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Antioxidant Intake in Sickle Cell Disease

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Abstract Sickle Cell Disease (SCD) clients experience hypermetabolic state. The objectives of this study were to determine whether there are differences in total dietary intake of antioxidants in both groups was in keeping with recommended dietary intake by the Caribbean Food and Nutrition Institute (CFNI). This case-control study was conducted using a validated Food Frequency Questionnaire among 42 clients with SCD and 42 normal controls who were matched for age and gender. Participants were SCD clients of varying phenotypes e.g. Thalassemia, HbSS and HbSc who were recruited from the Sickle Cell Unit at an urban clinic and controls were healthy individuals free of SCD drawn from a wider community embracing the urban clinic. There were 65.5% female and 34.5% male participants. The mean age of all participants was 35.4 years and their ages ranged from 18-69 years. There was no difference in age by group (p=0.19). The levels of intake of 12 antioxidants were examined (β carotene, Vitamin B group, Vitamin E group, Vitamin C, Zinc, and Selenium). There were no statistical differences in the mean intake level of each antioxidant between controls and SCD clients. The study also found that all participants consumed antioxidants in excess of Recommended Dietary Allowances with the exception of zinc (mean intake level= 14.4 mg/d) and selenium (mean intake level= 61.8 µg/d). There was no difference in the antioxidant intake between SCD clients and their controlled counterparts and the daily intake of both groups were higher than CFNI recommendations. The study indicates that participants had adequate and higher than RDA intake levels of antioxidants which facilitates cell turnover and Red Blood Cell formation in Sickle Cell Disease Clients.

Keywords: *nutrition, antioxidants, Sickle Cell Disease, nutrients, Recommended Dietary Allowances*

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1. Introduction

Sickle Cell Disease (SCD) is a genetic condition which is characterized by sickling that Red Blood Cells (RBC) undergo when they become deoxygenated. This condition affects millions globally and is most prevalent in people from sub-Saharan Africa; the Western Hemisphere (South America, the Caribbean, and Central America); Saudi Arabia; India; and The Mediterranean [1]. In Jamaica it is reported that approximately 10% of the population carries the sickle cell gene [2]. SCD is typified by RBC having shorter lifespan (less than 100-120 days), reduced oxygen carrying capacity, vasoocclusion, inflammation as well as impairment in iron metabolism. The etiology at present is documented as a genetic change in the β- chain of the adult hemoglobin which results in a deformity of RBC [3]. The condition can be modified favourably or undesirably by fluid intake, concomitant diseases, thermoregulation and antioxidant capacity.

SCD patients experience increased oxidative stress compared to their healthy counterparts. Therefore, antioxidant capacity is vital in SCD to control the extent of tissue injury that may occur as a result of increased oxidative stress [4]. SCD condition may further impair antioxidant demand as sickle erythrocytes may form clumps with healthy RBC damaging them and increase circulating reactive oxygen species such as superoxides and hydroxyl radicals [4]. It is theorized that individuals who have characteristic hypermetabolic processes, such as oncological patients and SCD patients will require an increased antioxidant capacity to combat oxidative stress [5].

The vitamin antioxidant capacity of an individual may be increased either by de novo synthesis or by increased dietary intake. The relationship between the antioxidant content of a food sample consumed and the subsequent antioxidant activity in the target cell while strong is not directly correlated [6]. In another intervention study with 112 participants it was reported that specific antioxidants are increased in plasma following fruit and vegetable intake. The author cites increase in lutein, lycopene, β-carotene, and vitamins C and B_6 [7]. Antioxidant requirements and levels increase when there are higher levels of markers of inflammation. Correspondingly, a moderate direct relationship was found between markers of reactive oxygen species (ROS) and in vivo folic acid (p= 0.0007 and r=0.58) [3]. Consequently, increasing antioxidant intake beyond particular levels provided no additional antioxidant benefit. Another intervention study reported that a diet containing 600g of fruits and vegetables per day, or having additional vitamin and mineral supplements provided no additional reduction in markers of oxidative damage [8].

Fruits and vegetable have been inversely associated with inflammation and antioxidant effects [4]. In addition to functioning as an oxygen radical scavenger γ-tocopherol scavenges reactive nitric oxide species and inhibits prostaglandin E_2 have been found to mediate inflammation [4]. Other amine antioxidants function as lipid peroxide and scavenge ROS [7,9,10].

Individuals diagnosed with SCD have a greater requirements for the antioxidant (Glutathione) to facilitate metabolic processes, than controlled counterparts [9]. This increase in demand is documented to be potentiated by increased requirements of substrates for active synthesis. The review cites in vitro experiments which demonstrate a reduction in sickling following Glutathione supplementation [9].

FFQs are advantageous in examining dietary intake as they are inexpensive, expedient and provide data on usual intake. A detailed search, has found that data linking antioxidant intake and sickle cell disease is limited. Similarly, no data is presently available regarding fruit and vegetable consumption in persons with SCD in Jamaica. Therefore, we used a validated FFQ to examine a group of 84 matched participants to identify whether there was a difference in antioxidant intake. The primary aim of this study is to determine whether nutritional differences exist between cases and control groups in relation to:-

1. anthropometric indices including stature, weight and BMI
2. total dietary intake of antioxidants
3. total dietary intake of antioxidants adjusted for body mass
4. total dietary intake of antioxidants and Recommended Dietary Allowances (RDAs) by the Caribbean Food and Nutrition Institute.

2. Materials and Methods

2.1. Subjects

This was a cross sectional case control study involving 42 SCD and 42 participants matched within 5 years of age and gender controls (29 males and 55 females p=0.19, with a mean age of 35.4 years old, ranging between 18 and 69 years old). Forty two participants (Mean age, 37.2 years) with SCD of varying phenotypes – Thalassemia, HbSS and HbSc were recruited from the Sickle Cell Unit at an urban clinic and consented to participate. Subjects were recruited as participants of an original study approved by the Institutional Review Board of the Faculty of the UHWI/UWI/FSM. Participants were recruited as cases if they had SCD and were clients of the Sickle Cell Unit at an urban clinic and controls were healthy individuals free from SCD drawn from the wider community adjacent to the urban clinic. This study was conducted over a three month period from October to December, 2009.

2.2. Tools

The instruments utilized in the data collection included a five item questionnaire that educed medical history and demographic data. Additionally, a 25-item pre-tested and validated Food Frequency Questionnaire (FFQ) was administered to collect dietary history particularly fruit and vegetable intake over the past month. The tool was validated in comparison with twelve repeated 24-hour recalls ($p \leq 0.001$ - mean FFQ intake significantly different from repeat recalls) [11]. The data collection process lasted thirteen weeks and all tools were interviewer administered.

2.3. Analysis

The dietary intake of participants over a month was aggregated into servings per day. Three samples of each fruit and vegetable on the FFQ were weighed to establish average weight. The average weight of each fruit and vegetable was used to convert serving intake per day into gram of fruit/vegetable intake per day. Serving intakes from the FFQ were entered into the database as gram of fruit and vegetable consumed. Fruits on the Questionnaire were based on seasonal availability, as well as popularity on the market. Legumes were included into the total vegetable intake.

Data were sorted and entered into Nutribase Version 10. This software analyzed the food intake and provided nutrient value according to Food and Drug Administration protocols. The analysis produced were quantitative values of vitamins and minerals including Alpha Tocopherol, Vitamin C, Thaimin, Riblofavin, Zinc, and Selenium and their values were used as proxies of antioxidant intake.

2.4. Statistical Analysis

The results generated from the nutritional software were collated and entered into statistical software, Stata version 19. Results are presented as counts, means with standard deviation or 95% confidence intervals, or medians with ranges as appropriate. For categorical outcomes, the Pearson's chi square, statistic was used to assess associations between groups. For continuous outcome variables, the Shapario-Wilk test was done to examine normality of the intake by group. For normally distributed continuous outcome variables differences by group were determined by independent t-test. Continuous outcome variables that could be normalized by Napier logarithm transformation, differences by group were determined by independent t-test on the transformed scale. The Mann-Whitney test was used to determine differences in distribution by group for skewed variables. Linear regression techniques were used to compute differences in outcome variables by group, adjusting for body mass. For all inferential statistics a p- value of less than 0.05 was considered to represent a significant statistical difference.

3. Results

The demographic characteristics of subjects enrolled in the study are displayed in Table 1. A sample of 84 men and women with and without SCD participated. There were 42 persons with SCD (SCD group) and 42 persons without SCD (control). There was an unequal distribution of gender among the participants; 65.48% were female and 34.52 % were male. In the SCD group, 11 were males and 31 females. There was no significant difference in proportion of males or females by participant group (p=0.11).

Table 1. Mean Intake of fat soluble vitamins of participants compared with CFNI RDA values for nutrients

Fat soluble Vitamins	Mean Intake	Standard Deviation	CFNI RDA
Vitamin A precursor (β carotene) µg	80121.7	48359.7	600
Vitamin E (alpha tocopherol) mg	79.0	54.3	10
Vitamin E (gamma tocopherol) mg	3.0	2.1	10

The mean age of controls (37.2 years was greater than that of SCD group, 33.6 years but this difference was not statistically significant (p=0.19). The mean age of all participants was 35.4 years and their ages ranged from 18-69 years (Figure 1).

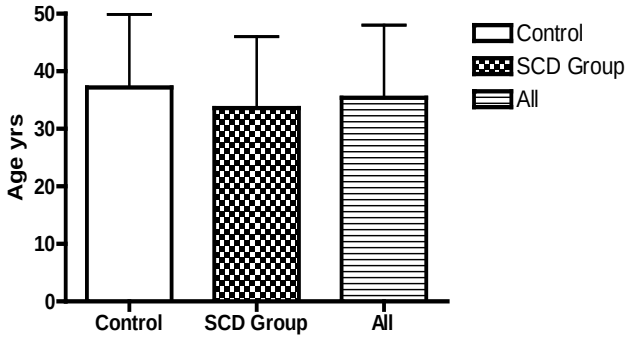

Figure 1. Mean Age of participants, SCD cases and normal AA controls, enrolled in the study

The mean intake of vitamins among participants was generally higher than the Recommended Dietary Allowances (RDA) stipulated by the Caribbean Food and Nutrition Institute (CFNI).

The most notable difference between participants' intake and RDA was observed with β-carotene, with the reported mean intake being 80121.7µg/d and with a corresponding RDA of 600µg/d (Table 1).

The differences with the intake of the all the other vitamins were not as large as that noticed with β-carotene (Table 1 & Table 2). The mean recorded intake of Vitamins B_1, B_2 and B_3 were 6.1mg/d, 6.3mg/d, and 59.2mg/d, higher than the corresponding RDA values of 0.7mg/d, 1.3mg/d and 14.52mg/d respectively.

Table 2. Intake of water soluble vitamins of participants compared with CFNI RDA values for nutrients

Water soluble Vitamins	Mean Intake	Standard Deviation	CFNI RDA
Vitamin B_1 (Thiamine) mg	6.1	4.2	0.7
Vitamin B_2 (Riboflavin) mg	6.3	3.7	1.3
Vitamin B_3 (Niacin) mg	59.2	37.1	14.52
Vitamin B_5 (Pantothenic acid) mg	26.6	17.1	5
Vitamin B_6 (Pyridoxine) µg	14.2	9.0	15
Vitamin B_9 (Folate) µg	2397.5	1428.4	200
Vitamin C (Ascorbic acid) mg	7722.3	4726.7	60

In contrast, the mean reported intake of γTocopherol was lower than the corresponding RDA for the vitamin. The participants reported a mean intake of 3.0mg/d compared to the RDA of 10mg/d for the vitamin.

There were 3 persons in the SCD group (median-2208mg, iqr=2537 mg) who reported dietary intakes greater than 1.5 x the interquartile range and 1 person in the control group (median-2115mg, iqr=2139). There was no difference in the reported intake of vitamin C by participant groups (Figure 2).

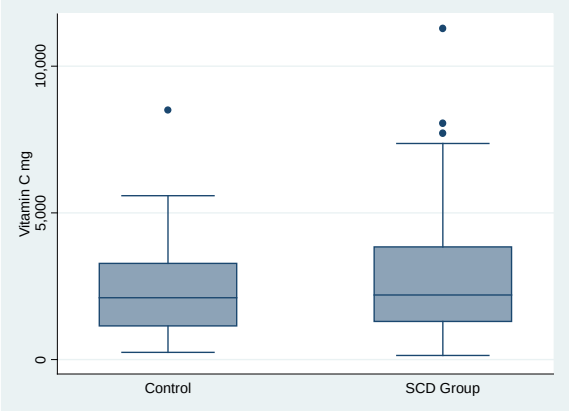

Figure 2. Comparative intake of Vitamin C of participants, SCD cases and normal AA controls, enrolled in the study

Table 3. Differences in intakes of Antioxidants of SCD group and AA controls

Antioxidant	Intake of SCD group	Intake of controls	Difference	(95%) Confidence Interval for difference in intake		p-value
Fat soluble						
Vitamin A (β carotene) µg	84791.53	75451.89	2125.79	69627.02	90616.40	0.52
Vitamin E (alpha tocopherol) mg	72.16	85.92	13.76	67.26	90.83	0.25
Vitamin E (gamma tocopherol) mg	3.06	3.02	0.03	2.58	3.50	0.94
Water Soluble						
Vitamin B_1 (Thiamine) mg	5.62	6.63	1.01	5.21	7.04	0.27
Vitamin B_2 (Riboflavin) mg	5.80	6.75	0.95	5.47	7.09	0.25
Vitamin B_3 (Niacin) mg	54.15	64.21	10.06	51.14	67.22	0.22
Vitamin B_5 (Pantothenic acid) mg	24.11	29.18	5.07	22.92	30.36	0.18
Vitamin B_6 (Pyridoxine) µg	13.03	15.43	2.41	12.27	16.19	0.22
Vitamin B_9 (Folate) µg	2241.4	2553.65	312.25	2087.54	2707.51	0.32
Vitamin C mg	2414.82	2981.02	566.40	2246.39	3149.66	0.21
Trace Elements						
Selenium (µg)	55.86	67.76	11.81	53.00	70.52	0.18
Zinc (mg)	13.60	15.13	1.54	12.75	15.98	0.35

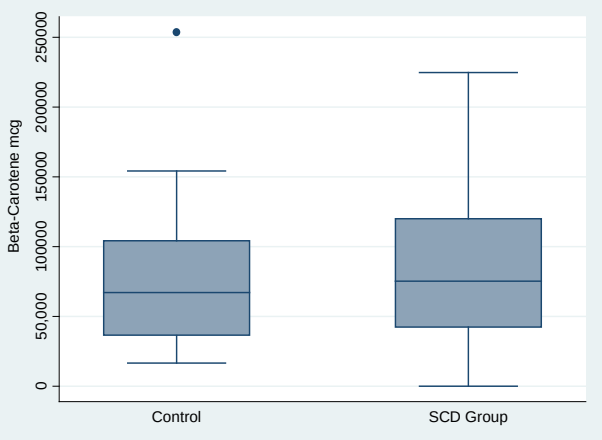

Figure 3. Comparative intake of Beta Carotene of participants, SCD cases and normal AA controls, enrolled in the study

Figure 3 shows the distribution of participants consuming β carotene. There was no significant difference in the consumption of β carotene between SCD group and controls. Similarly for all the other vitamins studied there were no differences in the dietary intakes between controls and SCD group (Table 3).

Table 4. Mean intake of trace elements of participants

Trace Elements	Mean Intake	Standard Deviation	CFNI RDA
Selenium (µg)	61.8	40.4	55-70
Zinc (mg)	14.4	7.4	12-15

The trace elements examined produced contrasting findings. The participants mean intake of selenium (61.8±40.8) was within normal ranges (RDA 55-70 µg) (Table 4). While, the mean intake for zinc by participants was 14.4 mg/d compared with 12-15 mg/d recommended (Table 4). However, as was the case with antioxidant vitamins there was no difference in the reported dietary intakes between controls and SCD group with p-values that were not statistically significant (Table 5).

Table 5. Differences in Intakes of Antioxidant Trace Elements of SCD group and AA controls

Antioxidant	Intake of SCD group	Intake of controls	Difference	(95%) Confidence Interval for difference in intake		p-value
Trace Elements						
Selenium (µg)	55.86	67.76	11.81	53.00	70.52	0.18
Zinc (mg)	13.60	15.13	1.54	12.75	15.98	0.35

Table 6. Differences in the Weight (kg), Height (cm) & BMI (kg/m^2) of Participants

Variable	Group					
	Males			Females		
	SCD group	Controls	Difference [p value]	SCD group	Controls	Difference [p value]
Weight (kg)	65.34	66.26	1.48 [0.82]	64.36	67.55	3.20 [0.48]
Height (cm)	169.6	168.46	1.84[0.56]	166.03	169.74	3.71 [0.12]
BMI (kg/m^2)	22.59	23.92	1.33 [0.56]	23.23	23.25	0.023 [0.99]

Table 7. Weight adjusted intake of participants

Variable	SCD group(se)	Control (se)	p-value
Fat soluble			
Vitamin A (β carotene) µg	145791 (21303.59)	167095 (21303.59)	0.298
Vitamin E (alpha tocopherol) mg	72.03 (14.02)	86.06 (14.02)	0.786
Vitamin E (gamma tocopherol) mg	0.31 (0.02)	0.33 (0.02)	0.783
Water Soluble			
Vitamin B_1 (Thiamine) mg	5.62 (1.02)	6.63 (1.02)	0.276
Vitamin B_2 (Riboflavin) mg	5.80 (0.97)	6.76 (0.97)	0.244
Vitamin B_3 (Niacin) mg	54.0 (10.36)	64.36 (10.36)	0.206
Vitamin B_5 (Pantothenic acid) mg	24.05 (5.18)	29.23 (5.18)	0.172
Vitamin B_6 (Pyridoxine) µg	12.97 (2.51)	15.49 (2.51)	0.208
Vitamin B_9 (Folate) µg	2242.21 (310.63)	2552.84 (310.63)	0.326
Vitamin C mg	2412.33 (571.39)	2983.72 (571.39)	0.215
Trace Elements			
Selenium (µg)	55.76 (12)	67.76 (12)	0.179
Zinc (mg)	13.61 (1.52)	15.12 (1.52)	0.358

Values are adjusted means with standard errors

The mean weight, height and Body Mass Indices of the control group were higher than that of SCD group. Male controls were 0.82kg heavier than SCD group, 0.56cm shorter and had a higher BMI of 0.56kg/m^2 more than

SCD group. Female controls were 0.48kg heavier, 0.12cm shorter and had a higher BMI of 0.99kg/m^2 greater than SCD group (Table 6). The difference was also evident across genders, except that when analyzed; SCD group males were taller than male controls, 169.6 and 168.46 cm respectively. The mean BMI of all participants was 23.30 kg/m^2 and their BMI ranged from 15.53- 46.59 kg/m^2. The anthropometric assessments of the participants were not statistically significant (p= >0.05).

After adjusting for differences in weight, there was a higher intake of all vitamins and trace elements that were studied in the control group compared with the SCD group. However the differences were not statistically significant (Table 7).

4. Discussion

This experimental study of a group of Jamaican SCD clients and equivalent non-SCD controls found that, all participants consumed quantities of vitamins and trace elements in excess of the Recommended Dietary Allowances (RDA) of the Caribbean Food and Nutrition Institute. Adult females and males (18-65) are advised to consume 600µg of β carotene, 10mg Vitamin E, 10 µg Vitamin B_6, 60mg Vitamin C, and 200µg Folate per day in addition to adequate macronutrients in order to facilitate satisfactory metabolism, growth, development and maintenance of body functioning [11].

This study demonstrated that participants consumed adequate quantities of fruit and vegetables that provided necessary dietary vitamins and trace elements to meet their daily dietary recommendations [11].

Antioxidants, which are provided by the intake of fruit and vegetable, provide many vital functions indispensible in maintaining healthy body functioning. Their contribution to the management of the clinical manifestation of SCD is well documented [4,9,10]. This study investigated whether a difference existed in the intake of antioxidants among SCD clients compared with healthy controlled counterparts and whether the levels of intake were in keeping with the RDA of CFNI.

When examined, non-SCD individuals who were heavier had higher BMI than SCD group individuals and were also shorter than their counterparts (p= >0.05). SCD individuals experience greater metabolic demands than their health controlled counterparts, which makes fat deposition less probable and could account for SCD individuals being lighter. This formed the basis for the weight adjusted analysis. These findings are supported by current data which suggest that SCD clients are thinner than AA counterparts because of higher metabolic rates (particularly children and adolescents [12,13]. Sickle crises and pain have been documented as contributors of physiological weight loss in SS individuals [14]. Current evidence describes high metabolic demands and with resultant loss of lean body mass in SCD. HbSS may present with signs of protein energy malnutrition which is a manifestation of increased energy use and requirement [11]. Existing case control descriptive studies have made similar conclusions, identifying that HbSS whole body protein breakdown was faster than normal counterparts (5.0 ± 0.3 vs. 3.8 ± 0.2 mg/kg FFM^{-1} $\cdot min^{-1}$; $P,< 0.05$ vs. controls) [11].

The weight adjusted analysis of this study revealed that controls consumed higher quantities of antioxidant than SCD group; however the results were not statistically significant (p-values by vitamin 0.18 – 0.94).

The study identified that all participants consumed antioxidants in excess of RDA, which may be potentially unhealthy. An intake of nutrients at or above the threshold level is expected to pose a health risk, with the extent of the risk being dependent on the type of nutrient and the actual level of the intake [16]. Furthermore, adverse effects arise when intake is exceeded on a regular basis.

The nature of an individual's intake plays an important role in the development of toxic effects. To illustrate, Vitamin A in this study was supplied through β carotene bioactive retinol metabolites that are not as potent as retinol and functionally acts a precursor to the active metabolite. These compounds are metabolized differently in the body than primary Vitamin A and thus the adverse reactions are less potent [17]. Similarly, the continuous lower intake of a vitamin may lead to the development of adverse reactions. Of note this study reported that two of the antioxidants tested were within RDA ranges. The consumption of zinc and selenium were reported to be within RDA, both in SCD group and controls. Studies have shown that zinc status in SCD patients is associated with wound healing [18], improving hyperammonemia and encephalopathy [19]. Animal sources, particularly red meats provide the best sources of zinc [20]. However, this study did not examine total dietary intake. It focused on fruit and vegetable intake and zinc may be supplied by the consumption of fish and fish oils, thus this finding may be higher than reported.

Increased antioxidant intake may be beneficial for SCD clients as they support cell turnover and RBC formation [7,9]. The intake of nutrients physiologically impacts the body in two main ways; either through the physiological maintenance of the body systems or causing adverse effects [16]. The adverse effects may result from either inadequate intake (of an essential nutrient), or excess intake (of most nutrients). Thus, for many nutrients, two threshold levels are presumed to exist: 1) an intake level that must occur on a regular basis to prevent the adverse effects of deficiency, and 2) an intake level that must be exceeded on a regular basis for a toxic effect to occur [16].

Excess intake of vitamin A or its products has been associated with organ damage and weakened tissues (e.g., bones) in addition to teratogenic effects [1,21]. This study showed that all participants across both groups consumed way in excess of CFNI Recommended Daily Allowances. These findings have public health implications associated with them. There is a need for continued dissemination of information about the balanced intake to prevent hypo/hyper vitaminosis. Thus it points to the need for additional research to examine whether this higher intake above RDA is consistent and usual or seasonal.

The period assessed is typified by the availability of inexpensive seasonal fruits and vegetables. The FFQ used, assessed in particular seasonally available fruits and vegetables, and could not assess off- peak consumption. Furthermore, SCD group were recruited from the Sickle Cell Unit which has dietary counseling, and fruit and vegetable promotion as part of the treatment strategies employed. There is statistically significant difference in the intake patterns of people across agricultural seasons

for fruits and vegetables. This supports the findings of the study and may indicate that the intake patterns are not generalizable year round [22].

SCD group of individuals is a unique group not unlike pregnant women. In the latter case the Caribbean Food and Nutrition Institute has developed adjusted RDA values to meet their additional requirements [11].

Current literature identify that SCD individuals should consume higher levels of antioxidants than controlled healthy counterparts [5,23]. Though the data regarding the increased needs of SCD individuals is available it has not yet been used to generate a standardized level of intake or an adjusted RDA of antioxidant that would be sufficient to meet the unique demands of the SCD group. Therefore, further analysis using an experimental cross-over design may be effective in identifying whether an increase in specific antioxidants above RDA for controlled counterparts results in better clinical outcomes for SCD individuals. These findings could assist in generating the RDA of antioxidants unique to SCD. Present evidence identifies that HbSS clients may experience protein/energy malnutrition despite macronutrient supplementation and supports this recommendation that RDAs for nutrients be established for HbSS clients like pregnant women due to this increased nutrient requirement [11].

Additionally, studies designed with other measurement tools may provide more robust results than FFQ. The FFQ has several limitations and the results it generates could be better validated with Daily Food Records and Diet History [4]. Some studies have successfully used a nutritional index to evaluate nutritional behavior [7]. This strategy may improve the quality of the data collected.

This is a pilot study and consequently supports the need for further research in antioxidant intake and development of hepatomegaly, splenomegaly in SCD clients as well as antioxidant therapy and a reduction in the need for hospitalization in this group of individuals.

Current data suggest that the availability and demand of fruits and vegetables does impact the intake patterns of many individuals [16]. Seasonal availability and higher market prices are inversely related to adequate intake. However, this study did not design methodologies to test demand of fruits and vegetable on intake during the study period. Therefore additional research should be conducted to examine if the intake of SCD and Non SCD individual differs with market pricing and availability year round.

5. Limitations

This study examined 12 antioxidants. The data collection methods limit the generalizability of the study. The FFQ that was used to assess Zinc intake only accounted for contribution from fruit and vegetable. Animal products particularly, red meat are the best sources of zinc. Meats that are leaner have higher zinc content, that is, the higher the fat free content, the higher the zinc levels [20]. The FFQ also did not account for fortified cereals and zinc content.

Additionally, the FFQ had good relative validity for all antioxidants examined except Vitamins A and E [24].

The results of the study listed higher than RDA intake for all antioxidants except zinc. This may be related to the nature of the data collection process of interviewer administered questionnaire. Current evidence points to misreporting as the main error identified in dietary assessment. Therefore, care must be taken when the results of this study are interpreted [25].

6. Conclusion

In summary, this is a pilot study that concurs with the available data on SCD and fruit and vegetable intake. In this study the participants met and, in some instances, surpassed the RDAs for antioxidants. Increasing fruit and vegetable intake may provide better clinical outcomes for SCD clients.

There was no difference in the antioxidant intake between cases and controls and the daily intake of both groups were higher than CFNI recommendations. The study indicates that participants had adequate and higher than RDA intake levels for antioxidants which facilitates cell turnover and Red Blood Cell formation in Sickle Cell Disease Clients. Further evidence regarding the efficacy, safety and appropriate dosage of antioxidants in relation to chronic disease is needed. The most prudent public health advice to SCD clients is to increase the consumption of plant foods, as dietary patterns are associated with reduced risk of chronic disease [26]. Antioxidant intake protects individuals from oxidative damage of in vivo lipids and proteins [27].

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