Research, Society and Development, v. 11, n. 9, e54611932144, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i9.32144

Nutritional profile and its relationship with severity markers in adults with sickle cell anemia

Perfil nutricional e sua relação com marcadores de gravidade em adultos com anemia falciforme

Perfil nutricional y su relación con marcadores de gravedad en adultos con anemia falciforme

Received: 06/25/2022 | Reviewed: 06/04/2022 | Accept: 07/11/2022 | Published: 07/18/2022

Ingrid Cristiane Pereira Gomes
ORCID: https://orcid.org/0000-0001-9328-8581
Federal University of Sergipe, Brazil
E-mail: ingridcpg@yahoo.com.br
Mariana Amaral Carvalho
ORCID: https://orcid.org/0000-0002-7194-627X
Tiradentes University, Brazil
E-mail: mari-amaralc@hotmail.com
Maria Carollyne Passos Cruz
ORCID: https://orcid.org/0000-0002-8596-3951
Federal University of Sergipe, Brazil
E-mail: nutrimariacarollyne@outlook.com
João Pedro Costa Machado Teles
ORCID: https://orcid.org/0000-0002-3775-1436
Tiradentes University, Brazil
E-mail: jpteles31@outlook.com
Paula Gabriella Pereira Rosa de Oliveira
ORCID: https://orcid.org/0000-0002-8275-5612
Federal University of Sergipe, Brazil
E-mail: paulagabriela13@hotmail.com
Lindemberg Costa de Albuquerque
ORCID: https://orcid.org/0000-0002-8391-4929
Tiradentes University, Brazil
E-mail: lcostaa95_@gmail.com
Gabriela Maria Araújo Costa
ORCID: https://orcid.org/0000-0001-9620-4160
Tiradentes University, Brazil
E-mail: gabrilacosta449@gmail.com
Alessandro Freire Carvalho
ORCID: https://orcid.org/0000-0003-1311-2688
Tiradentes University, Brazil
E-mail: alessandrofreire_19@hotmail.com
Rosana Cipolotti
ORCID: https://orcid.org/0000-0001-9070-2302
Federal University of Sergipe, Brazil
E-mail: rosanaci@yahoo.com

Abstract
Objective: To assess the nutritional profile and its relationship with the severity markers in adults with sickle cell anemia (SCA). Methodology: This is a cross-sectional, analytical study with 55 adults with SCA and 60 members of the control group. Sociodemographic, nutritional and laboratory data, as well as physical activity level were collected between March 2019 and June 2020. Mann-Whitney tests were used to compare groups and the Spearman correlation coefficient to test the relationship between variables. Results: The SCA group presented lower weight, height and body mass index. In addition, there was a positive correlation of hemoglobin and hematocrit with food intake and a negative correlation with platelets in this group. Conclusion: In light of the studied link between food intake and blood count, the importance of adequate nutritional support as part of the therapeutic management of individuals with SCA becomes evident, which impacts their prognosis.
Keywords: Sickle cell disease; Dietary intake; Anthropometry; Hemolysis; Adults.

Resumo
Objetivos: Avaliar o perfil nutricional e a sua relação com marcadores de gravidade de adultos com anemia falciforme (AF). Metodologia: Trata-se de um estudo transversal, analítico com 55 adultos com AF e 60 controles. Dados sociodemográficos, nutricionais, laboratoriais e nível de atividade física foram coletados entre março de 2019 e junho

de 2020. Utilizou-se teste de Mann-Whitney na comparação entre grupos e coeficiente de correlação de Spearman para testar relação entre variáveis. Resultados: O grupo AF apresentou menores peso, altura e índice de massa corporal. Além disso, constatou-se correlação positiva da hemoglobina e hematócrito com o consumo alimentar e negativa com as plaquetas nesse grupo. Conclusão: Diante da relação observada entre consumo alimentar e índices hematimétricos, torna-se evidente a importância de um adequado aporte nutricional como parte do manejo terapêutico dos indivíduos com AF, o que impacta no seu prognóstico.
Palavras-chave: Doença falciforme; Consumo alimentar; Antropometria; Hemólise; Adultos.

Resumen
Objetivo: Evaluar el perfil nutricional y su relación con los marcadores de gravedad en adultos con anemia falciforme (AF). Diseño: Se trata de un estudio analítico transversal con 55 adultos con AF y 60 miembros del grupo control. Se recogieron datos sociodemográficos, nutricionales y de laboratorio, así como el nivel de actividad física entre marzo de 2019 y junio de 2020. Se utilizaron las pruebas de Mann-Whitney para comparar grupos y el coeficiente de correlación de Spearman para probar la relación entre las variables. Resultados: El grupo AF presentó menor peso, altura e índice de masa corporal. Además, hubo una correlación positiva de la hemoglobina y el hematocrito con la ingesta de alimentos y una correlación negativa con las plaquetas en este grupo. Conclusão: Diante da relação observada entre consumo alimentar e índices hematimétricos, torna-se evidente a importância de um aporte nutricional adequado como parte do manejo terapêutico dos indivíduos com AF, o que impacta no seu prognóstico.
Palabras clave: Doença falciforme; Consumo alimentario; Antropometria; Hemólisis; Adultos.

1. Introduction

Sickle cell anemia (SCA), the most prevalent hereditary hemoglobinopathy in the world, with an autosomal recessive character, resulting from a mutation in the β-globin gene, characterized by homozygosity for the βS allele (Nartey et al., 2021; Sunnd et al., 2019; Piccin et al., 2019). In the SCA, the most severe form of sickle cell disease (SCD), the erythrocytes acquire a sickle shape, a cellular expression of the polymerization of deoxygenated hemoglobin S (HbS), a process that leads to hemolysis and adhesion of erythrocytes to the vascular endothelium, which results in obstruction, chronic inflammation and recurrent episodes of blood vessel occlusion (Piccin et al., 2019; Salinas Cisneros & Thein, 2020).

SCA is a multisystemic pathology, that has high morbidity and mortality rates and is a severe public health problem (Abdul-Hussein et al., 2021; Nartey et al., 2021). It predominantly affects people of African, Indian and Arabic descent, with most cases occurring in Sub-Saharan Africa (Nartey et al., 2021; Inusa et al., 2019). In this scenario, barriers to a better health care stand out, such as low socioeconomic status and precarious health conditions, which affects the nutritional status and hemoglobin levels of patients with SCD (Animasahun et al., 2011). In Brazil, its incidence varies between states, which reflects ethnic heterogeneity, with the highest concentration of cases in the North and Northeast regions of the country (Kamal et al., 2021; Ministério da Saúde, 2016).

Despite several studies highlighting inadequate nutritional status in children with SCA, few of them involved adults (Odetunde et al, 2016; Oredugba & Savage, 2002; Singhal et al., 2002). Due to the natural progression of the disease, already linked to increased resting energy expenditure (REE), low nutrient intake and a reduced level of physical activity (PAL), individuals with SCA have lower anthropometric measurements, such as weight, BMI, and several nutritional deficiencies. These factors are linked to a worse prognosis of the disease, expressed through lower levels of RBC indices, and higher levels of hemolysis and hospitalization rates (Oyedeji et al., 2019; Craig et al., 2003; Kammal et al., 2021). Recognition of the nutritional status of patients with SCA is of fundamental importance for the best management of this disease (Kammal et al., 2021).

As the nutritional status of individuals with SCA can impact their morbidity and mortality rates and their prognosis, recognizing their nutritonal pattern becomes an essential endeavor. Therefore, this study aims to evaluate the nutritional profile and its relationship with markers of severity in this population.

2. Methodology

This is a cross-sectional, analytical and controlled study (Soares et al., n.d.) involving patients with SCA trough the

Hematology service of the Federal University of Sergipe's University Hospital, a university center of regional stand in Aracaju, capital of the state of Sergipe, in the Northeast of Brazil.

The project was approved by the Ethics Committee in Research Involving Human Beings of the Federal University of Sergipe (CEP HU/UFS), through Serial Number 2.897.835, with the goal to meet the recommendations of resolution number 466/12 of the National Health Council. Individuals who expressed their consent by appreciating and signing the Free and Informed Consent Term participated in the study.

The sample was selected by intentional non-probabilistic sampling during routine outpatient consultations. The sample group consisted of patients aged 19 years or older, with SCA confirmed by hemoglobin electrophoresis, in a stable clinical condition: no pain or infection in the last four weeks before blood collection. Exclusion criteria were as follows: pregnant or breastfeeding; blood transfusion or infection in the last month prior to collection; pre-existing chronic pathology, such as kidney and liver disease, or malabsorption disorder.

Healthy individuals, academics, resident physicians and hospital employees, matching age and gender with the sample group, made up the control group. The control group underwent hemoglobin electrophoresis to confirm the absence of any hemoglobinopathy or sickle cell trait. The exclusion criteria applied to the group of patients were also applied to the control group. Data collection took place between March 2019 and June 2020, with some breaks due to the Sars-CoV-2 pandemic.

Patients were assessed using a structured collection instrument based on sociodemographic and clinical data such as name, age, gender, clinical history, associated chronic pathologies, medications in use, hospitalization and blood transfusion history. Patients were submitted to nutritional assessment, through a 24-hour food recall (24hR), anthropometric assessment and assessment of laboratory tests.

The intaking of calories, macronutrients, proteins, lipids and carbohydrates (CHO) was performed through a 24-hour recall (R24h) by a nutritionist and consisted of a form in which the amount of food ingested in the last 24 hours was recorded prior to the time of the interview. Information was collected on household measurement containers and industrial packaging, with meal times and preparation methods also being questioned. In order to ease the measuring of food portions, standardizing and increasing the reliability of the information provided, a photo album with images of both food and kitchen utensils was made available, according to the recommendations of Pinheiro (2006) (Sales et al., 2004).

The energy and macronutrient intake calculation was performed using the Nutwin software version 1.6. The food used came from the Brazilian Food Composition Table (TACO) and the IBGE Food Table, but in the absence of food preparation in the program, they used the nutritional information of the products described in the preparation recipe so that it was possible to quantify the nutritional content of the food. In order to analyze the adequacy of micronutrients intake trough eating food, the recommendations of the Dietary Reference Intakes in relation to the Estimated average requirement (EAR) of 2011 (DRI; 2011) was used.

Participants were assessed regarding anthropometric data, weight and height, measured using a digital scale (Tanita BF-679®) and wall stadiometer (Tonelli®), according to a standard technique. Then, their body mass indices were calculated using the formula BMI = weight/(height)², expressed in kg/m². Individuals with BMI < 18.5 kg/m² were considered low weight; adequate weight, BMI between 18.5 and 24.99 kg/m²; overweight, BMI between 25 and 29.99 kg/m² and obese; BMI ≥ 30 kg/m² (World Health Organization technical report series, 1995).

For physical activity level (PAL) analysis, the short version of the International Physical Activity Questionnaire (IPAQ) was used and the individuals were categorized into two groups, sedentary and active, with those who practiced at least 150 minutes of physical activity per week being considered in the latter group (Craig et al., 2003).

To perform the biochemical tests, the research participants were instructed to maintain a regular diet in the days prior to the evaluation, also fasting for 12 hours and without vigorous physical activity in the 24 hours prior to the collection. A total

of 15mL peripheral blood was collected for serum measurements of hemoglobin (Hb), hematocrit (HT), leukocytes, platelets, reticulocytes, lactic dehydrogenase (LDH), total bilirubin (TB), and indirect bilirubin (ID).

Standard automated methods for clinical analysis were used for hematological and biochemical tests, performed at the Clinical Analysis Laboratory of the Federal University of Sergipe's University Hospital.

The collected data were charted in an Excel spreadsheet and the statistical analysis was performed using the R program, version 4.0.4 (THE R CORE TEAM, 2021). To portray the distribution of the studied groups, a descriptive analysis was performed in which the categorical variables were described through their absolute and relative frequencies. Initially, the normality of continuous data was verified through the Shapiro-Wilk test (Shapiro; Wilk, 1965). For the analysis of parametric data, the Student's T test was used and the average and standard deviation were calculated for each group, while for non-parametric data, the Mann-Whitney test was used (Mann; Whitney, 1947), and the averages and interquartile range were calculated for each group. To verify the correlation between continuous variables, Spearman's correlation was used and for stablish the relationship between the categorical variables, the chi-square test ($\chi 2$) was used (Pearson, 1992) and when the observed frequency was less than 5, we used the Fisher's exact test (Fisher, 1922) with a significance level of 5% ($p<0.05$) being adopted.

The authors declare that the research was carried out in the absence of any commercial or financial relationship that could be interpreted as a potential conflict of interest.

3. Results

Fifty-five patients with SCA were assessed, with an average age of 26.5 (± 5.2) years, 29 of whom were women (52.7%). Regarding anthropometric indices, patients with SCA had lower weight, height, and BMI than members of the control group. In the SCA group, the average BMI was within the normal range, but 14% (8) were underweight (BMI< 18.5 kg/m²). As for PAL, there was no difference between the groups and it was found that 61.1% (33) of the SCA group and 58.2% (46) of the control group were active individuals (Table 1).

Table 1: Sociodemographic and clinical characteristics of adults with sickle cell anemia and healthy members of the control group.

Variable	SCA Group		Control Group		P
	N (%)	Average (SD)	N (%)	Average (SD)	
Age		28.4 (5.2)		28 (5)	0.7880
Gender					
Female	29 (52.7)		30 (50.0)		
Male	26 (47.3)		30 (50.0)		
Weight (kg)		56.6 (8.2)		68.9 (11.8)	0.0000*
Height (cm)		164.5 (8.0)		169.1 (8.8)	0.0040*
BMI[a] (kg/m²)		20.9 (2.7)		24.0 (2.7)	0.0000*
PAL[b]					
Active	33 (61.1)		46 (58.2)		
Minutes/Week		619.03 (759.44)		590.05 (518.71)	0.0850

*p < 0.05. [a:] Body mass index; [b:] Physical activity level. Source: Authors (2019-2020).

In the analysis of the consumption of calories and macronutrients it was evidenced that individuals with SCA had a higher intake of calories, proteins and carbohydrates (Table 2).

Table 2: Calorie and macronutrient intake of adults with sickle cell anemia and healthy members of the control group.

Variable	Case Group	Control Group	p
	Average (SD)	Average (SD)	
KCAL[a] (kcal)	1.706.4 (614.9)	1.403.8 (637.8)	0.0220*
PTN [b] (g)	328.8 (143)	279.3 (172.9)	0.0480*
LIP [c] (g)	475.7 (255,7)	525.8 (850.2)	0.4110
CHO [d] (g)	898.9 (340,8)	795.5 (568)	0.0400

*p < 0,05. [a:] Kilocalories; [b]: Proteins; [c]: Lipids; [d]: carbohydrates. Source: Authors (2019-2022).

There was no noticeable variance in the percentage of macronutrient consumption between the groups. In addition, both showed the intake of calories, proteins, lipids ,carbohydrates and macronutrients within the recommendations of the DRIs (Table 3).

Table 3: Connection between the percentage of caloric contribution of macronutrients of adults with sickle cell anemia and the control group.

Variable	Case Group	Control Group	p
	MÉDIA (SD)	MÉDIA (SD)	
PTN[a] (% kcal)	19.4 (5.6)	19.9 (8)	0.9610
LIP[b] (% kcal)	27.1 (7.9)	36 (45.5)	0.1090
CHO[c] (% kcal)	53.5 (9.2)	55 (24)	0.7270

[a:] Proteins; [b:] Lipids; [c:] Energy. Source: Authors (2019-2020).

Regarding the hematimetric indices, the SCA group had lower levels of Hb, HT and higher levels of leukocytes, platelets and ferritin. As for hemolysis markers, the SCA group had higher levels of reticulocytes, BI and LDH. (Table 4).

Table 4: RBC indices and hemolysis markers of adults with sickle cell anemia and healthy members of the control group.

Variable	SCA Group	Control Group	p
	Average (SD)	Average (SD)	
HB[a]	9.1 (1.6)	14.5 (1.6)	0.0000*
HT[b]	26.5 (4.6)	43.3 (6.7)	0.0000*
LEUKOCYTES	10444.6 (4255.9)	6436.9 (1592.3)	0.0000*
PLATELETS	386358.2 (142334.3)	237288.3 (60384.9)	0.0000*
RETICULOCYTES	11.4 (5.3)	1.4 (0.4)	0.0000*
IB[c]	2.6 (2.2)	0.5 (0.2)	0.0000*
DHL[d]	840.6 (437.9)	296.6 (56.8)	0.0000*

*p < 0.05. [a:] Hemoglobin; [b]: Hematocrit; [c]: Indirect Bilirtubin; [d]: Lactic dehydrogenase. Source: Authors (2019-2020).

In the analysis of the link between consumption of macronutrients and anthropometric indices within the SCA group, a moderate connection was observed between carbohydrate consumption and weight (Table 5).

Table 5: Correlation between macronutrient intake and anthropometric indices of adults with sickle cell anemia.

Variable	r [1]		
	Weight	Height	BMI
KCAL[a] (kcal)	0.26	0.20	0.20
PTN [b] (g)	0.07	-0.09	0.24
LIP [c] (g)	0.15	-0.02	0.28
CHO [d] (g)	0.33*	0.35*	0.07

*p < 0.05. [a:] Energy; [b]: Proteins; [c]: Lipids; [d]: Carbohydrates. 1: Correlation coefficient. Source: Authors (2019-2020).

When analyzing the link between hematimetric indices and hemolysis markers with anthropometric indices, a moderate negative connection was found between the platelet level with weight and with BMI, in addition to a moderate positive connection of bilirubin with height. In the assessment of the link between these laboratory indexes and food intake, a moderate positive connection of Hb with the intake of calories, lipids and CHO was proven, as well as of TH with the caloric and lipid intake. Platelets showed a moderate negative link with the intake of kilocalories.

Table 6: Correlation of hematimetric indices and hemolysis markers with anthropometric indices and macronutrient intake of adults with sickle cell anemia.

Variable	r[1]						
	Weight	Height	BMI	KCAL	PTN	LIP	CHO
HB[a]	0.13	0.07	0.19	0.38*	0.28	0.31*	0.39*
HT[b]	0.14	0.06	0.24	0.36*	0.22	0.36*	0.32
LEUKOCYTES	-0.08	0.03	-0.25	-0.06	-0.12	-0.18	0.00
PLATELETS	-0.39*	-0.11	-0.40*	-0.35*	-0.26	-0.35	-0.38
RETICULOCYTES	0.05	0.10	-0.14	0.09	-0.01	-0.05	0.07
IB[c]	0.26	0.34*	-0.11	0.14	-0.05	-0.01	0.19
DHL[d]	0.13	0.3*	-0.14	0.06	0.02	-0.15	0.03

*p < 0.05. [a:] Hemoglobin; [b]: Hematocrit; [c]: Indirect Bilirtubin; [d]: Lactic dehydrogenase. 1: Correlation coefficient. Source: Authors (2019-2020).

4. Discussion

This study main goal was to assess the nutritional profile and its relationship with severity markers in adults with SCA. Focusing on these issues in this specific age group is necessary because, despite advances in the treatment of SCA and an increased survival rate, most studies have assessed the impact of nutrition on hematimetric and anthropometric indices in children. In addition to that, SCA is a chronic, multisystemic disease, with high morbidity and considerable mortality rates, and constitutes a public health problem (Piel et al., 2017; Hankins et al., 2018; Oyedeji et al., 2019).

Regarding the findings of this research, individuals with SCA had lower weight, height and BMI than members of the control group, but they remained eutrophic on average (World Health Organization technical case report, 1995). A previous

cohort showed similar findings in relation to the weight and BMI of adults with SCA (Gomes et al., 2018). In this study, the fact that individuals with SCA showed to have lower weight and BMI than members of control group, despite the higher caloric and macronutrient intake, reflects the pro-catabolic state, a characteristic of SCA, linked to factors such as increased resting energy expenditure (REE) and persistent hemolysis (Reid, 2013; Singhal et al., 1993).

Regarding the assessment of PAL, 61.1% of individuals with SCA and 58.2% of controls were active, which differs from a previous study with children and teenagers, which showed reduced PAL in individuals with SCA, associated, among other factors, to fatigue and orthopedic complications.(Segava et al., 2014)

Although there is no indication that individuals with SCA should perform intense physical activity, which can increase the demand for oxygen and precipitate vaso-occlusive crises (Woods, 1997), there is a consensus that the practice of regular physical activity reduces oxidative stress, as well as a decrease in inflammatory and endothelial activation in experimental models with SCD (Martin et al., 2017) and may help to reduce hospitalization in children with SCA with vaso-occlusive crises, especially when it does not exceed the limit of 30 minutes in the modality of moderate resistance (Connes et al., 2011). It is well documented that collected data such as frequency, duration and, mainly, intensity rates are essential items for a precise physical exercise program, which reduces cardiovascular risk and avoids triggering pain crises in this group.

In addition, the controlled exercise can help in reducing the hospitalization of children with SCA with vaso-occlusive crises (Protocolo Clínico e Diretrizes terapêuticas Anemia Falciforme, 2016), especially when it doesn't last longer than 30 minutes in the mode of moderate resistance (Connes et al., 2011). It is known that data such as frequency, duration and intensity are essential items for a specific physical exercise program, which reduces cardiovascular risk and avoids triggering pain crises in this population.

This study did not find a deficit in the caloric proportion of macronutrients assessed in individuals with SCA, considered adequate according to the Dietary Reference Intake (DRI), nor any change in these proportions in relation to the control group. Previous studies with children and teenagers found that, although there is little to no difference in energy intake when compared with DRI or with the food consumption of healthy individuals, the relationship between intake and energy expenditure at rest is altered, which indicates an inability to compensate for hypercatabolism by increasing energy intake in this population (Kawchak et al., 2007; Singhal et al, 2002). The scientific literature points out that some factors can reduce the caloric intake, resulting in lower weight for the individual with SCA, such as a chronic inflammatory and the natural history of the disease, with frequent hospitalizations due to pain crises, which often lead to inappetence during the period of acute pain (Smiley et al., 2008).

Furthermore, the study pointed out that ind/ividuals with SCA tend to have worse nutritional conditions, usually due to socioeconomic hindrances (de Jesus et al., 2018). It is worth to point out that the individuals with SCA studied were in a stable clinical condition and socioeconomic factors were not taken into account.

The lower hematimetric indexes and higher levels of hemolysis markers in the SCA group compared to the control group reflect the pathophysiology of the disease, which is defined by hemolysis findings observed in previous studies.(Wongtong et al., 2015; Mikobi et al., 2015). Hemolytic anemia is defined by low levels of Hb and TH, in addition to high levels of LDH and BT, at the expense of IB, which result from the destruction of red blood cells in the circulation also linked with hemolysis, with compensatory bone marrow hyperplasia justifying the reticulocytosis found in these patients. Finally, due to the inflammatory process, these individuals have leukocytosis, in addition to thrombocytosis, resulting from hyposplenism.

When the connection of nutritional intake with the hematimetric indices and hemolysis markers was researched, it was seen that caloric, protein and CHO consumption were linked with higher levels of Hb and HT, as well as with a lower number of platelets. Within this context, the scientific literature points out that low levels of Hb are traditionally considered independent factors connected to increased morbidity and mortality in patients with SCA (Makani et al., 2011). Thus, the importance of adequate nutritional support as part of the therapeutic management of individuals with SCA becomes evident. Although

hemolysis markers, such as BI, are also considered an independent risk for greater disease severity, this study did not find a link between macronutrient consumption and this variable.

Kammal et al. identified an inverse connection between the intensity of the disease and the levels of energy consumption and BMI, also finding an attributable risk percentage for nutritional deficiencies of 88%. which also corroborates the fact that adequate food intake is essential for a better prognosis of individuals with SCA.

5. Conclusion

The findings of this study reinforce the standing of a multidisciplinary team in the management of patients with SCA, with emphasis on programs aimed at nutritional support and physical activity. Thus, it is essential to investigate, based on longitudinal studies, the impact of nutritional monitoring on the prognosis of individuals with SCA, which allows for a better therapeutic management of this population.

This study also had some limitations. As this is a cross-sectional study with patients in a stable clinical condition, food intake may differ from when they are in an unstable condition. The socioeconomic pattern not measured in this study is another limiting factor for food intake. In addition, the NAF was based on the degree of reliability of the self-reported information, as the use of accelerometers faced some challenges (technology, application and cost of the instrument).

Finally, we suggest that prospective studies, with larger samples and a longitudinal approach, should be conducted to further elucidate the relationship between nutrient insufficiencies and SCD and to determine whether nutrient supplementation can improve the course of the disease.

References

Abdul-Hussein, H. K., Al-Mammori, H. S., & Hassan, M. K. (2021). Evaluation of the expression of red blood cell CD36, interleukin-6 and interleukin-8 in sickle cell anemia pediatric patients. *Cytokine*, *143*, 155534. https://doi.org/10.1016/j.cyto.2021.155534

Animasahun, B. A., Temiye, E. O., Ogunkunle, O. O., Izuora, A. N., & Njokanma, O. F. (2011). The influence of socioeconomic status on the hemoglobin level and anthropometry of sickle cell anemia patients in steady state at the Lagos University Teaching Hospital. *Nigerian journal of clinical practice*, *14*(4), 422–427. https://doi.org/10.4103/1119-3077.9174

Connes, P., Machado, R., Hue, O., & Reid, H. (2011). Exercise limitation, exercise testing and exercise recommendations in sickle cell anemia. *Clinical hemorheology and microcirculation*, *49*(1-4), 151–163. https://doi.org/10.3233/CH-2011-1465

Craig, C. L., Marshall, A. L., Sjöström, M., Bauman, A. E., Booth, M. L., Ainsworth, B. E., Pratt, M., Ekelund, U., Yngve, A., Sallis, J. F., & Oja, P. (2003). International physical activity questionnaire: 12-country reliability and validity. *Medicine and science in sports and exercise*, *35*(8), 1381–1395. https://doi.org/10.1249/01.MSS.0000078924.61453.FB

de Jesus, A. C. da S., Konstantyner, T., Lôbo, I. K. V., & Braga, J. A. P. (2018). Socioeconomic and nutritional characteristics of children and adolescents with sickle cell anemia: a systematic review. *Revista Paulista de Pediatria*, *36*(4), 491–499. https://doi.org/10.1590/1984-0462/;2018;36;4;00010

Gomes, I. C. P., Melo, H. N., Melo, S. I. A., Menezes, N. V. de, Dantas, T. V. P., & Cipolotti, R. (2017). Growth and puberty in a prospective cohort of patients with sickle-cell anaemia: an assessment over ten years abstract. *Journal of Human Growth and Development*, *27*(1), 91. https://doi.org/10.7322/jhgd.127681

Hankins, J. S., Estepp, J. H., Hodges, J. R., Villavicencio, M. A., Robison, L. L., Weiss, M. J., Kang, G., Schreiber, J. E., Porter, J. S., Kaste, S. C., Saving, K. L., Bryant, P. C., Deyo, J. E., Nottage, K. A., King, A. A., Brandow, A. M., Lebensburger, J. D., Adesina, O., Chou, S. T., & Zemel, B. S. (2018). Sickle Cell Clinical Research and Intervention Program (SCCRIP): A lifespan cohort study for sickle cell disease progression from the pediatric stage into adulthood. *Pediatric Blood & Cancer*, *65*(9), e27228. https://doi.org/10.1002/pbc.27228

Inusa, B., Hsu, L. L., Kohli, N., Patel, A., Ominu-Evbota, K., Anie, K. A., & Atoyebi, W. (2019). Sickle Cell Disease-Genetics, Pathophysiology, Clinical Presentation and Treatment. *International journal of neonatal screening*, *5*(2), 20. https://doi.org/10.3390/ijns5020020

Kamal, S., Naghib, M. M., Al Zahrani, J., Hassan, H., Moawad, K., & Arrahman, O. (2021). Influence of Nutrition on Disease Severity and Health-related Quality of Life in Adults with Sickle Cell Disease: A Prospective Study. *Mediterranean journal of hematology and infectious diseases*, *13*(1), e2021007. https://doi.org/10.4084/MJHID.2021.007

Kato, G. J., Piel, F. B., Reid, C. D., Gaston, M. H., Ohene-Frempong, K., Krishnamurti, L., Smith, W. R., Panepinto, J. A., Weatherall, D. J., Costa, F. F., & Vichinsky, E. P. (2018). Sickle cell disease. *Nature reviews. Disease primers*, *4*, 18010. https://doi.org/10.1038/nrdp.2018.10

Kawchak, D. A., Schall, J. I., Zemel, B. S., Ohene-Frempong, K., & Stallings, V. A. (2007). Adequacy of dietary intake declines with age in children with sickle cell disease. *Journal of the American Dietetic Association*, *107*(5), 843–848. https://doi.org/10.1016/j.jada.2007.02.015

Martin, C., Pialoux, V., Faes, C., Charrin, E., Skinner, S., & Connes, P. (2018). Does physical activity increase or decrease the risk of sickle cell disease complications?. *British journal of sports medicine*, *52*(4), 214–218. https://doi.org/10.1136/bjsports-2015-095317

Makani, J., Cox, S. E., Soka, D., Komba, A. N., Oruo, J., Mwamtemi, H., Magesa, P., Rwezaula, S., Meda, E., Mgaya, J., Lowe, B., Muturi, D., Roberts, D. J., Williams, T. N., Pallangyo, K., Kitundu, J., Fegan, G., Kirkham, F. J., Marsh, K., & Newton, C. R. (2011). Mortality in sickle cell anemia in Africa: a prospective cohort study in Tanzania. *PloS one*, *6*(2), e14699. https://doi.org/10.1371/journal.pone.0014699

Mikobi, T. M., Lukusa Tshilobo, P., Aloni, M. N., Mvumbi Lelo, G., Akilimali, P. Z., Muyembe-Tamfum, J. J., Race, V., Matthijs, G., & Mbuyi Mwamba, J. M. (2015). Correlation between the Lactate Dehydrogenase Levels with Laboratory Variables in the Clinical Severity of Sickle Cell Anemia in Congolese Patients. *PloS one*, *10*(5), e0123568. https://doi.org/10.1371/journal.pone.0123568

Moreira G., Neto L, Fernandes P, Ficarelli V. (2002) Aspectos fisiológicos da atividade física em portadores da anemia falciforme (monografia) UNIFESP/EPM. São Paulo.

Nartey, E. B., Spector, J., Adu-Afarwuah, S., Jones, C. L., Jackson, A., Ohemeng, A., Shah, R., Koryo-Dabrah, A., Kuma, A. B., Hyacinth, H. I., & Steiner-Asiedu, M. (2021). Nutritional perspectives on sickle cell disease in Africa: a systematic review. *BMC nutrition*, *7*(1), 9. https://doi.org/10.1186/s40795-021-00410-w

Odetunde, O. I., Chinawa, J. M., Achigbu, K. I., & Achigbu, E. O. (2016). Body mass index and other anthropometric variables in children with sickle cell anaemia. *Pakistan journal of medical sciences*, *32*(2), 341–346. https://doi.org/10.12669/pjms.322.9046

Oredugba, F. A., & Savage, K. O. (2002). Anthropometric finding in Nigerian children with sickle cell disease. *Pediatric dentistry*, *24*(4), 321–325.

Oyedeji, C., Strouse, J. J., Crawford, R. D., Garrett, M. E., Ashley-Koch, A. E., & Telen, M. J. (2019). A multi-institutional comparison of younger and older adults with sickle cell disease. *American journal of hematology*, *94*(4), E115–E117. https://doi.org/10.1002/ajh.25405

Piccin, A., Murphy, C., Eakins, E., Rondinelli, M. B., Daves, M., Vecchiato, C., Wolf, D., Mc Mahon, C., & Smith, O. P. (2019). Insight into the complex pathophysiology of sickle cell anaemia and possible treatment. *European journal of haematology*, *102*(4), 319–330. https://doi.org/10.1111/ejh.13212

Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. (1995). *World Health Organization technical report series*, *854*, 1–452.

Piel, F. B., Steinberg, M. H., & Rees, D. C. (2017). Sickle Cell Disease. *The New England journal of medicine*, *376*(16), 1561–1573. https://doi.org/10.1056/NEJMra1510865

Protocolo Clínico e Diretrizes Terapêuticas Doença Falciforme. (2016). http://conitec.gov.br/images/Consultas/Relatorios/2016/Relatorio_PCDT_DoencaFalciforme_CP_2016_v2.pdf

Reid M. (2013). Nutrition and sickle cell disease. *Comptes rendus biologies*, *336*(3), 159–163. https://doi.org/10.1016/j.crvi.2012.09.007
Salinas Cisneros, G., & Thein, S. L. (2020). Recent Advances in the Treatment of Sickle Cell Disease. *Frontiers in physiology*, *11*, 435. https://doi.org/10.3389/fphys.2020.00435

Segava, N., Cavalcanti, A., Godoi De Paula, F., & Mendes, L. (1428). *Caracterização do uso de atividades físicas em crianças e adolescentes com anemia falciforme Characterization of the use of physical activities of children and adolescents with sickle cell anemia*. https://doi.org/10.11606/issn.2238-6149.v24i3p242-9

Singhal, A., Davies, P., Sahota, A., Thomas, P. W., & Serjeant, G. R. (1993). Resting metabolic rate in homozygous sickle cell disease. *The American journal of clinical nutrition*, *57*(1), 32–34. https://doi.org/10.1093/ajcn/57.1.32

Singhal, A., Parker, S., Linsell, L., & Serjeant, G. (2002). Energy intake and resting metabolic rate in preschool Jamaican children with homozygous sickle cell disease. *The American journal of clinical nutrition*, *75*(6), 1093–1097. https://doi.org/10.1093/ajcn/75.6.1093

Smiley, D., Dagogo-Jack, S., & Umpierrez, G. (2008). Therapy insight: metabolic and endocrine disorders in sickle cell disease. *Nature clinical practice. Endocrinology & metabolism*, *4*(2), 102–109. https://doi.org/10.1038/ncpendmet0702

Soares, A., Dorlivete, P., Shitsuka, M., Parreira, F., & Shitsuka, R. (n.d.). Metodologia da pesquisa científica. https://www.ufsm.br/app/uploads/sites/358/2019/02/Metodologia-da-Pesquisa-Cientifica_final.pdf

Sundd, P., Gladwin, M. T., & Novelli, E. M. (2019). Pathophysiology of Sickle Cell Disease. *Annual review of pathology*, *14*, 263–292. https://doi.org/10.1146/annurev-pathmechdis-012418-012838

Wongtong, N., Jones, S., Deng, Y., Cai, J., & Ataga, K. I. (2015). Monocytosis is associated with hemolysis in sickle cell disease. *Hematology (Amsterdam, Netherlands)*, *20*(10), 593–597.