This abnormal morphology leads to increased rigidity and fragility of the erythrocytes, promoting their premature destruction in the spleen and circulation. As a consequence, the haemoglobin concentration is chronically reduced, leading to haemolytic anaemia.[2,3] In steady state SCA patients, chronic hemolysis leads to significant changes in the their haematological profile, primarily chronic anaemia characterized by a reduced lifespan of red blood cells to 10 to 20 days (normal is 120 days) and low haemoglobin levels (below 10 g/dL) as seen in haemolytic anaemia.[15] In SCA patients, elevated reticulocyte counts and leucocytosis is seen due to inflammation and increased bone marrow activity, which also leads to increased platelet counts during crises, all these contributes to an hypercoagulable state.[16]

In recent years, researchers have explored a potential therapeutic role of L-arginine in the management of sickle cell anaemia patients. L-Arginine acts as a substrate for nitric oxide (NO) production, which is critical for vascular function and maintaining endothelial integrity.[17] In SCA, chronic haemolysis depletes L-arginine and disrupts the L-arginine-NO pathway, leading to endothelial dysfunction and increased vaso-occlusive crises which is common in sickle cell patients. L-arginine supplementation has also shown to increase nitirc oxide level and reduces oxidative stress in steady state subjects.[18] Supplementation of L-arginine in SCA children has showed a reduction in pain and crisis episode, and also a shorten hospital stay.[19,20,21] Supplementation of L-arginine has shown potential in enhancing NO levels, improving blood flow, and reducing pain in patients.[22] Additionally, L-arginine supports energy metabolism and tissue repair in human.[23] Therefore, it is important to consider restoring L-arginine and NO levels in order to significantly improve vascular health and study how it affects their haematological profile. Nevertheless, not enough studies have been conducted to study the effects of L-arginine on physical and haematological parameters, especially in steady state SCA adults. While some studies show improvements in endothelial function and vascular tolerance,[24] there is limited evidence on its short term or long term impact on physical health. Also, haematological outcomes in some of these studies shows inconsistent responses to L-arginine supplementation.

As stated earlier L-arginine is known to enhance nitric oxide production and improve vascular function,[17] its specific impact on physical changes and haematological parameters in stable state conditions remains underexplored. Understanding these effects could provide valuable insights into whether L-arginine can improve physical health, improve the haematological profile in steady state SCA subjects. Therefore, this study aimed to fill critical knowledge gaps and support evidence-based research for alternative therapy in sickle cell management.

METHOD

Forty (40) Sickle cell anaemic patients (Haemoglobin SS) in steady state, male and female between the ages of 18 and 65 years old were recruited from Haematology clinic, Ladoke Akintola University of Teaching Hospital (LTH), Ogbomoso, Oyo state, Nigeria. Another 40 undergraduate, postgraduate students and staff of College of Health sciences, Ladoke Akintola University of Technology, Ogbomoso who are Haemoglobin AA, of same age range and gender were matched to serve as control for the test subjects.

Inclusion criteria: Patients diagnosed with Sickle cell anaemia, patients in a stable health condition, without acute crises or significant changes in health status for at least four weeks prior to enrollment, patients that were old enough to give an informed consent (above 18 years of age), and patients with no recent blood transfusion.

Exclusion criteria: Patients with other haematological conditions or disorder, Pregnant patients with sickle cell anaemia, unstable patients in recurrent crisis, and paediatrics/children who are not old enough to give consent, and patients with chronic cardiovascular and metabolic disorder

Ethical consideration was obtained from the Lautech Teaching Hospital ethical committee with protocol no LTH/OGB/EC/2024/573 before the start of this study. Also, informed consent was obtained from the participants of this study through the use of an informed consent form signed by all participants. 1000mg oral L-arginine (Natures Field) supplement was procured at a licensed pharmaceutical store in Lagos.

Physical Parameter

a. Height was measured using a stadiometer (SECA 217, Germany) in centimeters (cm), subjects standing erect without footwear against the stadiometer while the height was recorded.

b. Weight: Subjects weight was measured using a calibrated digital weighing scale (SECA 874, Germany) in kilograms. Weight was measured by allowing the subjects to stand erect on the scale while the weight was recorded from the scale

c. Body Mass Index (BMI): BMI was calculated based on the widely acceptable formula BMI, dividing the weight by a square of heights in meters.

$BMI = Weight (kg)/Height (m)^2$ [25]

d. Waist Circumference: this was measured using a measuring tape at the narrowest point between the lower rib and the iliac crest, typically just above the belly button.[26]

e. Hip Circumference: Same principle as waist circumference but at the hips, just below the waist at the trochanter level (widest protrusion of the buttocks).

Haematological Parameter: A full blood count (FBC) for all 80 subjects before administration and post administration was conducted. The collected blood samples were used to determine the haemoglobin (Hb) concentration, red blood cell (RBC), mean corpuscular volume (MCV), mean corpuscular haemoglobin concentrated (MCHC), white blood cell (WBC), granulocyte (GRAN), lymphocytes (LYMP) and platelet (PL) counts using auto- analyzer (Mindray BC -10, Guangzhhou).

Standard Operating Procedure for FBC

Blood samples were taken from the subjects' antecubital fossa using the standard venipuncture techniques. The blood samples were collected into an several labelled Eppendorf tubes containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant to prevent clotting and keep the integrity of the cellular components intact. The samples were mixed gently but thoroughly by inverting the tube 8–10 times immediately. The labelled samples were logged and loaded onto the Mindray BC -10, Guangzhhou automated analyzer. The analyzer measures various parameters, including Hb conc., RBC, MCV, MCHC, WBC, GRAN, LYMP, and PL counts and crossed reference from the manufacture's manual. All values were recorded and exported into an MS. Excel sheet for further analysis.

All numerical data were analyzed using the Graphpad prism version 8, while SPSS version 22 was used to analyze the descriptive statistics like age range and gender, no inferential statistics was performed, all results are presented with Mean±S.E.M at 95% confidence interval, and with $p<0.05$ considered statistically significant. Tukey Post-Hoc was also used for multiple comparison.

RESULTS

This study was conducted among adults above the age of 18 years. Ages 18-25 years and 26-33 years old, represent 80% of the participants in this study. Only a small proportion were above 34 years old (20%). This shows that the study population was predominantly young adults. Females participants were the majority gender (55%) in this study while the male gender constitute the remaining 45% as seen in table A

There were marked differences between the control and test groups in terms of physical characteristics, including weight, BMI, waist circumference, and hip circumference, all of which were statistically significant (P<0.0001 for all parameters, hip circumference except height). Steady state HbSS participants had significantly lower body weight and BMI compared to the HbAA group (45.30.30±1.40kg and 20.91±0.69kg/m^2, respectively with p=0.001) as seen in table B.

Six weeks post administration of oral L-arginine supplement (1000mg), the haematological profile of both control and test group showed some changes.

A. **Table A: Age Distribution and genders of study participants**

Variables	N= 80	Frequency	Percentage (%)
Age(years)	18 to 25	32	40
	26 to 33	32	40
	34 to 41	4	5
	42 to 50	8	10
	51 to 70	4	5
	Total	80	100
Gender		*Frequency*	*Percentage (%)*
	Female	44	55
	Male	36	45
	Total	80	100

Table B: Table B shows that there were marked differences between the control and test groups in terms of physical characteristics, including weight, BMI, waist circumference, and hip circumference, all of which were statistically significant (P<0.0001 for all parameters, hip circumference except height). Steady state HbSS participants had significantly lower body weight and BMI compared to the HbAA group (45.30.30±1.40kg and 20.91±0.69kg/m^2, respectively with p=0.001)

	Before Supplementation (A, B)		After Supplementation(C,D)		Multi. Comp.(p-values)			
Parameters	**HbAA**	**HbSS**	**HbAA**	**HbSS**	**AvsB**	**AvsC**	**BvsD**	**CvsD**
Height (cm)	160.9±2.69	158.3±1.20	160.9±2.69	158.3±1.20				
Weight (kg)	70.30±1.88	45.30±1.40	74.20±1.85	45.91±1.38	0.0001	0.0001	0.0001	0.0001
BMI (kg/m^2)	24.84±0.62	18.25±0.72	26.94±0.42	20.91±0.69	0.0001	0.0001	0.0001	0.0001
Waist Circumference(cm)	80.10±2.06	70.22±1.12	82.40±1.37	76.40±1.50	0.0001	0.0001	0.0001	0.0001
Hip Circumference(cm)	88.60±1.77	79.30±1.46	97.40±1.56	84.80±2.28	0.002	0.0001	0.0001	0.0001

HbSS= Hemoglobin SS, HbAA=healthy Control, BMI=Basal Metabolic Index, Multiple comparison (Tukey post-hoc), NS(not significant P>0.005).

Haemoglobin concentration was significantly increased post-supplementation in both healthy control (9.59 to 12.00 g/dL) and HbSS (7.93 to 11.72 g/dL) groups, with highly significant differences in *AvsC, BvsD,* and *CvsD* comparisons (p=0.0001). Mean Corpuscular Volume (MCV) showed no statistically significant changes across all comparisons. Red blood cell count increased significantly in the control group six weeks post-supplementation (4.82 to 4.71 ×10^9/L) and decreased in the test group post-supplementation (from 3.74 to 3.12 ×10^9/L). All comparisons were statistically significant (p=0.0002). MCHC showed a statistically significant increase in HbAA post-supplementation (AvsC: p=0.02), while other

comparisons were not significant. Both white blood cell count and granulocytes significantly increased in HbSS and remained elevated post-supplementation (BvsD: p=0.0001), with no significant differences post-supplementation between groups (CvsD: Not significant). And, lymphocytes significantly increased in the test group (HbSS) six weeks post-supplementation (BvsD: p=0.0001; CvsD: p=0.03), while it remained stable in the control group. The platelet count increased significantly in the healthy control group post-supplementation (AvsC: p=0.003), with no significant differences observed in other comparisons as seen in table C.

Table C: The changes in haematological profile of the control (HbAA) and sickle cell subjects (HbSS) six weeks post administration of 1000mg of oral L-Arginine supplement. Tested at the level of significance (P<0.05) and expressed in mean ± standard error of mean (SEM).

Table C: **Haematological Parameters**

	Before Supplementation(A,B)		**After Supplementation(C,D)**		**Multi.Comp(p-values)**			
Parameters	HbAA	HbSS	HbAA	HbSS	AvsB	AvsC	BvsD	CvsD
Hb(g/dL)	9.59±0.36	7.93±0.22	12.00±0.28	11.72±0.21	0.89(NS)	0.0001	0.0001	0.0002
MCV (fL)	79.66±0.27	80.85±1.11	79.12±0.40	82.05±1.06	0.96(NS)	0.72(NS)	0.053(NS)	0.71(NS)
RBC (×10^9/L)	4.82±0.08	3.74±0.14	4.71±0.05	3.12±0.10	0.0001	0.0001	0.0001	0.0002
MCHC(×10^9/L)	311.2±1.90	319.2±1.95	313.4±2.03	313.5±1.91	0.85(NS)	0.02	0.9999(NS)	0.17(NS)
WBC (x 10^9/l)	5.28±0.14	9.58±0.48	5.86±0.12	10.09±0.90	0.86(NS)	0.0001	0.0001	0.9(NS)
Granulocytes(×10^9/L)	2.14±0.10	4.90±0.31	2.28±0.06	4.75±0.45	0.985(NS)	0.0001	0.0001	0.98(NS)
Lymphocytes (%)	51.96±1.13	38.02±1.51	52.28±1.02	43.00±1.33	0.998(NS)	0.0001	0.0001	0.03
PLT (x 10^9/l)	212.4±15.91	304.6±19.96	261.0±16.53	286.2±20.60	0.24(NS)	0.003	0.767(NS)	0.766(NS)

HbSS= Haemoglobin SS, HbAA= healthy Control, Hb=haemoglobin, MCV= Mean cell Haemoglobin, RBC=Red cell concentration, MCHC=Mean cell haemoglobin concentration, WBC=White cell count, FL=Femtolitre, PLT=Platelet count, Multiple comparison (Tukey post-hoc), NS (not significant P>0.005).

DISCUSSION

The demography explored in this study aligns with the typical age range in which individuals with steady-state sickle cell disease (HbSS) begin to exhibit physiologic adaptations to chronic anaemia and oxidative stress. It is very important to note that a higher representation of female participants (55%) compared to males (45%) seen in this study may have implications for interpreting metabolic and haematological responses, as gender differences in nitric oxide metabolism, hormonal status, and body composition are known to influence arginine uptake, utilization and vascular function in human.[27]

The significant changes observed in physical parameters following six weeks of oral L-arginine supplementation (1000mg) demonstrate a systemic impact of the amino acid on anthropometric indices. The significant increase in weight and BMI seen in the HbSS group as well as the healthy control group are in contrast with the state of the physical changes seen in adults with sickle cell anemia,[28] this is also consistent with studies that show that L-arginine may influence metabolic efficiency and energy balance and reduces BMI, possibly through its role in nitric oxide synthesis and protein anabolism.[29] While the significant increase in waist and hip circumference seen in the HbSS group (table B) supports an existing evidence of L-arginine effect on waist circumference.[29]

Post-supplementation (six weeks oral dosage of 1000mg L-Arginine supplement) haematological analysis revealed a notable increase in haemoglobin concentration across both control and test groups, with highly significant differences (p = 0.0001). This significant increase from 9.59 to 12.00 g/dL in HbAA and from 7.93 to 11.72 g/dL in HbSS indicates a potentially beneficial effect of L-arginine on erythropoiesis and hemoglobin synthesis, although in previous study, L-arginine only increased fetal haemoglobin(HbF) but the findings in this study could be a further evidence of the erythropoietic role of L-arginine.[23,30] Arginine is a known substrate for nitric oxide synthase, and nitric oxide role has been reported in enhancing erythropoietin sensitivity and improving microcirculatory oxygen delivery, which could explain the improved haemoglobin levels.[17]

The mean corpuscular volume (MCV) showed no significant change post-supplementation (table C), suggesting that red blood cell morphology and volume remained stable, despite improvements in haemoglobin concentration. This stability implies that this L-arginine effect may have been primarily on

haemoglobin synthesis rather than erythrocyte size and through it antioxidant activity on red cells.[31] The red blood cell (RBC) count between group showed an increase in the control group and a decrease in the test (HbSS) group, both statistically significant (p = 0.0002). The reduced RBC count in the HbSS group could reflect transient haemolysis, this is in contrast to the erythropoietic role of L-arginine supplement.[23]
Mean corpuscular haemoglobin concentration (MCHC) increased significantly in the HbAA group post-supplementation (p = 0.02), whereas other comparisons remained non-significant. This improvement in MCHC seen in this study implies enhanced haemoglobin packing within erythrocytes in the healthy group (HbAA), potentially due to increased bioavailability of arginine derived metabolites that support globin synthesis.[32] However, the reduction seen in HbSS group, although not statistically significant, which may indicate continued reduction in intracellular haemoglobin concentration through it activity on the Gardos-Channel.[32,33]
White blood cell (WBC) increased significantly in HbSS individuals post-supplementation (p = 0.0001), which might represent a physiological response to nitric oxide mediated modulation of immune cell activity or a reflection of the persistent inflammatory state inherent in sickle cell disease.[34] The reduction in the post supplement granulocytes in HbSS groups contrast with studies that showed L-arginine enhanced immune response.[13]

Furthermore, the significant rise in lymphocyte count observed in HbSS group (BvsD: p = 0.0001) implies an immune stimulatory effect of L-arginine, consistent with its known role in lymphocyte proliferation and T-cell activation through nitric oxide-dependent mechanisms.[35] A significant increase in platelet count was observed in healthy controls (p = 0.003) but no statistical significant changes were observed in HbSS participants. In healthy individuals, improved nitric oxide bioavailability should limit platelet formation, whereas in HbSS, chronic endothelial dysfunction and platelet activation may increase platelet formation if NO availability is not improved. [36]

CONCLUSION

In conclusion, six weeks post administration of oral dose of 1000mg L-Arginine improves the haematological profile of steady state sickle cell anaemia subject through the increase in haemoglobin concentration (Hb), improved immune response possibly via NO availability. Also, the significant increase in weight and BMI of the steady state sickle cell subject supports the existing evidence of the role of L-arginine in metabolic and energy balance.

Declaration

The authors declare that the work was our original work carried out by us

Author Contribution

All authors contributed significantly to the design and execution of the research work.

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CONFLICTS OF INTEREST

The author declares no conflicts of interest in this study.

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