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ORIGINAL ARTICLE

Body composition, energy expenditure, and markers of hemolysis in adults with sickle cell disease

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Abstract

Background: Historically, malnutrition is described in individuals with SCD. However, more recent studies have shown a change in the profile of the nutritional status and distribution of body composition of SCD patients, mainly adult individuals. **Aims:** To assess the body composition (BC), resting energy expenditure (REE), and the biomarkers of hemolysis in adults with sickle cell disease (SCD). **Subjects and Methods:** A cross-sectional observational study was performed with 64 individuals over 39 years old in the treatment from two reference centers for SCD located in the city of Rio de Janeiro, Brazil. The dual-energy X-ray absorptiometry (DXA) and indirect calorimetry were used to assess BC and REE, respectively. Blood levels of hemoglobin, reticulocytes, lactate dehydrogenase (LDH), leukocytes, platelets, total and direct bilirubin, total protein, and albumin were measured to assess the hemolysis and protein status. The descriptive and inferential analysis was composed of the different methods (one-way ANOVA with the multiple comparison test of Tukey, Student t-test, and Pearson's correlation coefficient). Were considered statistically significant when the p-values were ≤ 0.05. **Results:** Most participants with SCD were female sex, colored (brown/black), and mean age of 51.2 years old. The obesity prevalence was 70.7% according to the body fat (BF%), with a major mean among women ($p < 0.0001$). Men had a higher mean of lean mass (LM) ($p=0.0005$) and fat-free mass (FFM) ($p=0.0007$). There was no difference for REE in comparing the genotypes ($p= 0.53$), and genders ($p=0.075$). The hemolysis markers (LDH, reticulocytes, and TB) correlated inversely with BMI ($p=0.013$), FM ($p=0.022$), and FFM ($p=0.034$). **Conclusions:** The important change observed in body composition in people with sickle cell disease was characterized by a high percentage of fat body and a decrease in lean mass. The hemolysis markers LDH, reticulocytes, and BT correlated inversely with BMI, FM, and FFM indicating that high levels of hemolysis may affect nutritional status, without influencing the REE.

Keywords: sickle cell disease, body composition, fat mass, fat-free mass, energy expenditure, hemolysis.

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1 Introduction

According to global estimates, approximately 5% of the population has some type of hemoglobin variant and more than 300,000 babies are born each year with hemoglobinopathies, with sickle cell disease (SCD) being the most prevalent type [1, 2].

It is estimated that the prevalence of live births with the disease is 4.4% in the world and 1.1% in the Americas [2]. In the United States, it is estimated that 113,000 hospitalizations are in the occurrence of the disease and the cost of hospitalization for SCD reaches 488 million dollars per year [3]. In Brazil, the estimated incidence of SCD is 1 case per 2700 live births: Bahia, Rio de Janeiro, and Minas Gerais being the main states with the highest prevalence [4-6].

According to data from the World Bank and World Health Organization (WHO), child and perinatal care lethality rates can reach 80% and between 20% and 50%, respectively, of uncared children who cannot reach five years of life [7]. Among the adults followed in the high prevalence states, such as Bahia and Rio de Janeiro, the median age of death due to SCD is still low, 26.5 years and 31.5 years respectively [8].

Nevertheless, in the last thirteen years, the Federal Government of Brazil implemented several public health policies focused on the detection of new cases by neonatal screening and on improving the quality of treatment provided to these patients, implying an increase in life expectancy, with individuals reaching the fourth, fifth and up to the sixth decade of life [9-12].

Sickle cell disease (SCD) is identified by the presence of hemoglobin S (Hb S). The formation of Hb S polymers triggers dehydration and increased cell stiffness, giving rise to the vaso-occlusion event. This phenomenon leads to the appearance of several pathophysiological events such as tissue ischemia, anemia, inflammation, and hemolysis [13-17].

Hemolysis consists of the early destruction of the erythrocytes by membrane rupture, being a common event in the pathophysiological process of SCD [18-20]. During hemolysis, vasodilation, transcriptional activation of endothelin, and vascular adhesion molecule are reduced, whereas nitric oxide is exposed directly to free Hb S, causing its degradation [21, 22].

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Chronic hemolysis in SCD causes vascular imbalance, reflecting directly on hemoglobin concentration, reticulocyte count, bilirubin levels, lactic dehydrogenase (LDH), and nitric oxide bioavailability [21, 23, 24].

SCD frequently presents acute and chronic complications [25], having hematological, clinical, nutritional, and metabolic effects that affect nutritional status [26, 27] and increasing energy needs [28-35].

BMI, commonly used to measure adiposity, cannot estimate or quantify fat mass nor determine the presence of conditions such as sarcopenia [36].

Body composition analysis is required to quantify fat mass (FM) and fat-free mass (FFM), and it is recognized that the amount of FFM is essential to health [37, 38]. DXA provides an accurate and safe assessment of body composition, with minimal radiation exposure [39].

Historically, malnutrition is described in individuals with SCD [30] however, more recent studies have shown a change in the profile of the nutritional status and distribution of body composition of SCD patients [40], mainly adult individuals.

The study of body composition in adults with SCD is necessary for a better understanding of the influence of energy expenditure and some laboratory markers, especially some hemolysis biomarkers in SCD. Therefore, this study proposed to assess body composition (BC), resting energy expenditure (REE), and hemolysis biomarkers in adults with sickle cell disease (SCD). Additionally, we sought to determine the relationship between BC and REE with hemolysis biomarkers in adult patients with SCD.

2 Subjects and Methods

2.1 Design and study population

We performed a cross-sectional observational study in two reference centers for the treatment of SCD in the state of Rio de Janeiro, Brazil.

The study was conducted on 64 patients, aged over 39 years with confirmed laboratory diagnosis of different genotypes of SCD by hemoglobin electrophoresis.

2.2 Inclusion and exclusion criteria

Patients with genotypes Hb-SS, HbSC, HbSD, and Hb-Stal were included. They were without pain crisis or vaso-occlusive in the last 14 days; they did not have acute lung disease or some type of infection and that not been hospitalized in the last 14 days.

Adults with chronic use of immunosuppressive drugs, barbiturates, steroids or replacement thyroid hormones; the presence of HCV in use ribavirin and interferon; addiction of drugs and alcohol; use of vitamin-minerals supplements during the last 60 days, except folic acid; the presence of acute lung disease or some type of infection; who had been hospitalized in the last 14 days; the previous presence of a diagnosis of secondary osteoporosis or metabolic diseases to submit any neurological or cognitive impairment that would prevent the proper collection of information and pregnancy were excluded from the study.

2.3 Anthropometric proceedings

The measurements of body weight (W) and height (H) were obtained and were calculated as body mass index (BMI). The classification of the nutritional status of adults was carried out using the categories proposed by the World Health Organization[41], and the elderly according to Lipschitz [42].

2.4 Body composition (BC) proceedings

IDXA scanner (Lunar GE Medical Systems, Madison, WI, USA) was utilized to measure subjects' body compartments using dual-energy X-ray absorptiometry (DXA), a gold standard method in accuracy and precision of body composition estimates [43].

The basic principle of DXA is to produce a two-dimensional image that uses X-rays with two different energy sources [44]. When an X-ray or photon source is placed on one side of the object, the intensity of the beam on the opposite side of the object is related to its thickness, density, and chemical composition, thus defining the term attenuation [45]. Therefore, DXA applies the attenuation characteristics in three compartments: bones (BMC), lean mass (LM), and fat mass (BF), and estimates these three components in selected regions of the entire body through specific software [46].

In the present study, DXA was performed in the morning by a trained radiologist. Acquisition, calibration, and body analysis were performed by enCORE software (GE® Health care) and followed the International Society for Clinical Densitometry (ISCD) recommendations validated by the Brazilian Correlation of Bone Evaluation and Osteometabolism (ABRASSO).

All subjects had previously been instructed to take exams wearing underwear only, without metal accessories, avoid consuming calcium and zinc-rich foods before the test, and calcium supplements up to two months before the test. Participants were also previously instructed to report whether they had cardiac pacemakers. The examinations in women of reproductive age were only performed after stating that they were not pregnant during the study period.

Participants underwent a whole BC analyses using a DXA between 07:00 and 08:00 after a 12h fast and abstinence from coffee and alcohol and moderate to intensive exercise for more than eight hours. During the examination, every individual remained supine, with his arms along his body for complete scanning of the body compartments. Transverse scans were made to the longitudinal axis of the body lasting 20 minutes.

The participants' results report followed the NHANES reference[47] and were prepared, reviewed, and signed by a densitometric.

2.5 Body Composition proceeding

Total fat mass (FM, kg), the percentage of body fat (%BF), lean mass (LM, kg), the fat-free mass (FFM, kg), and bone mineral content (BMC, kg) were calculated. The tests in women of reproductive age have only been performed after declaring they were not pregnant during the study period.

Obesity can be defined by the percentage of fat mass (%FM), the cut points for %FM that are sex-specific (>25 % for males and >30 % for females).

Another important constituent of body composition is Fat-free mass, also known as lean body mass, which refers to all of its body components except fat. FFM includes the body's water, bone, organs, and muscle content. Females have below FFMI and higher FB than males. We adopted as a cut-off point for FFMI the values for female of < 15 kg/m^2 and males of < 17 kg/m^2.

Body composition was assessed by DXA and described as lean mass (LM, kg), total body fat percentage (BF%), and bone mineral content (BMC, kg). Obesity was defined based on %BF, using the sex-specific cut-off points (>25% for males and >30% for females). The classification of obesity according to BF% was based on reference values proposed by Kelly *et al.* [47].

2.6 Indirect calorimetry proceedings

The indirect calorimetry method measures gas exchange (VO_2/VCO_2) to estimate the quantities of oxidized substrates, combining their density for the determination of total energy expenditure (TEE) [48]. Indirect calorimeter operation has an air traction system, which is suctioned of the room in a smaller exhaust system (canopy), which allows free-breathing with ventilator, diluting the breathing in a large volume or volume over time (flow) [48].

In the current study, MEE was measured by open-circuit indirect calorimetry (Vmax Encore 29 Sensormedics® System), between 7:00 AM and 8:00 AM, ever including two participants for the day. All participants had been previously instructed to after 12h of fasting without coffee and alcohol, without moderate-to-intensive exercise for >8 hours, and sleep for 6 to 8 hours the night before the assessment. In addition, participants were instructed to report symptoms such as fever 24 hours before the day of the test.

Perform indirect calorimetry, a general protocol was developed according to the specifications of the manufacturer Vmax Encore 29 Sensormedics® System which includes the preparation of the environment, the preparation of the participant, the calibration of the apparatus, the registration of the participant data in the program, the procedure test, and completion. Indirect calorimetry was turned on 30 minutes before the start of the test with participants.

Preparation of the environment consisted of providing a reserved and quiet place, low-light, comfortable temperature to avoid changes caused by cold or anxiety, and to provide a good performance of the calorimeter.

Preparation of the participants was performed through an adherence protocol to know if they were able to perform the exam. Being able to perform the procedure, the participant was put to rest for 15 minutes. During this time, the research team turned off the air conditioner to start the flow sensor calibration step in the Vmax program.

A good contour of the circular lines was signalized by each sidebar indicating the permission to pass the next adjacent outer lines until the graphs generated by the calibration process were satisfactorily completed according to the signaling of the Vmax program. At the end, the procedure was saved Vmax program and the air conditioner turned on again to initiate the participant registration step, in which the participant data was included by selecting "New Study".

After the registration was saved, the gas cylinders were opened counterclockwise, the sensor was connected directly to the device, placing the left wire attached to the rightmost input of the device and thus starting the gas calibration in session "Exercise Metabolic Test". At the end of calibration, the cylinders were closed and the left wire was reconnected to the sensor. The canopy helmet was placed on the participant, connected to the device through the breathing tube and finally, the fan was turned on. The test was started ("Start") and ended ("End Test") noting if the time for the correct accounting of the 25 minutes of the test.

At the end of the exam, the patient was disconnected from the device, the ventilator was turned off and the test was saved. MEE data was tabulated ("Tabular Edit") and saved to a USB stick.

2.7 Resting Energy Expenditure (REE)

For the evaluation of REE, the respiratory exchange was measured using an indirect calorimeter open circuit Vmax Encore 29 Sensor Medics®. The equation Weir (1949) [43] was used to convert the values of O_2 and CO_2 in kcal.min^{-1}. The REE was obtained by multiplying the average of the last 20 minutes 1440 minutes [19].

2.8 Laboratory markers

Hemolysis markers (lactate dehydrogenase -LDH, reticulocytes, and the total and direct bilirubin), complete blood count, and albumin (protein marker) were analyzed.

For measuring lactate dehydrogenase enzyme assay was used by spectrophotometry (adults: 230-480 U/L). Bilirubin and fractions were evaluated by colorimetric assay (total bilirubin up to 1.2 mg/dL, direct bilirubin up to 0.4 mg/dL). Reticulocytes were determined using the staining brilliant cresyl blue (adults: 0.5-2%).

Hematologic data was obtained using an automated cell counter (Horiba Pentra 60 C +). The Hb analysis and quantification were performed by electrophoresis in citrate agar, and high-performance liquid chromatography cation exchange (Variant TM, Bio-Rad Laboratories, Hercules, CA, USA). Albumin was determined using a colorimetric method (Albumin - 3.5 to 5.0 g/dL).

2.9 Statistical analysis

Descriptive analysis of observed data, presented in tables, was expressed by the mean and standard deviation for numeric data and frequency (n) and percentage (%) for categorical data.

The inferential analysis was composed of the different methods (one-way ANOVA with the multiple comparison test of Tukey; Student t-test; Pearson's correlation coefficient). The significance of the determination of criteria used was the level of 5%. Statistical

analysis was performed with the statistical software SAS® System, version 6.11 (SAS Institute, Inc., Cary, North Carolina).

The inferential analysis of the association between the variables BMI, BC, and REE with the hemolysis markers, was carried out by one-way ANOVA with the multiple comparison test of Tukey® (for comparison between the four subgroups), and the test Student's *t*-test for independent samples (for comparison between the two subgroups).

The multiple comparison test of Tukey was used to identify the level of 5%, in which classes of BMI differ significantly. The analysis of the association of the numeric variables was performed using Pearson's correlation coefficient (r) which measured the degree of association between two numerical variables.

2.10 Ethical considerations

Informed consent was obtained from all patients for being included in the study. The procedures in this study are following the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975. This study was approved by the ethics committees of the Pedro Ernesto University Hospital (2819/2010) and the State Institute of Hematology Arthur Cavalcanti (244/2010).

3 Results

3.1 Characteristics of the study population

Of the 64 participants, women (59.4%) and blacks/brown (89%) predominated. The mean age was 51.2 ± 7.7 years. General

Table 1: Characteristics of study participants

Variable	Categories	Total		Male		Female	
		n	%	*n*	%	*n*	%
Ethnicity	White	5	7.8	4	15.4	1	2.6
	Black	31	48.5	10	38.5	21	55.3
	Brown	26	40.6	12	46.1	14	36.8
	Not informed	2	3.1	0	0.0	2	5.3
	Total	64	100.0	26	100.0	38	100.0
Genotype	Hb SS	43	67.2	19	73.1	24	63.2
	Others	21	32.8	7	26.9	14	36.8
	Total	64	100.0	26	100.0	38	100.0
BMI Class	Low weight	5	7.8	5	16.7	0	0
	Normal	33	51.5	14	46.7	19	55.9
	Overweight	17	26.6	7	23.3	10	29.4
	Obesity	9	14.1	4	13.3	5	14.7
	Total	64	100.0	30	100.0	34	100.0
BF%	Normal	17	29.3	11	47.8	6	17.1
	Obesity	41	70.7	12	52.2	29	82.9
	Total	58	100.0	23	100.0	35	100.0
FFMI	Normal	43	74.1	19	82.6	24	68.6
	Decreased	15	25.9	04	17.4	11	31.4
	Total	58	100.0	23	100.0	35	100.0

Table 2: Age, anthropometric data, body composition by DXA, resting energy expenditure and laboratory values of adults with SCD

Variable	n	Mean	SD	Median	IR	Minimum	Maximum
Age, years	64	51.2	7.7	50.4	45.2-56.8	40.0	77.9
Weight, Kg	61	64.6	12.5	63.4	55.5-72.2	44.6	119.3
Height, m	61	1.64	0.09	1.63	1.58-1.70	1.41	1.85
BMI, Kg/m²	61	24.2	4.7	23.6	21.0-27.1	15.7	37.9
BF, %	58	33.0	10.2	35.5	25.9-39.6	11.4	58.5
FM, Kg	58	20.4	8.4	21.0	14.2-25.7	6.0	49.1
LM, Kg	58	41.2	7.7	40.9	35.7-46.1	29.5	66.6
BMC, kg	58	2.3	0.6	2.3	1.931-2.7	1.3	3.8
FFM, Kg	58	44.0	8.6	43.5	38.5-49.7	31.1	70.1
FFMI, Kg/m²	58	16.6	2.6	16.5	14.8-17.5	12.30	26.6
REE, kcal/d	36	1249	211	1222	1133-1408	744	1718
TB, mg/dL	39	1.9	1.5	1.4	0.8-2.4	0.5	7.3
DB, mg/dL	39	0.6	0.3	0.6	0.3-0.7	0.2	1.3
LDH, UI/L	36	835	437	653	481-1091	269	1860
Blood cells, millions/ mL	40	3.2	0.9	3.2	2.3-3.8	1.6	5.0
Hemoglobin, g/dL	40	9.3	2.4	9.2	7.5-11.4	5.5	14.7
Hematocrit,%	40	29.0	7.6	28.8	23.7-34.7	16.7	46.4
Reticulocytes,%	40	6.1	4.3	4.4	2.7-9.03	1.0	18.3
Leukocytes, cells/mm³	40	8.6	2.9	8.2	6.6-10.3	4.1	18.4
Platelets, cells/mm³	40	314	118	318	203-390	86	551
Albumin, g/dL	39	4.3	0.4	4.4	4.0-4.6	3.4	5.3

Abbreviations: DXA: dual-energy X-ray absorptiometry; SD: standard deviation; IR: interquartile range: Q1- Q3; BMI: body mass index; BF%: body fat percentage; FM: fat mass; LM: lean mass; BMC: bone mineral content; FFM: fat free mass; FFMI: fat free mass index; REE: resting energy expenditure; TB: total bilirubin; DB: direct bilirubin; LDH: lactate dehydrogenase.

characteristics of the study participants stratified by color, genotype, BMI classes, %BF, and FFMI are presented in Table 1.

3.2 Body mass index (BMI) and body composition (BC)

The comparative analysis of BMI and BC between SS patients with other genotypes showed no difference between them. Therefore, it was decided to present these data as a single group of SCD. The normal body weight predominated in more than half of the participants, followed by overweight and obesity (35.9%) by BMI but when we consider the % BF the prevalence of obesity rises to 70%, affecting more than 80% of women (Table 1).

The low body weight occurred exclusively in men. The mean BMI was 24.2 kg/m^2 since BF% was 33.0 and the FFMI 16.6 ±2.6 kg/m^2 (Table 2).

The analyses of BMI and BC for gender showed higher BMI, %BF, and FM in women, while men had higher LM, BMC, FFM, and FFMI. There was no difference between them REE (Table 3).

BF%, FM, FFM, and FFMI were significantly different between BMI classes, which did not occur with LM, BMC, and REE (Table 4).

The study of the correlation between age, anthropometric variables, and BC, found a significant positive correlation between BF% and age, weight, and BMI as well as the correlation between LM, BMC, FFM, and REE (Table 5 and 6).

The analysis of the variables BC by gender, has observed that the BMC of men had a positive correlation with body weight (r = 0.495; p = 0.016); and women, with the FFM (r = 0.729; p < 0.001) (data not shown).

As expected, weight was the main determinant for BF%, FM, and REE, but different from expected for LM, BMC, and FFM.

Comparison between the REE of people with SS genotype did not differ from other genotypes (1242 ± 220 kcal vs. 1313 ± 250 kcal, p= 0.53).

Table 3. Comparison of body mass index, body composition by DXA and resting energy expenditure by gender of patients with sickle cell disease

Variable	Male		Female		p value
	n	Mean	n	Mean	
Weight, Kg	23	62.0±15.1	35	62.7±16.7	0.89[a]
BMI, Kg/m²	23	22.4±4.3	38	25.3±4.6	0.019[a]
BF, %	23	25.5±8.8	35	37.1±7.3	< 0.0001[a]
FM, Kg	23	16.2±7.9	35	23.1±7.6	0.001[a]
LM, Kg	23	45.4±3.4	35	38.6±8.5	0.0005[a]
BMC, g	23	2.65±0.52	35	2.16±0.53	0.001[a]
FFM, Kg	23	48.0±3.6	35	41.5±9.8	0.0007[a]
FFMI, Kg/m²	23	16.9±2.1	35	16.4±2.9	0.162[b]
REE, kcal/d	13	1332±140	23	1202±232	0.075[a]

Abbreviations: DXA: dual-energy X-ray absorptiometry; SD: standard deviation; BMI: body mass index; BF%: body fat percentage; FM: fat mass; LM: lean mass; BMC: bone mineral content; FFM: fat free mass; FFMI, fat free mass; REE: resting energy expenditure. [a]Student's *t* Test of independent samples;[b]Mann-Whitney Rank Sum Test.

Correlations with REE with BC and anthropometric variables revealed a significant positive correlation between REE and body weight, height, LM, BMC, and FFM (*Table 4*). REE is not correlated with any laboratory marker as shown in Table 5. When correlating FFMI with BMI, BF%, BMC and REE, there was only Pearson correlation with BMI (r = 0.561; p <0.0001) and REE (r: 0.437; p = 0.008) (data not shown).

We found in men, REE was positive correlation with FFM (r = 0.604; p = 0.029). In women, REE displayed positive correlation with FFM (r = 0.657; p = 0.001) (data not shown). The correlation between REE and BMI in women was not significant (r=0.352; p=0.0999).

Table 4: Body composition by DXA and resting energy expenditure according to BMI classification of adults with sickle cell disease

Variable	Lowweight (LW)		Normal (N)		Overweight (OW)		Obesity (OB)		p *value*[a]	Significant difference between the categories of BMI[b]
	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD		
BF, %	5	14.7±3.2	33	32.2±9.4	16	37.±6.2	5	43.0±6.0	0.0001	LW< N, OW, OB e N < OB
FM, Kg	5	7.6±1.6	33	17.8±5.4	16	25.5±5.0	5	34.3±8.7	0.0001	LW< N <OW< OB
LM, Kg	5	44.6±4.6	33	38.9±6.7	16	43.4±7.3	5	45.9±13.3	0.068	
BMC, Kg	5	2.1±0.6	33	2.2±0.5	16	2.6±0.6	5	2.4±0.7	0.13	
FFM, Kg	5	47.1±5.2	33	41.1±6.9	16	47.7±8.9	5	48.3±14.0	0.030	N <OW
FFMI, Kg/m²	5	14.7±1.1	33	15.7±2.1	16	17.9±2.6	5	19.7±2.4	<0.001	LW<OB; N<OB; LW<OW
REE, Kcal	4	1279±56	18	1191±189	10	1311±285	4	1322±174	0.44	

Abbreviations: SD: standard deviation; [a]*one-way* ANOVA; [b] Tukey test; DXA: dual-energy X-ray absorptiometry; REE: resting energy expenditure; BMI: body mass index; BF%: body fat percentage; FM: fat mass; FFMI: fat free mass index; LM: lean mass; BMC: bone mineral content; FFM: fat free mass; LW: low body mass; N: adequate body mass; OW: excess body mass, OB: Obesity

Table 5. Correlation coefficient (r), p value, number of cases (n) per age, anthropometry, with variables of body composition by DXA and resting energy expenditure of individuals with sickle cell disease

Variable		BF (%)	FM (Kg)	LM (Kg)	BMC (g)	FFM (Kg)	REE (Kcal/d)
Age, years	*r*	0.280	0.241	-0.036	-0.157	-0.081	-0.067
	p	0.032	0.066	0.79	0.23	0.54	0.70
	n	59	59	59	59	59	36
Weight, Kg	*r*	0.289	0.751	0.746	0.567	0.707	0.553
	p	0.027	0.0001	0.0001	0.0001	0.0001	0.0005
	n	59	59	59	59	59	36
Height, m	*r*	-0.547	-0.240	0.682	0.528	0.610	0.411
	p	0.0001	0.067	0.0001	0.0001	0.0001	0.013
	n	59	59	59	59	59	36
BMI, Kg/m²	*r*	0.603	0.877	0.330	0.235	0.334	0.189
	p	0.0001	0.0001	0.011	0.074	0.010	0.27
	n	59	59	59	59	59	36
FM, Kg	*r*			0.135	0.154	0.168	0.054
	p			0.31	0.25	0.20	0.75
	n			59	59	59	36
LM, Kg	*r*				0.678	0.901	0.687
	p				0.0001	0.0001	0.0001
	n				59	59	36
BMC, g	*r*					0.677	0.506
	p					0.0001	0.002
	n					59	36
FFM, Kg	*r*						0.582
	p						0.0002
	n						36

Abbreviations-DXA: dual-energy X-ray absorptiometry; BMI: body mass index; FM: fat mass; LM: lean mass; BMC: bone mineral content; FFM: fat free mass; REE: resting energy expenditure; BF%: body fat percentage.

3.3 Resting Energy Expenditure

Comparison between the REE of people with SS genotype did not differ from other genotypes (1242 ± 220 kcal vs. 1313 ± 250 kcal, p= 0.53).

Correlations with REE with BC and anthropometric variables revealed a significant positive correlation between REE and weight, height, LM, BMC, and FFM (Table 4). REE is not correlated with any laboratory marker (Table 5). When correlating FFMI with BMI, BF%, BMC and REE, there was only Pearson correlation with BMI (r = 0.561; p <0.0001) and REE (r: 0.437; p = 0.008) (data not shown).

Table 6. Correlation coefficient (r), p value, number of cases (n) of the laboratory tests with the variables of body composition and resting energy expenditure of adults with sickle cell disease

Variable		BMI (Kg/m²)	FM (Kg)	LM (Kg)	BMC (g)	FFM (Kg)	REE (Kcal/d)
TB, mg/dL	*r*	-0.390	-0.392	-0.035	-0.121	-0.096	-0.027
	p	0.018	0.022	0.85	0.50	0.59	0.91
	n	36	34	34	34	34	20
DT, mg/dL	*r*	-0.399	-0.345	-0.107	-0.172	-0.184	0.070
	p	0.016	0.045	0.55	0.33	0.30	0.77
	n	36	34	34	34	34	20
LDH, UI/l	*r*	-0.429	-0.369	-0.179	-0.208	-0.234	-0.035
	p	0.013	0.038	0.33	0.25	0.20	0.89
	n	33	32	32	32	32	18
Blood cells, millions/mL	*r*	0.456	0.339	0.379	0.369	0.388	0.152
	p	0.005	0.046	0.025	0.029	0.021	0.51
	n	37	35	35	35	35	21
Hemoglobin, g/dL	*r*	0.455	0.369	0.385	0.458	0.455	0.335
	p	0.004	0.029	0.022	0.006	0.006	0.14
	n	37	35	35	35	35	21
Hematocrit,%	*r*	0.441	0.338	0.380	0.471	0.457	0.305
	p	0.006	0.047	0.024	0.004	0.006	0.18
	n	37	35	35	35	35	21
Reticulocytes, %	*r*	-0.385	-0.206	-0.304	-0.275	-0.358	-0.103
	p	0.018	0.23	0.076	0.11	0.034	0.66
	n	37	35	35	35	35	21
Leukocytes, cells/mm³	*r*	-0.054	-0.071	-0.181	-0.198	-0.207	-0.002
	p	0.75	0.69	0.30	0.25	0.23	0.99
	n	37	35	35	35	35	21
Platelets, cells/mm³	*r*	-0.327	-0.194	-0.134	-0.041	-0.217	-0.265
	p	0.048	0.26	0.44	0.81	0.21	0.25
	n	37	35	35	35	35	21
Albumin, g/dL	*r*	0.259	0.342	-0.017	-0.046	0.144	-0.065
	p	0.13	0.048	0.92	0.80	0.42	0.79
	n	36	34	34	34	34	20

Abbreviations-BMI: body mass index; FM: fat mass; LM: lean mass; BMC: bone mineral content; FFM: fat free mass; REE: resting energy expenditure; TB: total bilirubin; DB: direct bilirubin; LDH: lactate dehydrogenase.

We found in men, REE was positive correlation with FFM (r = 0.604; p = 0.029). In women, REE showed positive correlation with FFM (r = 0.657; p = 0.001) (data no showed). The correlation between REE and BMI in women was not significant (r=0.352; p=0.0999).

3.4 Body composition, resting energy expenditure, and laboratory marker

Table 6 presents the associations between biochemical tests with the components of the BC and REE. The hemolysis markers (LDH, reticulocytes, and TB) correlated inversely with BMI, FM, and FFM indicating that high levels of hemolysis may affect nutritional status, without influencing the REE. Hb and hematocrit were a significantly positive correlation with BMI, FM, LM, FFM, and BMC. The platelet count was inversely correlated with BMI and serum albumin levels were directly correlated with FM.

4 Discussion

This study investigated in a sample of adult males and females with sickle cell disease the body composition and REE and laboratory markers. The main results were: 1) higher prevalence of overweight/obesity than malnutrition; 2) BF% revealed a high prevalence of obesity while the reduced FFMI ranged from 25 to 31%; 3) REE correlated with the FFM, in men, and with BMI and FFM, in women; 4) BMI, FM, and FFM are related biochemical indicators of hemolysis of SCD.

The nutritional status of people with SCD is traditionally characterized by malnutrition [49, 50]. The identification of eutrophic predominance followed by overweight /obesity suggests that is experiencing a nutritional transition, characterized by the coexistence of malnutrition and overweight [51-53]. Some factors may have contributed to change the nutritional profile, such as improving the clinical treatment based on comprehensive care to patients with SCD [50], as well as the characteristic of dietary intake of individuals with SCD in which there is a predominance of high levels of poor quality fat, a simple sugar, and fried foods, as well as low consumption of fruits, and vegetables [51, 54, 55].

The BMI underestimated the number of overweight/obese individuals, only with the assessment of body composition by DXA found a high body fat percentage and a significant portion of lean mass loss. This condition is well known and described as sarcopenic obesity highly frequent in the aging process, especially between 60 and 70 years [56]. This was not expected, since the evaluated people were predominantly adults [57]. In BC normative data from Brazilian men demonstrated a significant reduction in FFM and a significant increase in fat content with age. That makes us assume that it is indeed SCD, since it is a chronic inflammatory disease promoting oxidative stress and compromising multiple organs with concomitant worsening of the eating pattern, a worldwide movement, can accelerate the common body changes in aging [28-30].

The fact that the BMI is underestimated in the prevalence of obesity is not novel, since it has an important limitation not to distinguish the fat mass from the lean mass and does not reflect the distribution of body fat [58].

In the present study, surprisingly, LM and BMC were not different between BMI classes because it was expected that in malnutrition the commitment of these compartments and that the higher BMC values were associated with increased body fat [59].

Unlike healthy subjects, it is believed that adults with SCD, even though a stable period without vaso-occlusive processes and complications secondary to disease has a slightly high energy requirement. However, with aging, it is expected that the REE tend to stabilize and then decline, as also occurs in the general population [60].

In healthy subjects, the REE is influenced by various factors such as size and BC, age, sex, hormonal status among others [61].

Regarding gender, the differences between energy expenditure are mainly determined by composition and body size [62]. Usually, men have more muscle mass, hence greater energy expenditure value than women [62, 63].

In our study, there was no significant difference in REE between men and women with SCD. When analyzing BC variables that were correlated with REE we noticed that both genders and FFM were moderately correlated, as was to be expected. However, only women showed the correlation between BMI and the REE. These findings are identical to those obtained by Van den Munckhof with patients without SCD [64]. This may be a result since we included people in the stable phase of SCD.

In our study, the hemolysis markers (LDH, reticulocytes, and TB) were inversely correlated with BMI, FM, and FFM, without changing the REE. The interference of hemolysis in the nutritional status observed, confirming existing reports of elevated levels of hemolysis, may be associated with depletion/malnutrition compartments of the body [65]. It is known that hemolysis may contribute to the increased mortality in SCD.

Hemolysis with the subsequent release of cell-free hemoglobin results in the generation of reactive oxygen species reducing nitric oxide reserves. This appears to predispose patients to vasculopathy and concomitantly the reticulocytes are more adhesive to fibronectin and vascular cell adhesion molecule-1. The degree of adhesiveness is correlated with the severity of disease in patients with SCD. Therefore, the more hemolysis the more clinical complications the person will present and this will affect the nutritional status.

5 Conclusions

This study found a change in the nutritional status of people with SCD, with a prevalence of adequate body weight, followed by overweight and obesity.

It is concluded that there is sufficient evidence to support the assertion of the existence of a negative linear correlation between the hemolysis markers LDH, reticulocytes, and BT and with BMI,

FM, and FFM. Evidence was obtained that the REE similarly decreases in men and women with SCD. Nevertheless, more studies are needed to better understand how these variables relate as well as, will be useful to compare the REE values and other variables among adult patients with SCD and healthy people.

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