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ORIGINAL ARTICLE

# Predictive equations overestimated the resting energy expenditure by indirect calorimetry in adults with sickle cell disease

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## Abstract

**Background:** Traditionally, sickle cell disease (SCD) is associated with hypermetabolism. Despite this, few studies have compared resting energy expenditure (REE) with estimated predictive equations (EPE) in the assessment of adults with SCD. **Aims:** To compare REE values determined by indirect calorimetry (IC) with EPE in adults with SCD. **Patients and Methods:** 46 patients over 34 years old who were in the treatment performed a cross-sectional observational study from two reference centers for SCD located in the city of Rio de Janeiro, Brazil. The assess body composition and REE used Dual-energy x-ray absorptiometry and IC, respectively. Blood levels were measured to assess hemolytic and protein markers. For the univariate correlation used the Pearson's correlation test. The comparison between EPE and REE used the Intraclass Correlation Coefficient and the Bland-Altman analysis. **Results:** 63% of patients were women, 80.4% of homozygous sickle cell disease genotype, and, 52.2% were black color. The mean age was 50 years old. Weight (r=0.469; p=0,001), lean mass (r=0.631; p=0.000), bone mineral content (r=0.508; p=0.000) and C-reactive protein (r=0.319; p=0.002) correlated positively with the REE. There was no linear correlation between markers of hemolysis such as total bilirubin, direct bilirubin, and lactic dehydrogenase with REE. The REE was overestimated in the EPE when compared to IC (p<0.001). **Conclusions:** The prediction equations developed for healthy populations are not accurate enough to determine the energy requirements in SCD.

## Article information

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## 1 Introduction

Sickle cell disease (SCD) is a type of structural hemoglobinopathy and monogenic (single glu6val/E6V missense mutation), characterized by the appearance of a variant of normal adult hemoglobin A called sickle cell hemoglobin (HbS) [1-3]. Worldwide, approximately 5.7 million babies are born annually with HbS, of which 300,000 have homozygous sickle cell disease genotype (HbSS) and 75% of them were born in Sub-Saharan Africa [4-6]. Estimates of the incidence of SCD in the United States and Brazil are 1:1.941 and 1:2.700 neonates, respectively [5,6]. Mortality from SCD is still early in the main Brazilian capitals, with medians ranging from 26.5 to 31.5 years [7]. However, these values have been increasing in Brazil, where recently the survival estimate is 53.3 years of life for men and 56.5 years for women with HbSS [8]. Chronic hemolysis, vaso-occlusive events, and increased susceptibility to infections characterize SCD [9]. SCD frequently presents with acute and chronic complications, such as hematological, clinical, nutritional, and metabolic effects, affecting the nutritional status and increasing energy needs [9-12]. The nutritional status influences the prognosis of various diseases[13]. Additionally, different types of diseases can also modify body composition (BC) [14]. SCD is a chronic disease, that course with higher cardiac output, hypermetabolism, increased protein turnover, erythropoiesis, inflammation, and oxidative stress, especially in children and adolescents [12, 15]. Some studies suggest that resting energy expenditure (REE) in children and adolescents with SCD is increased [12, 15, 16]. Despite this, few studies in adults

with SCD investigated the REE [12, 15]. Among existing techniques for the measurement of REE, indirect calorimetry (IC) is the most accurate [17]. However, the high cost of equipment, sophisticated procedures and the need for specialized personnel limit the use of REE in clinical practice [17, 18]. Therefore, several prediction equations develop an estimate of REE, based on easily applicable variables, e.g., age, sex, weight, and height [17, 18].

In patients with SCD, hemolysis is the early wreck of erythrocytes by membrane rupture and it is being a common event in the pathophysiological process in SCD [19, 20]. During hemolysis, there is a reduction in vasodilation, transcriptional activation of endothelin, and vascular adhesion molecule, concerning nitric oxide and directly exposed to free erythrocytes, causing its degradation [19-22]. Chronic hemolysis present in SCD causes vascular imbalance, directly reflected in Hb concentration, reticulocyte count, bilirubin levels, lactic dehydrogenase (LDH), and bioavailability of oxide [21-25]. So far, scientific investigations have studied the biochemical markers of hemolysis in SCD without considering the REE of these patients [15, 16, 26].

Therefore, this study aimed to assess BC, the hemolytic markers, and to determine their relationship with REE in adults. Furthermore, we intend to compare REE values determined by IC with EPE in adults with SCD.

# 2 Patients and Methods

## 2.1 Study population and protocol

Two reference centers for the treatment of SCD in Rio de Janeiro (Brazil) conducted the study: the HEMORIO and HUPE. The data were collected from August 2012 to March 2016.

For this study, a total of 162 patients participated with aged over 34 years, of both sexes, presented the confirmed laboratory diagnosis of SCD using hemoglobin electrophoresis, with homozygous Hb genotype (HbSS) and heterozygotes (HbSC, HbSD, and HbStal) (Figure 1). Ethnic and racial classification followed the standardization of the Brazilian Institute of Geography and Statistics [26-29].

The exclusion criteria of the study were pregnant women; patients hospitalized in the last 14 days or who experienced, at the time of assessment, pain or vaso-occlusive events or had acute lung disease (Figure 1). Additionally, adults with a diagnosis of acquired immunodeficiency syndrome; hepatitis B or C; secondary osteoporosis; neurological disease or cognitive impairment; or other metabolic diseases; chronically use immunosuppressive barbiturates, steroids, ribavirin, interferon, vitamin-mineral supplements (except folic acid); or hormone replacements in the last 60 days and with history of drug or alcohol addiction (Figure 1).

Also excluded from the sample are the patients who participated in the BC assessment but did not undergo the IC assessment (Figure 1). Patients using hydroxyurea were not excluded from the study.

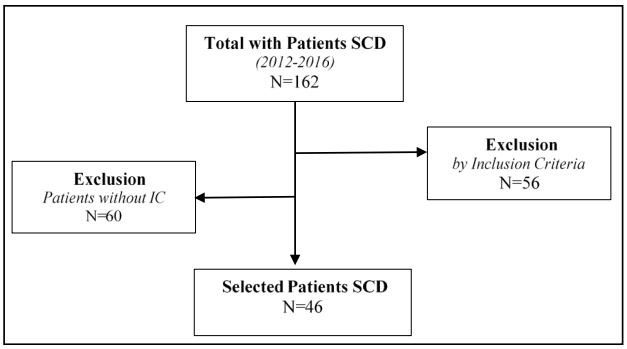



**Figure 1:** Flowchart of the study protocol. Acronyms: BC, body composition; IC, indirect calorimetry; SCD, sickle cell disease

## 2.2 Study design and ethical issues

This observational and cross-sectional study used non-probabilistic convenience sampling. The recruitment of patients eligible to participate in the study was during routine medical appointments in outpatient hematology clinics. The scheduled examinations of BC and REE for patients that agreed to participate in the study were at the Interdisciplinary Laboratory of Nutritional Assessment, Rio de Janeiro State University.

All patients received and signed the informed consent form before taking part in the study. All procedures were following the Declaration of Helsinki with approbation by the ethics committee of HUPE (2819/2010), HEMORIO (244/2010), and HEMORIO (365/2014).

## 2.3 Anthropometric assessment

Body mass (BM) in kilograms was measured by using the electronic scale (Filizola®), with a maximum capacity of 200 kg and an accuracy of 50g. Patients received instructions to distribute the BM equally on their feet. Height in meters was performed by using the vertical anthropometer (exact height®) through by orthostatic position at the standing base of the anthropometer and at right angles to the vertical edge of the device. The registers of measurement were of the accuracy of 0.1 cm.

Anthropometric measurements determined the body mass index (BMI), classified adults according to the proposal of the World Health Organization [30], and the elderly followed Lipschitz's classification [31].

Arm circumference (AC), arm muscle circumference (AMC), and triceps skinfold (TSF) whose values were compared with reference values (Percentile 50) from the NHANES [32], are shown in the tables of percentiles by Frisancho (1974, 1981) [33-35]. The percentage of adequacy followed the categorization according to Blackburn and Thorton (1979) [36].

## 2.4 Dual-energy X-Ray absorptiometry proceedings

A densitometer scanner (Lunar GE iDXATM Medical Systems, Madison, WI, USA) measured the patients' body compartments

using Dual-Energy X-Ray Absorptiometry (DXA), a gold standard method for accuracy and precision of BC estimates [37].

The basic principle of DXA is to produce a two-dimensional image that uses X-rays with two different energy sources [38]. 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 [39].

Therefore, DXA applies the attenuation characteristics in three compartments: bones, lean mass, and fat mass, and estimates these three components in selected regions of the entire body through specific software [40].

In the present study, a trained radiologist performed DXA in the morning. The enCORE software (GE® Health care) realized the acquisition, calibration, and body analysis, and followed the International Society for Clinical Densitometry recommendations validated by the Brazilian Correlation of Bone Evaluation and Osteometabolism [37-40].

The patients had instructions 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. Patients had instructions to report whether they had cardiac pacemakers. Only when did women of reproductive age state that they were not pregnant during the study period, the examinations could be performed.

Patients 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 8 h. During the examination, the individual remained to lie supine, with his arms along his body for complete scanning of the body compartments. Transverse scans in the longitudinal axis of the body lasted 20 minutes.

The patients' results report according to the NHANES reference[41] and were prepared, reviewed, and signed by a densitometrist.

## 2.5 Body composition

BC was assessed by DXA and described as lean mass (LM, kg), 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 men and >30% for women) and according to reference values proposed by Kelly et al. [41].

## 2.6 Indirect calorimetry proceedings

The IC method measures gas exchange (oxygen and carbon dioxide) to estimate the quantities of oxidized substrates, combining their density for the determination of total energy expenditure [42]. Indirect calorimeter operation has an air traction system, which is suctioned from the room in a smaller exhaust system (canopy), which allows free-breathing with a ventilator, diluting the breathing in a large volume or volume over time (flow) [42].

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

To perform IC proceedings, a general protocol developed according to the specifications of the manufacturer Vmax Encore 29 Sensormedics® System, included 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. IC turned on 30 minutes before the start of the test with patients.

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

For exam preparation, the patients realized an adherence protocol to test their ability to perform the exam. Being able to perform the procedure, the participant stayed 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 signalized by each sidebar indicated the permission to pass the next adjacent outer lines until the graphs could be generated by the calibration process were satisfactorily completed according to the signaling of the Vmax program. In the end, the procedure could be saved in the Vmax program, and the air conditioner was turned on again to initiate the participant registration step, in which the participant data was included by selecting “New Study”.

After saving the registration, the gas cylinders could open counterclockwise, and the sensor could connect 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, closed the cylinders 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 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. REE data was tabulated (“Tabular Edit”) and saved to a USB stick.

## 2.7 Resting energy expenditure

REE was measured for 25 minutes with a bell jar to collect data on inspired O2 and expired CO2, which were used for the calculation of REE with the Weir formula (1949) [43]. The final 5 minutes of the test, considered an adaptive period, were disregarded. Values of 24-hour REE were determined by multiplying the average value of the last 20 minutes by 1440

minutes. During the test, the patients received instructions not to sleep, either to stand up or speak.

Four prediction equations calculated the EPE values: Harris-Benedict (1919), FAO/WHO/UNU (Food and Agriculture Organization of the United Nations -1985), Schofield (1985), and Henry-Ree (1991) [44-48]. These equations are widely used in clinical practice.

## 2.8 Laboratory exams

Analysis was made of hemolytic markers (LDH, reticulocytes, total bilirubin –TB, and direct bilirubin – DB), hemoglobin, leukocytes, CRP, and albumin. For performed the LDH assay used a spectrophotometry method. Evaluation of bilirubin and fractions performed a colorimetric assay. Reticulocyte levels were determined by brilliant cresyl blue staining. For to obtain hematologic data performed an automated cell counter (Horiba Pentra 60 C+).

The hemoglobin analysis and quantification used the electrophoresis in citrate agar and high-performance liquid chromatography cation exchange (Variant TM, Bio-Rad Laboratories, Hercules, CA, USA). Albumin levels were determined using colorimetry. ELISA (Sigma, Aldrich) determined the C-reactive protein (CRP) test. Only after 12 hours of fasting, performed the blood collection, in the morning.

## 2.9 Statistical analysis

The data were presented as mean ± standard deviation or median and IQR, depending on the distribution of the variable. The Kolmogorov-Smirnov test assessed the normality of the distribution of investigated continuous variables. All variables in our study were distributed normally. Pearson's correlation test investigated the univariate correlation between REE and the variables of nutritional status, body composition, and laboratory tests. According to Cohen [49], a value of r between 0.1 and 0.29 is classified as small; a value between 0.3 and 0.49 is classified as medium and between 0.5 to 1 is classified as large.

The intraclass correlation coefficient (ICC) used the test the reproducibility of EPE as determined by prediction equations, in comparison to IC. Values lower than 0.4 indicate low reproducibility; values between 0.4 and 0.75, moderate reproducibility; and values above 0.75, good reproducibility. The Bland-Altman analysis assessed individual dispersion and concordance between the two methods [50]. The software Statistical Package for Social Sciences (SPSS version 21.0; Chicago, IL) served to run the statistical tests. All tests regarded a significance level of 95% ($p < 0.05$).

# 3 Results

## 3.1 Characteristics of the study population

46 patients participated in this study and, realized laboratory exams, DXA, and calorimetry. Most patients were from the HbSS genotype (n=37, 80.4%). As predicted, African descent people were predominant (black and pardo) (n = 42), with a higher prevalence of black color (52.2%).

Table 1 shows the general characteristics of patients with SCD. As noted, the study population was middle-aged, showing an increase in life expectancy for these patients. There was a higher frequency of women (n=29).

The mean hemolytic markers, hemoglobin, and leukocyte blood levels observed in the group obeyed values considered typical of people with SCD. Plasma CRP levels were consistent with the inflammation present in patients with SCD, even in an asymptomatic steady state.

As expected, the mean LM analyzed by DXA was higher in men, as the mean BF% was higher among women. The EPE overestimated REE when compared to IC.

**Table 1:** General characteristics of adults with sickle cell disease (n=46) treated at an outpatient clinic of two reference centers in the state of Rio de Janeiro, Brazil, 2012-2016

| Variables | |
|---|---|
| Women (n; %) | 29 (63%) |
| Age (years)[a] | 50 (15.1) |
| Weight (kg)[b] | 63.4 (55.2; 73.5) |
| BMI (kg/m$^2$)[a] | 24.6 (4.8) |
| AC (cm)[b] | 91.5 (15.3) |
| AMC (mm)[a] | 92.5 (15.4) |
| TSF (cm)[b] | 94.9 (71.6; 111.5) |
| Men LM (kg)[a] | 45.1 (3.6) |
| Women LM (kg)[a] | 36.6 (7.3) |
| Men BF %[a] | 25.4 (9.1) |
| Women BF %[a] | 38.9 (6.0) |
| BMC - whole body (kg)[a] | 2.3 (0.5) |
| Hemoglobin (g/dL)[a] | 9.6 (2.4) |
| Leukocytes (cells/mm$^3$)[a] | 8.9 (3.3) |
| Reticulocytes (cells or %)[b] | 4.4 (2.7; 9.4) |
| Total Bilirubin (g/dL)[b] | 1.28 (0.91; 2.41) |
| Direct Bilirubin (g/dL)[a] | 0.53 (0.27) |
| LDH (g/dL)[b] | 658 (559; 1089) |
| CRP (mg/L)[b] | 4.4 (2.7; 9.4) |
| Albumin (g/dL)[b] | 4.4 (4.0; 4.6) |
| Calorimetry, REE (kcal)[a] | 1254.7 (206.0) |
| Harris-Benedict, REE (kcal)[a] | 1398.6 (163.1) |
| FAO/WHO/UNU, REE (kcal)[a] | 1488.0 (173.8) |
| Schofield, REE (kcal)[a] | 1470.2 (172.0) |
| Henry-Ree, REE (kcal)[a] | 1386.0 (157.2) |

Notes: The men were used as a reference value for this analysis. a Mean (SD).b Median (IQR). Acronyms: AC, arm circumference; AMC, arm muscle circumference; BF%, body fat percentage; BMC, bone mineral content; BMI, body mass index; CRP, C-reactive protein; FAO/WHO/UNU, Food, and Agriculture Organization of the United Nations; LDH, lactate dehydrogenase; LM, lean mass; REE, Resting Energy expenditure; TSF: triceps skinfold.

## 3.2 Body mass index, body composition, and resting energy expenditure

Considering the classification based on BMI, the mean of the patients was eutrophic even as the adequacy of the AC, MAC, and TSF (Table 1). The interquartile limits of TSF indicated the presence of both malnutrition and overweight/obesity.

Although the weight of patients with SCD positively correlated moderately with the REE (p = 0.001), there is insufficient evidence to support a claim that there is a linear correlation between BMI and REE (Table 2).

DXA assessment showed that the patients of both sexes had a lower median of BF% (25.8 for men and 38.8 for women). In addition, the results showed that there was no correlation between BF% and REE.

Nevertheless, LM (r = 0.631) and BMC (r = 0.508) were strongly correlated with REE, and this was statistically strong significant (p= 0.000).

**Table 2:** Univariate association between resting energy expenditure, determined by indirect calorimetry and the variables of nutritional status, body composition, and laboratory examinations of adults with sickle cell disease (n=46) treated in an outpatient clinic in two reference centers in the state of Rio de Janeiro, Brazil, 2012-2016

| Variables | Resting Energy expenditure (Kcal) | | |
|---|---|---|---|
| | N | r | p |
| Age (years) | 46 | -0.128 | 0.402 |
| Weight (kg) | 46 | **0.469** | **0.001** |
| BMI (kg/m$^2$) | 46 | 0.242 | 0.106 |
| AC (% adequacy) | 46 | 0.258 | 0.087 |
| AMC (% adequacy) | 46 | 0.264 | 0.080 |
| TSF (% adequacy) | 46 | 0.129 | 0.392 |
| LM (kg) | 38 | **0.631** | **0.000** |
| BF% | 38 | -0.213 | 0.199 |
| BMC (g) | 38 | **0.508** | **0.000** |
| Hemoglobin (mg/dl) | 27 | 0.310 | 0.116 |
| Leukocytes (000/mm$^3$) | 21 | -0.002 | 0.994 |
| Reticulocytes (%) | 27 | 0.040 | 0.842 |
| Total bilirubin (g/dl) | 26 | 0.000 | 0.999 |
| Direct bilirubin (g/dl) | 26 | 0.140 | 0.494 |
| LDH (U/L) | 23 | 0.128 | 0.562 |
| CRP (mg/l) | 25 | **0.319** | **0.020** |
| Albumin (g/dl) | 27 | -0.117 | 0.560 |

Notes: A value of r between 0.1 and 0.29 is classified as small; a value between 0.3 and 0.49 is classified as medium and between 0.5 to 1 is classified as large. Acronyms: AC, arm circumference; AMC, arm muscle circumference; BF%, body fat percentage; BMC, bone mineral content; BMI, body mass index; CRP, C-reactive protein; LDH, lactate dehydrogenase; LM, lean mass; TSF, triceps skinfold.

## 3.3 Hemolytic markers and resting energy expenditure

The univariate correlation performed the measure the correlation between hemolytic markers with REE in adult patients with SCD. Unexpectedly, there is insufficient evidence to support the existence of a linear correlation between hemolysis markers reticulocytes, TB, DB, and LDH with REE (Table 2).

Nevertheless, CRP, a laboratory marker of inflammation, had a medium positive correlation with REE (r=0.319), and this was statistically significant (p = 0.002).

## 3.4 Resting energy expenditure, estimated by predictive equations and predictive equations

The comparison between REE values and EPE values (Figure 2) shows that the mean EPE values of all equations were significantly higher than those of REE (p<0.001). The overestimated percentage of REE varied according to the equations: Henry-Ree (10.4%), Harris-Benedict (11.4%), Schofield (17.1%), and FAO/WHO/UNU (18.5%). There were significant differences between the values estimated by the four equations (p= 0.003).

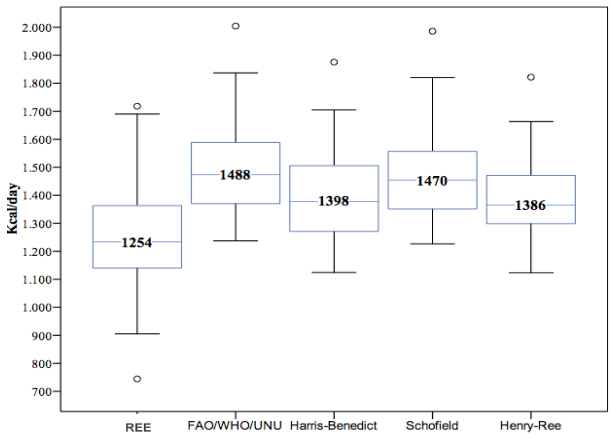



**Figure 2:** Comparison between resting energy expenditure, measured by indirect calorimetry and by prediction equations in adults with sickle cell disease (n=46) treated in an outpatient clinic in two reference centers in the state of Rio de Janeiro, Brazil, 2012-2016. Acronyms: FAO/WHO/UNU, Food, and Agriculture Organization of the United Nations

ICC for the four prediction equations was indicative of a weak to moderate degree of reproducibility with IC (Table 3). ICC values found for the equations of Harris-Benedict and Henry-Ree were stronger than for the equations of FAO/WHO/UNU and Schofield. For the latter two equations, the correlation was not statistically significant.

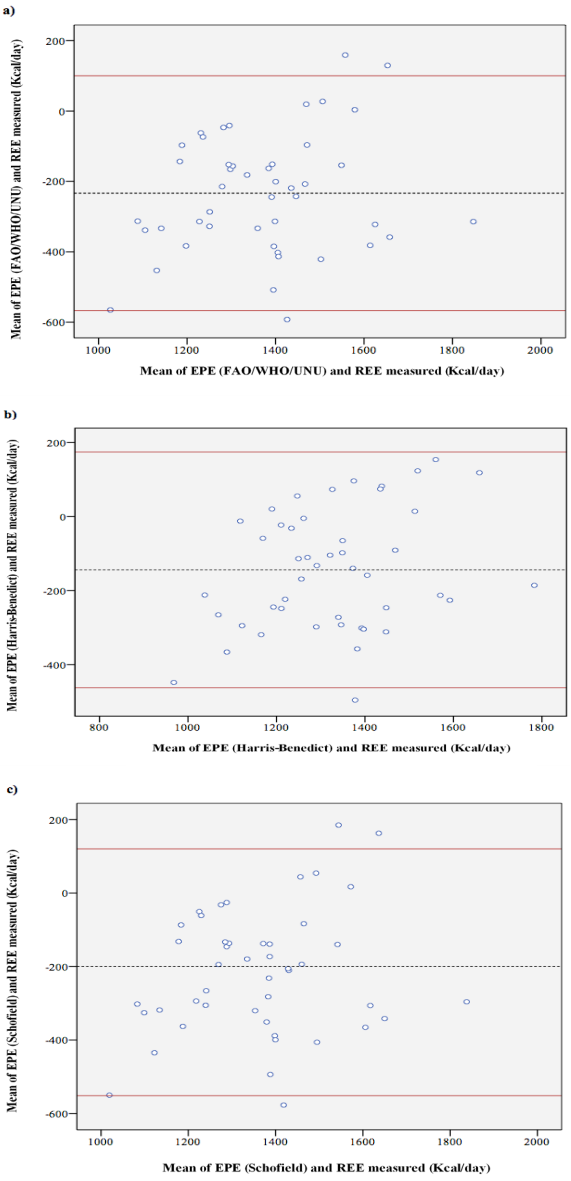
Figure 3 shows individual agreement between IC and the prediction equations by the Bland-Altman analysis. There was a positive correlation between the difference (y-axis) and the average (x-axis) of REE and the equations of Harris-Benedict (r = 0.291; p=0.049; Figure 3a) and Henry-Ree (r = 0.336; p=0.023; Figure 3b).

The same correlation was not statistically significant for the equations FAO/WHO/UNU 1985 (r = 0.219; p= 0.160; Figure 3c) and Schofield (r = 0.216; p=0.150; Figure 3d). These findings show that, for the equations of Harris-Benedict and Henry-Ree, the difference increased as the individual average increased. The individual variability shown in these graphs indicates the existence of patients whose REE values were both underestimated and overestimated, even though the average difference was positive (Table 2).

**Table 3:** Agreement analysis of resting energy expenditure, measured by indirect calorimetry with the values of the prediction equations in adults with sickle cell disease (n=46) treated in an outpatient clinic in two reference centers in the state of Rio de Janeiro, Brazil, 2012-2016

| Equation | ICC | 95% CI | p |
|---|---|---|---|
| FAO/WHO/UNU | 0.169 | -0.123; 0.434 | 0.127 |
| Harris and Benedict | **0.412** | 0.144; 0.625 | **0.002** |
| Schofield | 0.210 | -0.080; 0.469 | 0.076 |
| Henry and Ree | **0.440** | 0.176; 0.645 | **0.001** |

Acronyms: 95% CI, confidence interval of 95%; FAO/WHO/UNU: Food and Agriculture Organization of the United Nations. ICC, intraclass correlation coefficient;



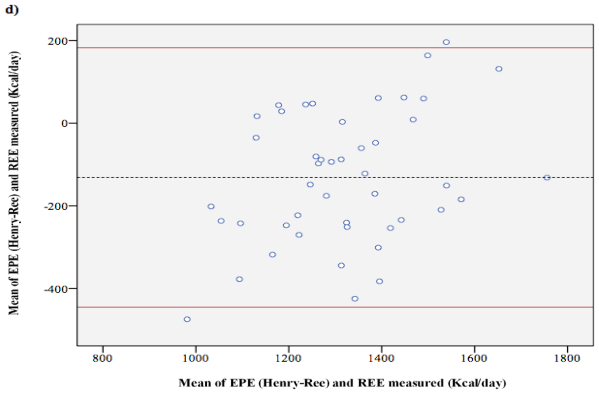




**Figure 3:** Bland-Altmann analysis between resting energy expenditure, determined by indirect calorimetry and prediction equations in adults with sickle cell disease (n=46) treated in an outpatient clinic in two reference centers in the state of Rio de Janeiro, Brazil, 2012-2016. Note: FAO/WHO/UNU **a**, Harris-Benedict **b**, Schofield **c**, and **d** Henry and Reed. Acronyms: EPE, estimated by predictive equations; FAO/WHO/UNU, Food, and Agriculture Organization of the United Nations; REE, measured resting energy expenditure

# 4 Discussion

The main results were as follows: (1) BF% and hemolytic markers were not correlated with REE; (2) weight, LM, BMC, and CRP were correlated positively with REE; (3) the mean EPE values of all equations were significantly higher than those of REE determined by IC; and (4) the equations that overestimated REE the least were the equations of Henry-Ree and Harris-Benedict.

## 4.1 Nutritional status, body composition, and energy expenditure in SCD

Historically, patients with SCD have malnutrition [51, 52]; however, more recent studies have shown changes in the nutritional status profiles [26, 53]. The identification of eutrophic predominance followed by overweight/obesity suggests that patients with SCD are experiencing a nutritional transition [54].

Some factors may have contributed to the changes in the nutritional profile, such as improvement in clinical treatment and increased consumption of foods with high levels of poor quality [51, 54, 55]. Considering the limited information about BC of men and women with SCD as well as whether the differences between both sexes were similar to those expected for men and women [31], comparative analyses revealed a similar behavior [41, 56, 57].

Nevertheless, the improvement in BMI indicator didn't reflect values close to normal parameters of body fat in SCD patients in the study. The BMI underestimated adiposity in patients; however, the BC assessment using DXA found a high number of

patients with excess BF% and a significant portion of patients with lean mass loss [58]. The fact that the BMI is underestimating the prevalence of obesity is not novel, because of its inability to distinguish the body fat from the lean mass and does not reflect the distribution of BF% [59].

This observational study showed a lower median in patients with SCD when compared to NHANES reference values according to age and sex [41]. Aging is usually characterized by a gradual increase in total body fat in adulthood, followed by a loss later in life, and remodeling of fat distribution [60]. Body fat has regulation hormonal and genetic control [61]. Environmental factors, lifestyle, and diseases can affect body fat [61].

The fact that BF% was lower in the population of the study, suggests that SCD pathophysiological process, early progress of organ degeneration, hypermetabolism, changes in metabolic pathways, decreased intake and food insecurity could over time negatively impact the body fat patients wich SCD, but to prove this hypothesis would be necessary future follow-up studies.

The adipose tissue contains the fattest triglyceride resides and has a lower mass-specific energy expenditure than adipose-tissue-free mass [62]. In the present study, we believed that REE could be lower in patients with lower BF%, but there is no evidence available to support the existence of a linear correlation between REE and BF% in patients with SCD. Perhaps the fact that study patients were in a steady-state period (without vaso-occlusive events) can contribute to no correlation.

Vaso-occlusive events and pain in SCD are the main events that stimulate the reduction of food intake and increase of energy expenditure due to hyperproduction of erythrocytes by bone marrow [63, 64]. In this context, there would have caloric restriction influencing the first phase of weight loss rapidly, followed by a second phase characterized by a slower weight loss, that if it continued, the body fat would have continuous depletion with a decrease of BF% [65].

In general situations of starvation, while decreases in body fat explained 34 % in phase 1, this proportion increased to 64-68 % during phase 2 and the energy content increased from 4409kcal during phase 1 to 5209-7105kcal during phase 2 [65]. Considering acute pathophysiological processes or secondary complications that could cause pain in patients with SCD, should observe a progressive decrease of BF% with a continuous increase of REE, in other words, the possibility of an inversely proportional relationship between REE and BF% [63-65].

Another noteworthy result involves factors correlated with REE by IC. REE had a direct and significant correlation with weight, LM, BMC, and serum levels of CRP. Corroborating these findings, Buchowski et al. [66] found a positive relationship between muscle mass and REE in men and women adolescents with HbSS.

Conversely, Akohoue et al. [67], in a study with 35 African American adolescents with HbSS, showed that inflammation assessed by serum levels of CRP and interleukin-8 had a direct correlation with REE. The finding that BMC correlated with REE is new for patients with SCD, although this correlation was already found in other groups [68, 69]. However, in the study of Buchowski et al. [66], both markers of bone formation and bone resorption correlated with REE in with Hb SS.

In addition to the physiological changes correlated with aging [62], the inflammatory characteristics of the disease [43, 55] and the quantitative change in food consumption due to multiple hospitalizations [70-73] may have contributed to these changes in BC. Based on these results, nutritional management for patients with SCD should be preventively adopted with a focus on adiposity control and maintenance of lean mass.

## 4.2 No correlation between hemolysis markers and resting expenditure energy in SCD

Hemolysis is known as a contributor to increased morbidity and mortality in patients with SCD [74, 75]. Hemolysis with the subsequent release of cell-free Hb results in the generation of reactive oxygen species that reduces nitric oxide reserves [76].

This may predispose patients to a vasculopathy, and concomitantly reticulocytes are more adhesive to fibronectin and vascular cell adhesion molecule-1 [77]. The degree of adhesiveness is correlating with the disease severity in patients with SCD. Therefore, the more hemolysis the greater the risk to develop clinical complications [77], which may affect the nutritional status.

Nevertheless, in this study, the hemolytic markers did not correlate with REE. Maybe the results are could reason like a no correlation between BF% and REE. The correlation between hemolysis and nutritional status corroborates with existing reports that elevated levels of hemolysis and consequently decreased Hb concentration may be correlated with poor nutritional status [77, 78].

## 4.3 Predicting equation in SCD by resting expenditure energy

Previous studies investigated the correlation between REE by IC and prediction equations in different sick populations [43, 44, 46-49, 79]. However, none of them were performed in adult patients with SCD; hence, current dietary plans are inaccurate for these patients.

In the present study, the predictive equations developed for the general population were not sensitive enough to estimate REE in patients with SCD. The equations of Henry-Ree and Harris-Benedict presented an ICC indicative of moderate reproducibility compared to IC, while for the equations of FAO/WHO/UNU and Schofield, the results were indicative of

low reproducibility. Because SCD is a disease characterized by hypermetabolism [80], the prediction equations can assume possibly underestimate energy requirements in adult patients. However, our results showed that the four evaluated prediction equations overestimated REE. Among the evaluated formulas, the equations of FAO/WHO/UNU and Schofield were the ones that showed the greatest difference between the average REE values as compared to EPE, while the equations of Henry-Ree and Harris-Benedict expressed the best results, although they also overestimated energy requirements.

When we think about energy expenditure and SCD, we need to keep in mind that these patients go through successive hospital admissions that can probably start from birth to adulthood [7, 8] . These recurrent hospitalizations refer to acute events or events secondary to the disease and directly interfere with nutritional status and energy expenditure [7, 12, 15, 81].

Although experience primary and secondary events when children and in older age groups, there is the impression that over time these events interfere differently, especially in middle-aged adults and elderly survivors [8, 82].

The energy expenditure of healthy children and adolescents is naturally high to compensate for factors related to growth and development [40, 12, 81]. In infanthood with SCD, probably due to primary and secondary events, there is an additional unknown energy addition that implies a much greater energy need [12, 15, 81].

These findings could be confirmed in the studies by Buchowski et al. [66], who compared REE by CI with the values estimated by the Harris-Benedict, FAO/WHO/UNU, and Schofield equations, noting that the EPE values were underestimating energy needs in the group of African-American adolescents (14 to 18 years old) with HbSS.

Another similar study by Koop-Hoolihan et al. [79] found that the formulas underestimated REE by 14% by the Schofield equation, followed by 15% by the FAO/WHO/UNU equations, and 18% by the Harris-Benedict. Similarly, Williams et al. [83] also showed that REE was underestimated (Harris-Benedict at 14% and FAO/WHO/UNU at 12%) in 18 children with HbSS aged 5 to 11 years.

Therefore, regarding REE and SCD, it is not possible to make a comparison or extrapolation between the children and young people concerning adults, especially middle-aged and elderly people. In our study, we found a mean age of 50 years and that EPE overestimated the REE of these patients with SCD.

It is expected in healthy patients that, upon reaching adulthood, energy expenditure stabilizes and, over the years until old age, there is a natural decline in REE together with changes in BC [40, 62].

Possibly, in our study, most of these adults with SCD experienced all the events of children and adolescents, and now probably continue to experience these same events differently over the years, with a progressive decline in energy expenditure due to the age group they reached. However, having to live with the gradual process of multiple organ degeneration, also called organ failure [8], supposedly may be interfering in an unknown way with the REE.

### 4.4 Study limitations and future directions

The sample consisted of patients with SCD who had different genotypes that could be influencing the heterogeneity of the REE. Another limitation is that for methodologies that approach IC as a method of studying the REE, a larger sample would be necessary, if possible above 50 patients.

From future perspectives, we hope that this study will help in the development of other research on this topic that could better understand the REE differences between genotypes; REE differences between age adulthood ranges; studies that could use control groups and with sample numbers greater than 50 patients; and with more advanced methodologies and more practicality to measure REE.

Finally, we believe that a population with a longer life expectancy must be a result of new circumstances arising from advances in the quality of health care provided to patients with SCD in the Brazilian scenario.

## 5 Conclusions

This study found the prediction equations developed for healthy populations are not accurate enough to determine the energy requirements of patients with SCD. In conclusion, there is sufficient evidence to support the assertion of the existence of a correlation positive of Weight, LM, BMC, and CRP with REE. There was insufficient evidence to support the existence of a linear correlation between hemolysis markers with REE. The EPE overestimated REE when compared to IC. However, more studies are needed to better understand how REE role in middle-aged and elderly adults with SCD, through the improvement of scientific and statistical methodologies, to provide a better quality of life for adult patients with SCD.

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