Original Article

Relationship between Zinc Levels and Anthropometric Indices among School-aged Female Children with Sickle Cell Anemia in Enugu, Nigeria

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Abstract

Background: Sickle cell anaemia is one of the most common inherited disorders globally. Some affected children have retardation of physical growth which is also seen in those with zinc deficiency. **Objective:** To assess the relationship between zinc levels and anthropometric indices of SCA children. **Methods:** A cross-sectional, case-control study on young females aged 6-18 years at the UNTH, Enugu. Relevant clinical data as well as 24 hour dietary recall were collected. Weights and heights were measured using standard protocols and BMI calculated. Serum zinc was determined using Atomic Absorption Spectrophotometer. Data was analyzed using SPSS version 15.0 while the level of statistical significance was set at $P < 0.05$. **Results:** Eighty-one subjects with HbSS and 81 matched controls with HbAA were studied. Mean weights of 34.58 ± 12.76kg found in patients were significantly lower than 40.19 ± 13.37kg in controls. Also mean BMI of 16.27 ± 2.76kg/m2 in patients were significantly lower than 18.40 ± 2.96kg/m2 in controls ($P = 0.01$). Mean heights of patients were lower than that of the controls though not significantly so ($P > 0.05$). Mean serum zinc levels of 58.01 ± 10.58µg/d1 in patients were significantly lower than 68.37 ± 8.6µg/dl in controls ($P = 0.01$). Positive correlation was found between serum zinc and BMI of the studied children. Serum zinc has a significant relationship with weight, height and BMI. **Conclusion:** Reduced serum zinc in SCA children was associated with low anthropometric indices. Estimation of serum zinc is also recommended in SCA children with low anthropometric indices.

Keywords: *Anthropometric indices, female children, serum zinc, sickle cell anemia*

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Introduction

Growth and development are fundamental and intrinsic characteristics of childhood and are marked by complex changes. They begin at conception and transit through several stages, prominent among which is adolescence.[1] This is a developmental period through which a child passes into adulthood.[2] It involves among other things, acceleration of physical growth, with changes in the shape, and composition of the body.

Anthropometric indices including weight and height are the two most commonly used measurements of growth.[3] The body mass index (BMI) is a body mass per unit area and a measure of adiposity of an individual and found to be a good indicator of nutritional status.[4]

Sickle cell disease including sickle cell anemia (SCA) is known to have a profound effect on physical growth. Several studies[5-10] have demonstrated that children with SCA have reduced weight, height, and BMI when compared with their counterparts with HbAA. Zinc is an

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essential trace element with widespread roles to sustain human health. It participates in the regulation of cell proliferation in several ways; it is essential to enzyme systems that influence cell division and proliferation. Removing zinc from the extracellular milieu results in decreased activity of deoxythymidine kinase and reduced levels of adenosine 5'-tetraphosphate. Hence, zinc may directly regulate DNA synthesis through these systems. Zinc also influences hormonal regulation of cell division. Specifically, the pituitary growth hormone (GH)-insulin-like growth factor-I (IGF-I) axis is responsive to zinc status. Both increased and decreased circulating concentrations of GH have been observed in zinc deficiency, although circulating IGF-I concentrations are consistently decreased. However, growth failure is not reversed by maintaining either GH or IGF-I levels through exogenous administration, which suggests the defect occurs in hormone signaling. Zinc appears to be essential for IGF-I induction of cell proliferation; the site of regulation is postreceptor binding. Overall, the evidence suggests that reduced zinc availability affects membrane signaling systems and intracellular second messengers that coordinate cell proliferation in response to IGF-I.

The dietary intake of zinc is about 10–15 mg/day. It is present in meat and other protein foodstuffs. Zinc is absorbed in the small intestines particularly the duodenum and proximal jejunum through an active, energy-dependent process.[11] It is known to affect normal growth and development and it's deficiency has been implicated as a possible factor which caused growth retardation and delayed sexual maturation in SCA.[12] Possible causes of zinc deficiency in SCA patients include inadequate intake, increased demand and consumption,[13] and increased urinary excretion due to impaired renal concentration. Prasad *et al*.[14] and Leonard *et al*.[15] found that decreased plasma zinc is common in children with HbSS genotype and is associated with decreased linear and skeletal growth, muscle mass, and sexual and skeletal maturation. SCA and zinc deficiency can both cause growth retardation,[16] and zinc supplementation was found to have a positive effect on growth and body composition in children with sickle cell disease.[17]

Considering the high burden of SCA in Nigeria with the prevalence rate of 2% in newborns[18] in a population of over 182 million,[19] there is need for robust studies to determine the relationship between micronutrient status and anthropometry of children with SCA and their effect on poor growth and delayed development. Growth restriction in children with SCA, especially females, constitutes a source of anxiety to these children and their parents, who often turn to the doctor for advice. It may have long-term psychological consequences which may affect the ability of the adolescent with SCA to form normal relationship with the opposite sex, thus leading to low self-esteem and depression. There is, therefore, a need for appropriate locally available data on which the counseling of such patients may be based. Furthermore, zinc is known to affect normal growth and development, but there is no study yet on the growth parameters of SCA children in the study locality that evaluated their zinc levels. Thus, the aim of this study was to determine the relationship between zinc levels and anthropometric indices of school-aged female children with SCA in Enugu, Nigeria.

Methods

This cross-sectional, descriptive study was carried out at the Department of Pediatrics, University of Nigeria Teaching Hospital (UNTH), Ituku-Ozalla, Enugu, Nigeria. Ethical approval for the study was given by the Health Research and Ethics Committee of the UNTH, Enugu, and informed written consent was obtained from the parents or caregivers, whereas assents were obtained from the selected studied children.

A total of 81 female children with SCA within the age range of 6–18 years were consecutively enrolled from the sickle cell clinic. Age- and social class-matched controls were selected from the children outpatient clinic. They comprise children who were seen for conditions such as minor aches and pains, minor skin lesions/trauma, and medical certificate of fitness for school enrollment. Adequate history, detailed medical examination, and laboratory investigations (where necessary) were carried out on these controls. Inclusion criteria included children that did not have fever associated with acute respiratory infection, malaria, diarrhea, or other clinical conditions known to affect serum zinc. They did not have other chronic illness(es) that affect physical growth such as bronchial asthma, congenital heart disease, chronic renal failure, diabetes mellitus, or malignancies. All the study participants (both patients and controls) were not on zinc-containing drugs and were not transfused with blood or blood products in the preceding 3 months before the study (to avoid contribution of zinc from the donor blood). They ate at least 4 h before blood samples were collected (to avoid using a fasting blood which will affect the serum zinc). During starvation, release of zinc from muscle tissues that are catabolized can result in transient, seemingly paradoxical elevations of serum zinc,[20] and hence giving a higher concentration. Information on biodata, parent's/guardian's highest level of education

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and occupation, present complaints, past medical and drug history, and recall of food taken in the past 24 h was documented using an interviewer administered questionnaire, which had been validated. The weights and heights of all the participants were measured by the investigator using the Health Scale RTZ-120A, Hecos, China. The error margin of the weighing scale is 0.1 kg (100 g) and that of the stadiometer is 0.1 cm (100 mm). In the weight measurement, the participants wore only light clothing, stood erect, touching nothing. Each measurement was recorded to the nearest 0.1 kg and the scale was calibrated after every twenty measurements. For the heights, measurements were taken with each participant standing erect, without shoes, heels together, and back as straight as possible. They were made to look forward with the lower border of the eye socket in the same horizontal plane as the external auditory meatus. The head piece was moved down until it touched the child's head. The investigator observed the procedure to ensure that the heels of the participant did not come off the ground. The measurement was then recorded to the nearest 0.1 cm.

The BMI or Quetelet's indices were calculated using the formula:

$$\text{BMI} = \frac{\text{Weight (in kg)}}{\text{Height (in m}^2\text{)}}$$

Social classification was done using the method proposed by Olusanya *et al*.[21] Here, the scores obtained from (a) father's occupation (maximum of 3) and (b) mother's highest level of education (maximum of 2) were added to give the social class. A maximum of 5 and minimum of 1 can be scored, and social class is inversely related to the score. Furthermore, grouping of scores into 1 or 2, 3, 4 or 5 represents the upper. middle and lower socio economic class respectively. The hemoglobin genotypes of the participants were determined using cellulose acetate paper in alkaline electrophoresis and were complimented with sickling test using 2% sodium metabisulfite solution at the hematology laboratory of the UNTH, Enugu. Five mililiters of venous blood was collected from each enrollee for serum zinc estimation using aseptic technique. All blood samples were collected between 9 am and 1 pm so as to eliminate the effect of diurnal variations in serum zinc concentration.[16,22] The clotted blood samples were centrifuged in test tubes with bench centrifuge Eppendorf 5702 at 1500 revolutions per minute for 10 min. The clear sera were transferred into plain bottles and stored at −68°C pending analysis. These materials had been washed clean of possible zinc contamination by the researchers using 10% nitric acid and rinsed thoroughly with deionized water. The serum zinc was determined using atomic absorption spectrophotometer (Model 210 VGP, Buck Scientific America), at the Projects Development Institute, Enugu. Data were analyzed using the Statistical Package for the Social Sciences Version 15.0 (IBM 233, South Wacker Drive, Chicago, USA). Statistical significance of continuous variables was assessed using Student's *t*-test, whereas categorical variables were tested using Chi-square test. Correlations were used to measure how variables were related and linear regression applied as indicated to test the predictive value of the associations. Level of significance was put at 0.05.

Results

A total of 81 patients were compared with 81 controls. In all age ranges, SCA children were found to weigh less than their controls [Figure 1]. These differences in weights were found to be statistically significant for all ages except for 14–15 years. The overall mean weights of the patients (34.58 ± 12.76 kg) was significantly lower than that of the controls (40.19 ± 13.37 kg), (t = −2.73, P = 0.007). For most ages, the controls were taller than the patients though not to a statistically significant degree except at 10–11 years age group, where the difference was significant (t = 2.22, P = 0.04) [Figure 2]. However, at 18 years, the patients were taller than the controls though not significantly so (t = −1.05, P = 0.32). There was no significant difference between the overall mean height of the patients (1.43 ± 0.17 m) when compared with that of the controls (1.45 ± 0.16 m) (t = −0.94, P = 0.35).

The overall mean BMI of the patients (16.27 ± 2.76 kg/m^2) was also significantly lower than that of the controls (18.40 ± 2.96 kg/m^2) (t = −4.75, P = 0.001), and these were statistically significant for all ages except for age 10–11 years. However, unlike the height, the mean BMI of the participants at 18 years remained significantly lower than that of the controls (t = 2.85, P = 0.02), [Figure 3]. The overall mean serum zinc levels of participants (58.01 ± 10.58 μg/dl) were significantly lower than those of the controls (68.37 ± 8.67 μg/dl) (t = 6.82, P = 0.001). When compared with their weights, there was a positive correlation between the serum zinc levels and weights of all the studied children [Table 1]. A similar comparison was made with the heights of patients and controls in Table 2. For patients aged 6–14 years, there was a strong positive correlation between serum zinc and height, whereas in those between age 16 and 18 years, there was a negative correlation. For the controls, the positive association was weak at ages 10–11 and 14–15 years. A positive correlation was also shown to exist between the serum zinc level and BMI of the study population [Table 3]. This association was strong in all age ranges for both

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Table 1: The relationship between serum zinc levels of patients and controls and their weights

Age range (years)	Patients			Controls		
	Mean weight±SD (kg)	Mean serum zinc±SD (μg/dl)	*r*	Mean weight±SD (kg)	Mean serum zinc±SD (μg/dl)	*r*
6-7	19.79±3.49	55.25±9.07	0.91	24.57±3.20	61.71±8.92	0.77
8-9	25.65±4.98	56.47±11.08	0.80	29.24±6.03	68.92±9.06	0.80
10-11	30.09±3.37	52.98±8.88	0.76	37.41±8.51	69.81±8.41	0.79
12-13	35.18±6.29	57.30±12.06	0.80	41.60±6.09	65.40±4.32	0.88
14-15	45.75±9.27	60.07±11.32	0.50	51.21±7.78	70.03±7.81	0.43
16-17	50.50±6.27	64.44±9.96	0.40	57.27±2.93	73.01±7.17	0.86
18	52.67±1.63	64.41±6.91	0.41	58.5±3.04	73.48±9.87	0.74

SD=Standard deviation

Table 2: The relationship between serum zinc levels of patients and controls and their heights

Age range (years)	Patients			Controls		
	Mean height±SD (m)	Mean serum zinc±SD (μg/dl)	*r*	Mean height±SD (m)	Mean serum zinc±SD (μg/dl)	*r*
6-7	1.17±0.09	55.25±9.07	0.52	1.22±0.05	61.71±8.92	0.72
8-9	1.32±0.08	56.47±11.08	0.75	1.34±0.09	68.92±9.06	0.82
10-11	1.39±0.06	52.98±8.88	0.63	1.46±0.09	69.81±8.41	0.16
12-13	1.52±0.05	57.30±12.06	0.50	1.53±0.06	65.40±4.32	0.69
14-15	1.58±0.07	60.07±11.32	0.50	1.59±0.06	70.03±7.81	0.16
16-17	1.59±0.03	64.44±9.96	−0.03	1.62±0.05	73.01±7.17	0.41
18	1.65±0.06	64.41±6.91	−0.32	1.62±0.02	73.48±9.87	0.32

SD=Standard deviation

Table 3: The relationship between serum zinc level of patients and controls and their body mass index

Age range (years)	Patients			Control		
	Mean BMI±SD (kg/m²)	Mean serum zinc±SD (μg/dl)	*r*	Mean BMI±SD (kg/m²)	Mean serum zinc±SD (μg/dl)	*r*
6-7	14.32±1.01	55.25±9.07	0.75	16.36±1.50	61.71±8.92	0.50
8-9	14.60±1.61	56.47±11.08	0.51	16.64±2.08	68.92±9.06	0.52
10-11	15.44±1.60	52.98±8.88	0.55	17.34±2.97	69.81±8.41	0.72
12-13	15.07±2.11	57.30±12.06	0.58	17.66±2.42	65.40±4.32	0.77
14-15	18.11±2.37	60.07±11.32	0.36	20.11±2.28	70.03±7.81	0.50
16-17	19.93±2.31	64.44±9.96	0.50	21.90±1.04	73.01±7.17	0.82
18	19.40±1.91	64.41±6.91	0.50	22.30±1.35	73.48±9.87	0.50

BMI=Body mass index; SD=Standard deviation

Table 4: Linear regression of the dependence of weight, height, and body mass index on serum zinc

Dependent variable	Beta coeffcients	*t*	*P*
Weight	0.69	8.84	0.001*
Height	0.007	6.01	0.001*
BMI	0.18	10.52	0.001*

*Statistically significant. BMI=Body mass index

Table 5: Mean serum zinc and social class of patients and controls

Social class	Patients		Controls		*t*	*P*
	n (%)	Mean serum zinc±SD (μg/dl)	*n* (%)	Mean serum zinc±SD (μg/dl)		
Class 1	19 (23.5)	65.53±8.95	18 (22.2)	69.51±8.41	−1.39	0.173
Class 2	24 (29.6)	57.13±10.04	27 (33.3)	70.88±9.23	−5.09	0.001*
Class 3	38 (46.9)	54.78±10.01	36 (44.5)	65.92±7.89	−5.29	0.001*
All	81 (100)	58.01±10.58	81 (100)	68.37±8.67	−6.82	0.001*

*Statistically significant. SD=Standard deviation

the patients and controls, except for the 14–15 age range in the patients where the association was weak (r = 0.36). A linear regression analysis was conducted [Table 4], and it was found that serum zinc has a significant

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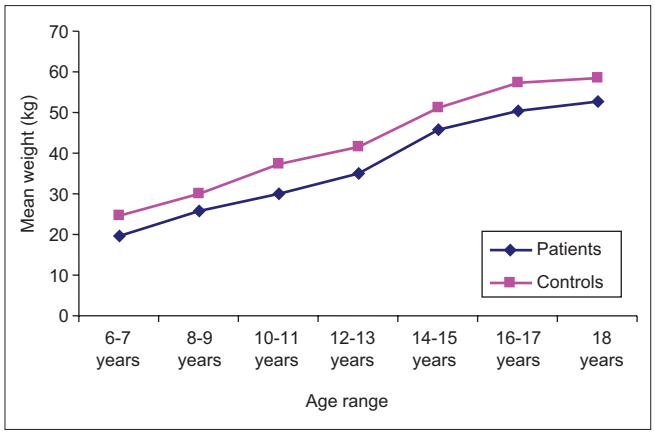

Figure 1: Mean weights of patients and controls according to their age ranges

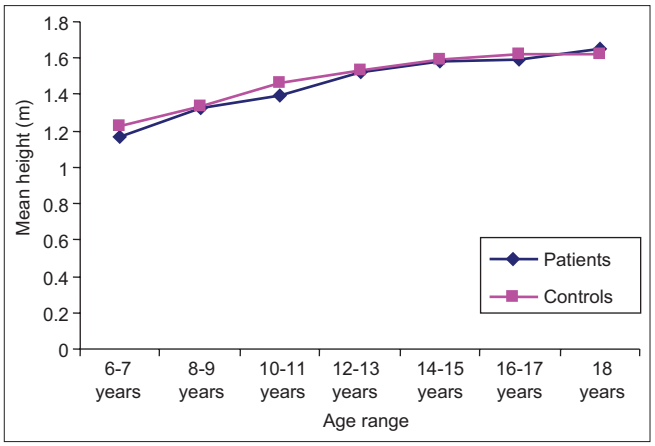

Figure 2: Mean heights of patients and controls according to their age ranges

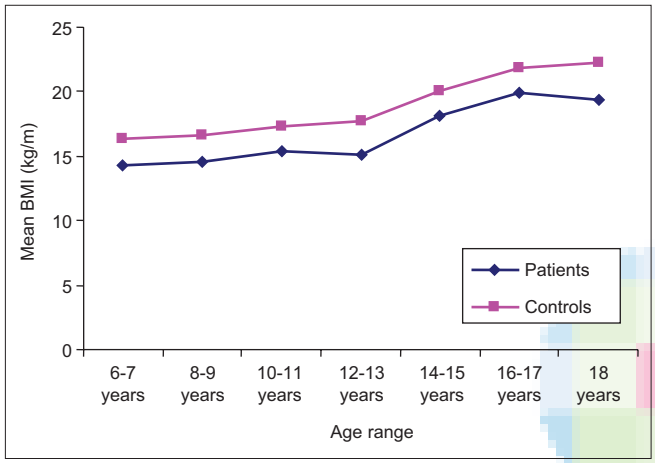

Figure 3: Mean body mass index of patients and controls according to their age ranges

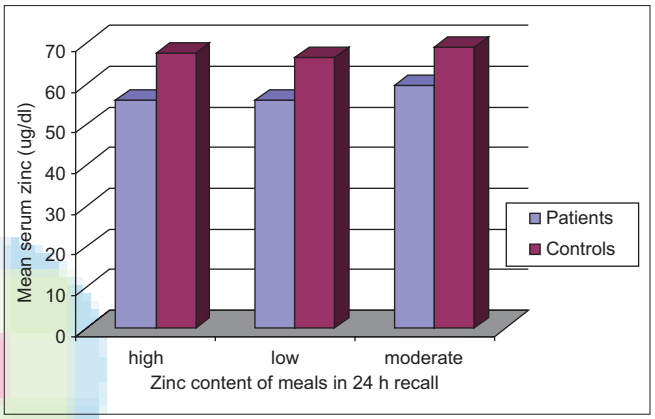

Figure 4: Mean serum zinc of patients and controls and zinc content of meals in 24 h recall

relationship with weight, height, and BMI as their *P* values were statistically significant.

Discussion

Children with SCA had low anthropometric indices when compared to their controls. This is in keeping with findings from previous studies.[6,7,9,22,23] Their weights were significantly less than those of the controls for most age ranges. The difference in weight between the patients and controls was noted from the age of 6 years. It increased with age and was most apparent at 10 years of age. This may have been the point of adolescent growth spurt among the controls. Interestingly, this difference in weight between the participants and their control was not significant at the age range of 14–15 years. This may also be the likely point at which the SCA patients had their adolescent growth spurt; about 4 years after their non-SCA counterparts did so. A similar pattern was observed in the heights of the younger patients and their controls. The SCA patients in this study were found to be shorter than their controls. Again, this was noticeable from 6 years of age but was significant only at the age range of 10–11 years, which may be a pointer to the onset of pubertal growth in the HbAA children. There was subsequently a narrowing in the gap and by 18 years of age; there was a reversal of the trend such that the SCA patients were actually taller than the controls, though not significantly so. Such pattern was observed in other studies.[7,8,24] This trend in deficit of height of SCA patients differed from that observed in their weight, and agrees with the fact that stunting is commonly a feature of younger SCA patients who later catch-up in growth to achieve a similar or even greater height with their HbAA counterparts.[8,25,26]

The mean body mass indices of the SCA children were shown to be lower than those of the controls. This remained statistically significant for most of the age range till 18 years of age, unlike what was seen with the heights. The mean BMI of both SCA patients and controls obtained in this study are higher than the values obtained in a similar study done by Emodi and Kaine[7] in the same locality. That study[7] documented a mean BM1 of 14.56 ± 1.5 kg/m^2 and 15.27 ± 3.02 kg/m^2 for

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the female patients and controls, respectively. The use of 16 years as the upper age limit in that study[7] may have accounted for the lower values. Furthermore, the study[7] was done more than 15 years ago, and improvement in socioeconomic status over the years with improved lifestyle and well-being may explain the higher value obtained in this study. The low BMI values in patients with SCA are a reflection of their low body weight. It also shows that they usually have greater increase in height than weight during the period of adolescence. The etiology of retarded growth in SCA patients includes disturbed GH-IGF-1 axis,[27] increased metabolism,[28,29] and possibly from increased erythropoiesis seen in this condition. Again, nutrition may be inadequate with deficiency of vitamins and trace elements including zinc – a growth factor which when deficient adversely affects growth.[12,30,31] A normal but delayed pattern of adolescent growth in most SCA children argues against an endocrine abnormality and suggests that these metabolic and nutritional factors affect the timing of the adolescent growth spurt but not the final height. However, since these children still achieve similar or even greater heights, it may be that there is a delay in the closure of the epiphyseal growth end of long bones allowing for catch-up growth among SCA patients.[22] This is important as most SCA patients with initial retardation of adolescent growth and development can be reassured as to their final height outcome.[29,32]

The SCA patients had low levels of serum zinc (58.01 ± 10.58 μg/dl) when compared with the controls (68.37 ± 8.67 μg/dl). This corroborates findings from several other studies.[14-16,33-35] This low level found in them could neither be explained by the differences in their social class nor the zinc content of their meal in 24 h recall as within each social class, the mean serum zinc levels of the controls were higher than those of the patients as shown in Table 5. Again, both patients and controls with moderate zinc content of meal taken in the previous 24 h before blood collection had the highest serum zinc level as shown in Figure 4. The reasons for the low zinc levels in the SCA patients may include chronic hemolysis. Zinc is an essential constituent of red blood cells and is also an antioxidant. Repeated hemolysis with continuous oxidative stress due to sickle cell reduction-oxidation imbalance, zinc is utilized, resulting in its increased demand.[36,37] Again, SCA children have increased urinary excretion of zinc due to impaired renal concentration. Furthermore, due to frequent hospitalization for painful crises and infections with poor appetite, nutrition may be suboptimal during these periods,[13] hence low zinc intakes with consequent low serum levels. This study showed a positive correlation between the serum zinc levels and weights of both the SCA patients and their controls. This corroborates findings from earlier studies,[15,34] and also supports the fact that both SCA and zinc deficiency can on their own cause growth retardation. A strong positive association was found to exist between the serum zinc levels and heights of the SCA patients between the ages of 6–15 years, which is also consistent with findings from earlier studies.[15,16,34] However, a negative correlation was noted beyond this age. The reason for this is not clear but may be due to the fact that this is the point of maximum catch-up growth, especially in height of the SCA patients. For the controls, a positive association was noted between serum zinc and height though the strength of the association was inconsistent. This study also revealed a positive correlation between serum zinc and the BMI of both patients and controls. This correlation spans across all age groups and lays credence to the fact that BMI is a better tool in assessing growth than weight or height used separately.[24,26] Zemel *et al*.[17] noted an improved rate of linear growth, but no effect on BMI following zinc supplementation in children with sickle cell disease. It is possible that a concurrent improvement in the weight of the studied children resulted in this finding. It has been proposed that the best test for zinc deficiency in children is to assess the growth response to zinc supplementation.[38,39] This has been demonstrated in a number of randomized clinical trials with otherwise normal children with growth retardation.[38,39] Provision of zinc supplements during nutritional rehabilitation has been associated with increased appetite and food consumption, weight gain, linear growth, and the synthesis of lean tissue.[38-41] This study found that zinc level has a significant relationship with weight, height, and BMI which may suggest that zinc deficiency may play a role in the prevalence and severity of growth failure in children with SCA.

Conclusion

Reduced serum zinc level found in SCA school-aged females was associated with reduced anthropometric indices. It is recommended that participants with reduced anthropometric indices should also have serum zinc estimation. Again, the study should be done on males to identify gender differences where they exist. In addition, a randomized study in this locality to assess the effect of zinc supplementation on SCA children with low anthropometric indices is recommended.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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