Serum Selenium and Its Impact on Children with Sickle Cell Anemia in Benin City, Nigeria

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Abstract

Background

Selenium is an integral component of several antioxidant enzymes especially glutathione peroxidase and plays a role in countering oxidative stress. Sickle cell anaemia (SCA) is a genetic disorder characterized by the presence of two mutant haemoglobins (HbSS). Individuals with SCA have chronic oxidative stress even in steady state which predisposes them to selenium deficiency.

Method

Children aged 1 – 16 years who are attending the Paediatric sickle cell clinic and age and sex matched haemoglobin AA controls were recruited for the study. An interviewer administered questionnaire was used in obtaining information from the participants; their anthropometric parameters were measured while blood was collected for serum selenium levels and Packed Cell Volume. The data was analysed using Statistical Package for Scientific Solutions (SPSS) version 21.

Results

Children with SCA had a significantly lower serum selenium level than controls($p < 0.0001$) The mean serum selenium levels of subjects were lower, though not significantly, in females, lower maternal educational status, lower socioeconomic class, lower haematocrit levels and in stunted and underweight children.

Conclusion

The mean serum selenium levels of children with sickle cell anaemia were significantly lower than children without sickle cell anaemia and the prevalence of selenium deficiency was very high

Introduction

Selenium is a micronutrient necessary for the normal functioning of humans and animals and is believed to be one of the most effective antioxidants in clinical settings.[1] It is an integral component of several antioxidant enzymes especially glutathione peroxidase (GPx)[2] and plays a role in countering oxidative stress, repairing cell membranes damaged by lipid peroxidation, modulation of body's response to infections, improvement in fertility, cardiovascular health and cancer prevention.[2,3]

There is no global consensus on the cut off for selenium deficiency in man because of the wide variations in selenium intake, content in food, soil and serum levels in human populations all over the world.[3] However, it is postulated that a serum selenium level of ≥70 µg/L is the minimum concentration required for maximal expression of plasma/serum seleno-protein containing enzymes like GPx while other researchers have stated that serum levels of 90-100 µg/L reflects selenium adequacy.[4] Inadequate dietary intake and increased consumption from sepsis and chronic oxidative states can lead to low selenium levels[5] which is associated with increased susceptibility to disease. Extremely low levels (< 20 µg/L) as seen in some areas of China can result in Keshan disease (endemic cardiomyopathy) or Kashin Becks disease (endemic chronic degenerative osteoarthropathy).[5]
Sickle cell anaemia (HbSS) is an inherited chronic haemolytic anaemia contributing to 5% of under-five deaths on the African continent.[6] Nigeria has the highest incidence of sickle cell anaemia which amounts to about 3%.[7] Individuals with Sickle cell anaemia (SCA) have chronic oxidative stress in steady state which worsens with crises. The mechanisms by which reactive oxygen species (ROS) are generated in SCA include recurrent ischaemia-reperfusion injury following vaso-occlusion, excessive levels of cell free haemoglobin as a result of the ongoing chronic haemolysis in SCA, and the chronic pro-inflammatory state characteristic of the disease. These processes generate reactive oxygen species that lead to multiple pathophysiologic pathways whose final outcome is accelerated haemolysis, endothelial damage, reduced levels of Nitric Oxide (a potent vasodilator), and

hypercoagulability. These mechanisms in turn, fuel a vicious cycle that leads to worsening vaso-occlusion, generation of more ROS and subsequent chronic organ dysfunction. In this way, important antioxidants to mitigate the effects of chronic oxidative stress (e.g. selenium) may become depleted. In addition, patients with SCA are prone to recurrent infections and sepsis which may also result in low levels of selenium.

Studies have shown that serum selenium levels are lower in individuals with sickle cell anaemia compared to those without, even in steady state.[8-10] Most of these studies were either in adults or in a mixed population involving adults and a few children. To the best of the researchers' knowledge, no study has been carried out in Nigeria specifically in children. This study was therefore done to determine the serum selenium levels in children with SCA in steady state.

Materials and methods

This is a descriptive cross sectional study carried out in the Paediatric sickle cell clinic of the University of Benin Teaching Hospital (UBTH), Benin City, Edo State and the Sickle Cell Centre (SCC) in Benin City, from August, 2016 to January, 2017.

Study Subjects and Controls

Children with SCA aged 1 to 16 years were recruited consecutively from the clinic for the study. Age and sex-matched Hb AA children attending the general practice clinic of UBTH for medical examination (for school entry) as well as Hb AA siblings that accompanied the SCA children that were attending clinic were recruited as controls within the study period.

An interviewer administered questionnaire was used to obtain information from the subjects. The fathers' profession and mothers' level of education were used in determining the socioeconomic class of the participants according to the method described by Olusanya *et al.*[11] Information on the number of vaso-occlusive crises, clinic attendance and packed cell volume over the past 6months was obtained from the patients and caregivers which was confirmed by the information in the case notes. Physical examination was carried out by the researchers and documented.

The participants were weighed using a Seca® scale (Secagmbh & co, Germany) with a sensitivity of 0.1kg. The scale was calibrated on each clinic day using a known weight. Children less than 2 years old were weighed naked (in a Bassinet scale) while older children were weighed wearing light clothing.

The height/length was taken using a stadiometer, with the child standing barefoot, legs together, upright and gazing straight ahead. Measurements were taken to the nearest centimetre. For children aged <2years, recumbent length was taken using an infant measuring board placed on a flat surface. The BMI of a child was calculated using the formula: [Weight (kg)/ (Length/Height)^2(m^2)]. Height for age Z-score (HAZ), weight for age Z-score (WAZ) and Body Mass Index Z- score were calculated for all the participants using the 2005 WHO anthro-calculator in comparison to the National Centre for Health Statistics (NCHS) standard population. Malnutrition (stunting, underweight and wasting) was defined as HAZ ≤ -2, WAZ ≤ -2 and BMI ≤ -2 respectively.

Blood samples were obtained from any peripheral vein on the upper limb for estimation of the packed cell volume, serum selenium levels and haemoglobin electrophoresis (for the controls alone). Selenium was assayed by a Chemical Pathologist using Flame atomic absorption spectrometry (AAS).

Ethical clearance was obtained from the Ethics and Research Committee of the UBTH **(ADM/E22/A/VOL.VII/1270)** and the Ethics Committee of the Hospital Management Board, Ministry of Health, Edo State **(HM.1208/146)**. A written consent was obtained from the caregivers of the participants.

The data obtained were analyzed using Statistical Package for Scientific Solutions (SPSS) version 21.0 (IBM SPSS version 21.0). Continuous variables were presented using means± (SD) while categorical variables were presented as frequencies and percentages. Student t-test was used to compare means of continuous variables while differences in means between three or more groups were analyzed using analysis of variance (ANOVA) test.

Chi-square statistical test of significance was carried out where applicable for categorical variables. Spearman Ranks Correlation was used to determine association between serum selenium levels and nutritional status and bone pain crises episodes. The level of significance was set at $p<0.05$ and confidence level at 95%.

Results

A total of 72 Hb SS patients and 72 Hb AA controls were recruited for this study.
The study population consisted of 45 males (62.5%) and 27 females (37.5%) in both study groups with a M:F of 1.7:1. The mean age of the subjects with Hb SS was 7.29 ± 4.46 years (range 1-16 years), while that of the Hb AA controls was 7.25 ± 4.45 years. There was no statistically significant difference between their mean ages (t = 0.58 *p* = 0.954).

A higher proportion of the subjects were of a low SEC (41.7%) as opposed to the control group where the highest proportion (40.3%) belonged to the middle SEC. There was however no statistically significant difference in the SEC of the subjects and controls (χ^2= 0.747, p=0.690)

The socio demographic characteristics of the study participants are shown in Table 1

Table 1: Sociodemographic Characteristics of the Study Subjects and Controls

Characteristics	**Subjects n=72 (%)**	**Controls n =72 (%)**	χ^2	**p value**
Age Group (years)				
<5	26 (36.1)	26 (36.1)		
5 – 9	21 (29.2)	21 (29.2)		
10 – 14	21 (29.2)	21 (29.2)	0.00	1.00
≥15	4 (5.6)	4 (5.6)		
Gender				
Male	45 (62.5)	26 (36.1)		
Female	27 (37.5)	21 (29.2)	0.00	1.00
Socioeconomic class				
Upper	18 (25.0	16 (22.2)		
Middle	24 (33.3)	29 (40.3)	0.747	0.69
Lower	30 (41.7)	27 (37.5)		

The mean weight (SD) of the HbSS children was 23.25 ± 11.88kg as against 28.27 ± 15.61kg obtained from the control group. The difference in the mean weight of the subjects and controls was statistically significant (p = 0.035). The mean height of the subjects was lower than that of the controls but the difference was not statistically significant (p = 0.159).

The mean values of other anthropometric parameters such as the weight for age z-score (WAZ), height for age z score (HAZ) and body mass index z score (BMIZ) were likewise higher in the control group and the difference was statistically significant. This is shown in table 2.

Table 2: Anthropometric measurements in subjects and controls

Characteristics	**Hb SS children (mean±SD)**	**Hb AA children (mean±SD)**	**T**	**p value**
Weight (kg)	23.25 ± 11.88	28.27 ± 15.61	-2.15	0.035*
Height (cm)	119.76 ± 24.77	125.48 ± 26.25	-1.42	0.159
WAZ	-0.65 ± 1.45	0.61 ± 1.39	-5.20	<0.0001*
HAZ	0.13 ± 1.88	1.41 ± 1.96	-4.25	<0.0001*
BMIZ	-0.98 ± 1.36	-0.32 ± 1.93	-2.35	0.021*

**p = < 0.05*

The mean serum selenium level of the Hb SS children was 53.98±8.52 µg/L (range 30.00-74.00 µg/L) while that of the Hb AA children was 67.13±5.93µg/L (range 53.80-82.60 µg/L). The difference was statistically significant (t = -10.03, *p* < 0.0001).

The prevalence of selenium deficiency among Hb SS children using serum selenium levels of >70µg/L as a reference cut off point[4] was 90.3% and was significantly higher than the 16.7% observed in the Hb AA children. (p<0.0001) This is shown in table 3.

TABLE 3: Prevalence of Selenium Deficiency in the study subjects and control group.

Selenium deficiency	Hb SS children n = 72 (%)	Hb AA children n = 72 (%)	χ^2	p value
Present (≤ 70µg/L)	65 (90.3)	12 (16.7)	78.41	<0.0001*
Absent (≤ 70µg/L)	7 (9.7)	60 (83.3)		
Total	72 (100)	72 (100)		

p = < 0.05

The mean serum selenium level of the male subjects (55.38 ± 7.28 µg/L) was higher than that of the female subjects (51.63 ± 9.98 µg/L), but the difference was not statistically significant. Subjects within the age group of 14 – 16 years had a lower mean selenium levels, which was not statistically significant, in comparison with other age groups.

The mean selenium levels of the subjects from high socioeconomic class (55.48 ± 9.68µg/L) was higher than that of those from the middle socioeconomic class (54.88 ± 8.42µg/L), which in turn was higher than that of those from the low socioeconomic class (52.98 ± 8.52 µg/L) but the difference was not statistically significant. A similar trend was observed with maternal educational status, in which children of mothers with tertiary level of education had the highest mean serum selenium level. The difference was however, not statistically significant. Subjects with haematocrit of less than 27% had a lower mean serum selenium level compared with those with a higher haematocrit level. The difference was however not statistically significant. This distribution is shown in table 4.

TABLE 4: Comparison of the subjects' Mean serum selenium levels across Sociodemographic and clinical characteristics.

Characteristics	Mean (SD)	n	F/t	p value
Sex				
Male	55.38 (7.275)	45	1.84	0.07
Female	51.63 (9.986)	27		
Age group (years)				
<5	53.51 (9.132)	26		
5 – 9	55.31 (7.317)	21	0.721	0.543
10 – 14	54.24 (8.757)	21		
>14	48.62 (10.176)	4		
Socioeconomic class				
High	55.48 (9.681)	18		
Middle	54.88 (8.419)	24	0.961	0.388
Low	52.98 (8.524)	30		
Maternal education				
Primary	53.01 (7.476)	15		
Secondary	53.26 (8.459)	31	0.553	0.578
Tertiary	55.38 (9.270)	26		
Haematocrit level (%)				
<27	53.46 7.930)	48	-0.721	0.473
≥27	55.00 (9.702)	24		

Apart from BMIZ the mean serum selenium levels of malnourished subjects were lower than those with normal nutritional status. There was no correlation between mean serum selenium levels and the nutritional status of the subjects.

There was a very weak correlation, which was not statistically significant, between the mean serum selenium level of the children with SCA and the number of bone pain crises over the past 6months. (r = 0.011, p = 0.929) These findings are shown in Table 5.

Table 5: Correlation (Spearman Rank) between mean serum selenium levels and nutritional status and bone pain episodes of the subjects

Characteristic	Mean serum selenium (µg/l) Mean±SD	r_s	p value
WAZ			
Severely underweight/underweight	49.89 ± 11.24	0.125	0.297
Normal	54.64 ± 7.92		
HAZ			
Severely stunted/stunted	50.60± 9.65	0.145	0.224
Normal	54.52± 8.27		
BMIZ			
Severely thin/thin	54.27 ± 9.31		
Normal	53.83 ± 8.40	0.011	0.928
Overweight/obese	55.40 ± 9.90		
Bone pain episodes			
0	54.05 ± 8.05		
1 – 3	53.74 ± 9.06	0.011	0.929
4 – 6	56.47 ± 7.91		

Discussion

The mean serum selenium level of 53.98±8.52 µg/L in children with sickle cell anaemia in this study was significantly lower than that of their Hb AA counterparts (67.13±5.93 µg/L), which is in keeping with the studies by Hamdy *et al*[8] in Egypt, Nnodim *et al*[9] in Imo state, Olaniyan *et al*[12] in Oyo state and Idonijie *et al*[10] in Edo state in Nigeria. Reduced selenium levels in SCA have been ascribed to chronic oxidative stress (even in patients in steady state) resulting from increased release of ROS due to repeated cycles of ischaemia and reperfusion, infections and haemolysis. The ROS released overwhelm available antioxidants including selenium. There is also an increased resting metabolic rate and resting energy expenditure in SCA with subsequent increased turnover of macro- and micronutrients and subsequent depletion of micronutrients like selenium which is an important antioxidant.[13] It can then be inferred from this study that there is increased oxidative stress in the children with SCA as compared to their Hb AA counterparts. Adelakun *et al*[14] however reported absence of increased markers of oxidative stress in children with SCA. The disparity between their conclusion and the finding suggested in this study may be because they only evaluated children <48 months while children aged 1-16 years were evaluated in this study. There is worsening oxidative stress and increased demand for antioxidant protection in children with SCA as they grow older[15]. Moreover, the sample size used by Adelakun *et al* [14] was very small (23) and might not be representative of children with SCA.

The mean selenium levels of children with SCA (53.98±8.52 µg/L) in this study was comparable to the findings in the study by Olaniyan *et al*[12] (55±4.0 µg/L) but were lower than the mean values recorded by Nnodim *et al*[9] (60.69±3.12 µg/L) and Idonijie *et al*[10] (60.98±7.29 µg/L). Hamdy *et al*[8] on the other hand had remarkably lower serum selenium levels than what was seen in this study (29.8±20.80 µg/L). These variations in the serum selenium levels reported in all these studies may be a reflection of the fact that serum selenium levels are influenced by intake in the diet which varies based on geographical location.

There was no significant gender difference in the mean selenium level in this study, which is comparable with the findings of Ubesie et al in Enugu, Nigeria[16] and Nhien et al in Vietnam.[17]Nhien et al however, reported a higher mean selenium level in males, though not significant, which is in consonant with the finding of this study. Krittaphol *et al*[18] and Amare *et al*[19] reported a significantly higher serum selenium level in males. Sources of selenium in diet are available to both sexes and it is not expected to differ between them but a sex-linked hormonal influence was postulated to be responsible for the higher levels in males.[19]

No significant difference was found in the mean serum selenium levels between the various age groups of the subjects but the mean level of children aged 14years and above was lower than other age groups. This finding may be a reflection of the increasing metabolic demand for growth and oxidative stress often found in older children with SCA.[20]

The absence of a significant difference in the mean selenium levels based on the haematocrit of the subjects could not be corroborated by other studies as there was no previous study found to compare with. The observation of a higher serum selenium levels in subjects with higher haematocrit (>27%) may indicate a relationship which needs further evaluation. Oxidative stress is a known contributory factor to both anaemia and depletion of anti-oxidants but other factors such as increased haemolysis, reduced production of red blood cells also play a role in anaemia. These other contributors of anaemia other than oxidative stress may account for the absence of a significant association between anaemia and serum selenium levels.

There was no correlation between the serum selenium levels and the number of vaso-occlusive crises (VOCs) experienced by the subjects. This may be because several other factors predispose to vaso-occlusive crises in these children e.g. dehydration, infections. Repeated VOCs result in depleted antioxidant status because of increased production of ROS. Whether depleted selenium levels would then in turn result in VOC is not clearly stated in the literature. No other study to the knowledge of the researchers has evaluated the relationship between selenium and VOCs in children. However, Fasola*et al*[21] in Ibadan showed that adult patients who had >3 VOCs in the preceding year had markedly reduced mean total antioxidant status (< 1.00 mmol/L) as compared to those who experienced less than 3 VOCs (>1.00mmol/L). They concluded that a pro- oxidant environment was conducive for crises. The difference in this current study from Fasola*et al*[21] may be related to the difference in the age group studied and the fact that only selenium was measured in this study while all biologic components that have antioxidant capacity including selenium were taken into cognizance in the study by Fasola *et al*.

No significant correlation between serum selenium levels and nutritional status was observed in the subjects. The mean selenium levels were lowest amongst SCA children who were underweight and in those who were stunted. This may infer variability in the magnitude of the deficiency in the macro-nutrients in comparison with the micro-nutrients in the subjects. Other studies have also reported absence of correlation between nutritional status and selenium levels.[16,17,19]

Although the mean serum selenium levels increased with increasing socioeconomic status, the difference was not statistically significant. This finding is similar to that of Krittaphol *et al*[18] in Thailand. The reason for this finding may be that the children across all the SECs are exposed to similar foods in this locale that probably have the same selenium content. There have been no studies to the knowledge of the researchers that has correlated socioeconomic status with serum selenium levels in children with SCA. Bates *et al*[22] found that there was a higher plasma selenium concentration in children from higher socioeconomic classes in the general population. The reasons put forward for this finding is that children from higher socio-economic class were exposed to a richer diet comprising more of animal proteins which are a better source of selenium. No other study has established this link.

Ninety percent of the Hb SS children compared to about 20% of the Hb AA children were deficient in selenium, with levels lower than the suggested range of 70-100µg/L[4] required for selenium adequacy and maximal expression and function of the selenoproteins.[23] No other study amongst children with SCA has compared the mean selenium levels with any reference point. This may be because there are no generally accepted reference values.

The mean serum selenium levels of the controls in this study (67.13±5.93 µg/L) is comparable to the findings amongst controls in Edo state (65.75±5.49 µg/L) [10] and Imo state (67.42±1.35 µg/L) [9] both in Nigeria but lower than the values reported in Sudan (85.40±8.82 µg/L) [24]. This low selenium levels even among children without SCA in the Nigerian studies might suggest low selenium content in the diet and soil in this locale. However, Kolawole *et al*[25]showed that the selenium content in soil in some parts of Southern Nigeria were within the mean global range of selenium in soil. The contribution of selenium content of locally available diet to this finding has not been evaluated in this locale.

Conclusion

The mean serum selenium level of children with sickle cell anaemia was significantly lower than that of children without sickle cell anaemia and the prevalence of selenium deficiency was very high in the subjects. The mean

serum selenium levels of subjects were lower, though not significantly, in females, lower maternal educational status, lower socioeconomic class, lower haematocrit levels and in stunted and underweight children. Further studies with larger sample size to ascertain the association between serum selenium levels and these parameters is recommended.

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MO participated in the conception and design of the work, interpretation of the data, revising the manuscript.

AA participated in the interpretation of the data, revising the manuscript. All authors participated in the final approval of the manuscript and agreed to be accountable for all aspects of the work.

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