Body composition of Fanconi anemia patients after hematopoietic stem cell transplantation

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ABSTRACT

Introduction: Fanconi anemia is a rare genetic disease linked to bone marrow failure; a possible treatment is hematopoietic stem cell transplantation. Changes in the nutritional status of Fanconi anemia patients are not very well known. This study aimed to characterize body composition of adult, children and adolescent patients with Fanconi anemia who were submitted to hematopoietic stem cell transplantation or not.

Methods: This cross-sectional study enrolled 63 patients (29 adults and 34 children and adolescents). Body composition was assessed based on diverse methods, including triceps skin fold, arm circumference, arm muscle area and bioelectrical impedance analysis, as there is no established consensus for this population. Body mass index was also considered as reference according to age.

Results: Almost half (48.3%) of the transplanted adult patients were underweight considering body mass index whereas eutrophic status was observed in 66.7% of the children and adolescents submitted to hematopoietic stem cell transplantation and in 80% of those who were not. At least 50% of all groups displayed muscle mass depletion. Half of the transplanted children and adolescents presented short/very short stature for age.

Conclusion: All patients presented low muscle stores, underweight was common in adults, and short stature was common in children and adolescents. More studies are needed to detect whether muscle mass loss measured at the early stages of treatment results in higher risk of mortality, considering the importance of muscle mass as an essential body component to prevent mortality related to infectious and non-infectious diseases and the malnutrition inherent to Fanconi anemia.

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Introduction

Fanconi anemia (FA) is a rare recessive genetic disease, usually inherited in an autosomal recessive manner, linked to bone marrow failure and an increased risk of developing a tumor. FA patients are more prone to presenting morphological and endocrine abnormalities, such as bone deformities, cardiac and kidney malformation, hyperpigmentation, glucose intolerance, changes in glycemic control, dyslipidemia, hypothyroidism and growth hormone deficiency. The only hematological treatment that offers a potential cure for this disorder is hematopoietic stem cell transplantation (HSCT), which aims to restore the impaired bone marrow. Some conditions may affect the success rate of HSCT, such as the stage of the disease, the type of transplant, the origin of donor stem cells and histocompatibility, the conditioning regimen, age, previous treatment, and nutritional status of the patient. Moreover, immunosuppression and the toxicity of the conditioning regimen have negative effects, in particular in respect to infections, bleeding, constipation, diarrhea, mucositis, nausea, and emesis.

In addition to the characteristic outcomes of the disease, such as short stature, transplanted patients with FA can be underweight, and present increased growth problems and dyslipidemia, whereas changes in glycemic and hormone control may result in an overweight condition or even obesity.

Malnutrition has substantial prognostic and socioeconomic implications for patients and caregivers. Consequences of malnutrition include increased complications after surgeries and prolonged hospitalization resulting in higher exposure to infectious agents, a reduced response to treatment, a poorer quality of life and ultimately a worse prognosis. Individually, methods of nutritional assessment are limited and a gold standard has not been established to date. Consequently, at least two instruments have been used to establish the nutritional diagnosis adequately. In the case of diseases that have complex metabolic demand and require a drug regimen that substantially affect cell structure and impose catabolism such as chemotherapy, the attention to nutritional status should be stressed, however, the criteria to choose the most adequate methods have not been clearly defined.

As FA patients are more prone to malnutrition not only due to treatment but also because of the metabolic burden related to the disease, and as they might have higher risk of mortality, this study investigated whether changes in body composition are evident after transplantation and whether there are differences between patients submitted to transplant and those who are not. There are few studies that analyze the nutritional status of these patients, which makes it difficult to discriminate this group from patients with hematological diseases and as a consequence, during the clinical practice, nutrition support may not be specified to achieve their needs resulting in chronic malnutrition. Studies to better characterize the nutritional status of FA patients after HSCT are needed to optimize supportive care in this unique population.

The present study aimed to characterize the body composition of children, adolescents and adult patients with FA one year or longer after HSCT as compared to patients undergoing clinical treatment in order to support future studies related to nutritional assessment.

Methods

This cross-sectional study was conducted with male and female FA patients who were two years of age or older and submitted to HSCT or not at the Bone Marrow Transplant Service (BMTS) of the Hospital de Clinicas da Universidade Federal do Paraná. Exclusion criteria were patients that had been submitted to HSCT within six months of the start of this study, presence of physical changes that could impair anthropometric assessments, and cognitive difficulties to read, understand and fill out questionnaires. To characterize the population, a structured questionnaire was used consisting of identification data (date of birth and gender) and clinical data (submission to and type of HSCT, time after HSCT, and comorbidities).

This study was approved by the Human Research Ethics Committee of the Hospital de Clínicas da Universidade Federal do Paraná (#347232140.0.0000.0096), and a written consent was obtained from all participants or their legal guardians.

Anthropometric assessment

Weight, height, arm circumference (AC) and triceps skin fold (TSF) were measured, and body mass index (BMI) and arm muscle area (AMA) were then calculated. The 15th percentile was used as a cut-off point for inadequacy. For adult patients (≥19 years old) BMI was classified according to the World Health Organization. To classify children and adolescents, the WHO Antro® program was used for children younger than five years old, and the WHO Antro Plus® program was used for those aged between five and less than 19 years old. Z-score values were used to classify weight for age (W/age), height for age (H/age), and BMI for age (BMI/age) ratios.

Body composition and phase angle assessment

Bioelectrical impedance analysis (BIA) was performed using a tetrapolar BIA device Quantum 101 (RJL System®, Inc. USA) with a current of 800 μA and a frequency of 50 KHz. It was applied according to the instructions provided by the guide for bioelectrical impedance analysis. Phase angle was calculated from the arc tangent resistance/reactance (Xc/R) value, which was expressed in degrees after being multiplied by 180/π. Phase angle standardization was based on the following equation: observed phase angle (°) - mean phase angle for gender and BMI (°)/phase angle standard deviation for gender and BMI.

As there is no reference for phase angle stratified by BMI under 18.5 kg/m², 18 individuals were not considered in this analysis. For adults, phase angle values below 5° were considered risk predictors for malnutrition and morbidity. Lean body mass (LBM) values were obtained using the Kushner equation for children between four and ten years old, the Houtkooper equation for children and adolescents aged from 11 to 18 years old, and the Lohman equation for adults aged between 19 and 29 years. Patients who did not meet the
age criteria were not included in this analysis. All measurements were performed at one timepoint and there was no follow-up.

Statistical analysis

The IBM® Statistical Package for the Social Sciences (SPSS) version 22.0 was used to perform statistical analyses. Demographic and anthropometric variables were evaluated by descriptive statistics. The Shapiro–Wilk test was used to verify the homogeneity of data. Sensitivity and specificity was determined by the receiver operator characteristics (ROC) curve, considering nutritional status (NS) and the time after HSCT. Student’s t-test and Mann–Whitney U test were used to compare the means of independent samples; both tests were used to compare transplanted and non-transplanted children and adolescents. A p-value <0.05 (95% confidence interval) was used to identify significant differences between the groups.

Results

Demographic characteristics

Sixty-eight patients were recruited but five were excluded due to the exclusion criteria were thus the total study population was 63 patients – 32 male and 31 female. Children and adolescents were aged between two and 18 years old (mean: 13.1 ± 3.85) while adults were aged from 19 to 40 years old (mean: 25.0 ± 5.16).

Most patients (84% – n = 53) underwent HSCT. Allogeneic related donor HSCT were most common in adults (69% – n = 20) and in children and adolescents (66.7% – n = 16). Haploidentical transplants were the most common type of transplant (62.5% – n = 10) for children and adolescents. The time after HSCT ranged from six months to 27 years (mean: 9.0 ± 6.75 years – Table 1). Comorbidities were present in 30.9% (n = 21) of patients with hypothyroidism (28.6% – n = 6), hyperthyroidism (23.8% – n = 5), diabetes (17.3% – n = 3), and hypertension (9.5% – n = 2) being the most common.

General body composition and anthropometric assessment

The children and adolescent population studied was homogeneous regarding age, anthropometric parameters and BIA assessments (Table 2). When the data were classified to give clinical relevance to the findings, differences between the groups were found as described below.

Body composition

Adults submitted to hematopoietic stem cell transplantation

Considering anthropometric data and BMI of all patients, 48.3% (n = 14) were underweight, followed by eutrophic (37.9% – n = 11) and overweight (13.8% – n = 4). The average height was 1.514 ± 0.097 m. Regarding body composition according to anthropometric assessments, 72.4% (n = 21) had adequate adipose tissue, 58.6% (n = 17) had reduced AC, and 69% (n = 20) had depleted muscle stores according to the AMA.

The mean percentage of lean body mass (%LBM) and body fat (%BF) by the BIA assessment were 77.1 ± 7.08% and 22.9 ± 7.08%, respectively. The mean phase angle was 6.5° ± 1.05°; however, only 15 patients had their phase angle standardized according to previous established criteria with a mean of 1.2° ± 1.36°. According to the risk classification, 14.3% of patients presented a phase angle of less than 5° (Table 2). In adults, to control the interference of chemotherapy regimens on nutritional status, the Chi-square test was used dichotomizing the treatment protocols as myeloablative versus reduced intensity conditioning (non-myeloablative) chemotherapy. Treatment did not represent a confounding variable for malnutrition with the outcome dichotomized as eutrophic versus undernourished according to the BMI (p-value = 0.53).

Children and adolescents submitted to hematopoietic stem cell transplantation

Most children and adolescents who underwent HSCT were eutrophic (66.7% – n = 16), considering their BMI/age ratio. However, some of these patients were overweight (8.3% – n = 2), and this group was the only one to present obese patients (8.3% – n = 2). Although the majority were eutrophic or obese, 16.7% were underweight. Regarding the H/age ratio, 50% had short or very short stature and the remaining 50% had adequate heights for age.

Body composition through anthropometric assessment revealed that 95.8% (n = 23) of patients presented adequate adipose tissue stores according to their TSF, whereas 37.5% (n = 9) had reduced AC, and 54.2% (n = 13) had depleted muscle stores according to the AMA.

Body composition analyzed by BIA found mean values for %LBM of 75.2 ± 7.79 and %BF of 24.8 ± 7.79. The mean phase angle was 6.0° ± 1.04°, and the mean standardized phase angle, established in 23 patients, was 0.7° ± 1.38°.

An assessment of NS using the ROC curve (Figure 1) showed a discriminatory power between BMI/age and time after HSCT. BMI/age presented greater specificity and sensitivity at 1.56 years after HSCT.

Children and adolescents not submitted to hematopoietic stem cell transplantation

Most children and adolescents who were not submitted to HSCT were eutrophic (80% – n = 8) considering BMI/age, followed by underweight in 10% (n = 1), and overweight in 10% (n = 1). Regarding H/age, 80% (n = 8) of the patients were classified as adequate height for age, and 20% (n = 2) as having very short statures for age.

Regarding the anthropometric assessment, 80% (n = 8) of patients presented adequate adipose tissue stores according to their TSF, while 30% (n = 3) had reduced AC, and 50% (n = 5) had depleted muscle stores according to the AMA. The BIA assessment revealed mean %LBM and %BF values of 73.3 ± 7.73% and 26.7 ± 7.73%, respectively. The mean phase angle was 6.1° ± 1.12°, and the mean standardized phase angle established in eight patients was 0.9° ± 0.90°. The anthropometric data of all groups are shown in Figure 2.
Table 1 – Demographic characteristics of patients with Fanconi anemia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adults – HSCT (n = 29)</th>
<th>Children and adolescents – HSCT (n = 24)</th>
<th>Children and adolescents – no HSCT (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (41.4)</td>
<td>13 (54.2)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (58.6)</td>
<td>11 (45.8)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Age (years) – mean ± SD</td>
<td>25.0 ± 5.13</td>
<td>13.7 ± 3.18</td>
<td>11.7 ± 5.00</td>
</tr>
<tr>
<td>HSCT – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allogeneic related donor</td>
<td>20 (69)</td>
<td>16 (66.7)</td>
<td>–</td>
</tr>
<tr>
<td>Allogeneic unrelated donor</td>
<td>9 (31)</td>
<td>8 (33.3)</td>
<td>–</td>
</tr>
<tr>
<td>Post-HSCT period (years) – mean ± SD</td>
<td>13.7 ± 5.37</td>
<td>3.3 ± 2.33</td>
<td>–</td>
</tr>
</tbody>
</table>

Demographic data are presented as percentages, the corresponding number of the population, mean, and standard deviation. HSCT: hematopoietic stem cell transplant; SD: standard deviation.

Table 2 – Body composition and anthropometric assessment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adults HSCT n</th>
<th>Children and adolescents HSCT n</th>
<th>Children and adolescents no HSCT n</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.0 (19.2–40.3)</td>
<td>13.7 ± 3.18</td>
<td>11.7 ± 5.00</td>
<td>0.15</td>
</tr>
<tr>
<td>Current weight (kg)</td>
<td>44.4 ± 11.08</td>
<td>39.1 ± 12.71</td>
<td>37.1 ± 19.91</td>
<td>0.77</td>
</tr>
<tr>
<td>W/age (Z-score)</td>
<td>–</td>
<td>–2.4 ± 2.73</td>
<td>–1.8 ± 1.57</td>
<td>0.68</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>151.4 ± 9.68</td>
<td>146.6 (84.0–175.8)</td>
<td>141.2 (81–172.4)</td>
<td>0.75</td>
</tr>
<tr>
<td>H/age (Z-score)</td>
<td>–</td>
<td>–1.9 (–7.9–1.8)</td>
<td>–0.7 (–7.6–0.2)</td>
<td>0.43</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.4 ± 3.59</td>
<td>18.5 ± 3.54</td>
<td>18.1 ± 3.78</td>
<td>0.76</td>
</tr>
<tr>
<td>BMI/age (Z-score)</td>
<td>–</td>
<td>–0.5 ± 1.61</td>
<td>–0.4 ± 1.34</td>
<td>0.89</td>
</tr>
<tr>
<td>AC (cm)</td>
<td>25.0 ± 4.36</td>
<td>22.7 ± 4.10</td>
<td>21.7 ± 5.28</td>
<td>0.56</td>
</tr>
<tr>
<td>TSF (mm)</td>
<td>14.9 ± 5.88</td>
<td>14.5 ± 5.41</td>
<td>11.5 ± 4.78</td>
<td>0.14</td>
</tr>
<tr>
<td>AMA (cm²)</td>
<td>33.8 ± 10.72</td>
<td>26.9 ± 8.44</td>
<td>27.4 ± 11.82</td>
<td>0.92</td>
</tr>
<tr>
<td>Resistance (Ω)</td>
<td>772.2 ± 129.4</td>
<td>747 ± 147.6</td>
<td>746.5 ± 165.8</td>
<td>0.99</td>
</tr>
<tr>
<td>Reactance (Ω)</td>
<td>85.5 ± 9.57</td>
<td>76 ± 9.88</td>
<td>76.8 ± 10.63</td>
<td>0.85</td>
</tr>
<tr>
<td>Phase angle (°)</td>
<td>6.5 ± 1.05</td>
<td>6.0 ± 1.04</td>
<td>6.1 ± 1.12</td>
<td>0.82</td>
</tr>
<tr>
<td>Standardized phase angle (°)</td>
<td>1.2 ± 1.36</td>
<td>0.7 ± 1.38</td>
<td>0.9 ± 0.9</td>
<td>0.51</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>34.3 ± 6.81</td>
<td>31.4 ± 7.42</td>
<td>36.5 ± 12.12</td>
<td>0.36</td>
</tr>
<tr>
<td>%LBM</td>
<td>77.1 ± 7.08</td>
<td>75.2 ± 7.79</td>
<td>73.3 ± 7.73</td>
<td>0.61</td>
</tr>
<tr>
<td>%BF</td>
<td>22.9 ± 7.08</td>
<td>24.8 ± 7.79</td>
<td>26.7 ± 7.73</td>
<td>0.61</td>
</tr>
</tbody>
</table>

HSCT: hematopoietic stem cell transplant; BMI: body mass index; BMI/age: body mass index for age; H/age: height for age; %LBM: percentage of lean body mass; %BF: percentage of body fat; AC: arm circumference; TSF: triceps skin fold; AMA: arm muscle area.

Parametric data were presented as averages and standard deviation, and non-parametric data were presented as median, minimum, and maximum. In order to compare independent groups that presented different normality tests for the same parameter, the results were shown as median, minimum, and maximum. Statistical significance: p-value < 0.05.

Discussion

In this study, adult FA patients submitted to HSCT presented a high prevalence of underweight according to their BMI, and a substantial muscle mass depletion when their AMA was studied. When the phase angle was analyzed, the majority of the adult patients had normal values. Most of the children and adolescents submitted to HSCT or not had adequate body weights according to their BMI, but they also had depletion of muscle mass considering their AMA. Furthermore, an analysis of the ROC curve, even considering only the potentially healthier patients since they were evaluated more than six months after the transplant, showed that more than one and a half years would be necessary to reach normal weight parameters according to their BMI. Studies indicate that from 22% to 38% of FA patients are underweight, this may occur due to anatomical alterations of the gastrointestinal tract, chronic inflammation, infection, or as consequences of pharmacological treatment, resulting in early satiety, reflux, nausea, emesis, and diarrhea. This study found similar results: 20% of non-transplanted children and adolescents had decreased BMI. In transplanted adult patients, this study found an even greater prevalence of underweight subjects, nearly half of the adults. In contrast, these patients are also at risk for excessive weight including obesity, in most cases, probably due to metabolic alterations, especially abnormalities in the glucose and insulin metabolism as was observed in studies performed with humans and animals. Excessive weight was found in at least 10% of the members of all groups analyzed in this study, with obesity only found in children and adolescents. Rose et al. identified similar results on assessing an adult population, in which 11% were overweight. However, in children and adolescents, only one individual was overweight. Denardi et al. assessed adults, children and adolescents with FA who were submitted to HSCT, and identified 10% of overweight and obese subjects.
loss. It is worth mentioning that children and adolescents submitted to HSCT or not seem to have higher increases in total body mass compared to adults. In this regard, as this study did not analyze paired data, nutrition transition might explain the fact that children and adolescents were classified as eutrophic, overweight and even obese, while most adults were classified as underweight. The growing amounts of highly processed food eaten by young people should be considered, however, food intake analysis would be necessary to make this inference.

As most methods available to determine nutritional status are indirect and can be limiting parameters as they are influenced by non-nutritional factors, this study used different methods to assess nutritional status in order to have complementary information. It seems that the BIA method, which assesses the cell membrane and changes in the hydro-electrolytic balance, can be used to detect early structural cell changes as a response to nutrition inadequacy.21 The phase angle has been studied as an important prognostic indicator for many processes related to cell membrane dysfunction, as seen in undernutrition, acting as a predictor for clinical or nutritional changes. Low phase angles are associated with a loss of cellular integrity,22,23 which is expected as a result of chemotherapy and that may worsen with very low food intake during conditioning before HSCT and during the first two weeks after the event, which has already been reported in previous studies.20 The phase angle detects cell alterations earlier than those observed by anthropometric and laboratory tests.24 Studies demonstrated that the phase angle for healthy individuals can vary from 4° to 10° or from 5° to 15°.25,26 Barbosa-Silva et al. prospectively evaluated 279 patients submitted to elective gastrointestinal surgery and reported that phase angles below 5° indicate risk for malnutrition and morbidity. After assessing adult patients submitted to HSCT, this study identified a phase angle greater than 5° in most cases indicating integrity of body cell mass and preserved cell membranes.

Comparing the standard phase angle of children and adolescents submitted to HSCT or not, the current study did not find any significant differences between the groups suggesting cell membrane recovery in the post-HSCT period. It is important to emphasize that changes in electrical properties of tissues and membrane ion conductivity reduce the phase angle in the post-HSCT period, however, the electrical properties tend to be restored with nutritional recovery.27 In fact, Farias et al. observed that the phase angle standard can be a survival indicator for children and adolescents 180 days after HSCT with the current analysis occurring at least six months after the transplant. Even considering the late period of assessment in the present study, the recovery of cell mass may not follow the same path as the depletion of muscle mass was found to be lower than expected in the adults with FA. In fact, the present study showed that approximately half of the transplanted children and adolescent population presented Z-scores for H/age below the expected. These results are similar to the ones found by Denardi et al. Barnum et al.28 performed a temporal analysis to demonstrate the association between short stature for age after HSCT and noted that under 10-year-old transplanted patients presented an incidence of short stature of 62%, while those aged between 10 and 16 presented

Figure 1 – Receiver operator characteristics curve representing time after HSCT versus nutritional status according to body mass index/age ratio (eutrophic and undernourished). Area over the curve 0.875.

Figure 2 – Comparison of inadequate percentages for arm muscle area, body mass index and height/age ratio.

Even though the anthropometric data of transplanted and non-transplanted patients were not statistically different, the nutritional status reached normal values, based on the BMI/age, only 1.56 years after the HSCT. Apparently, this recovery was not explained by muscle mass considering that AMA values showed depleted muscle stores in all the patients. The average fat free mass (%) found in children submitted to transplant in this study was higher than the average found in our previous study,20 however, the first population studied was different because it was not exclusively FA patients. Thomáz et al. assessed 56 adult patients who received allogeneic HSCT, and identified that reduced muscle mass was directly associated with mortality within 180 days post-HSCT. Therefore, during the nutritional assessment, BMI as a nutritional status predictor should be used carefully as it might underestimate muscle
an incidence of 50%. Patients who did not receive HSCT and were older than 16 years old did not present short stature. In this study, when that same age range stratification was performed related to HSCT, the incidence of short stature was 41.7% and 63.6% for under 10-year olds and those between 10 and 16, respectively, however, short stature was not present in patients older than 16 years old.

On taking the body composition and cell integrity results together, it is important to mention that the nutritional assessment should be performed carefully since BMI indicates that most patients were eutrophic, however, muscle mass depletion is present in at least 50% of the cases. BMI could be useful to analyze weight recovery, however, it should not be the only parameter considered for these patients. Moreover, it seems that the standard phase angle is an important parameter to verify cell integrity before transplant as a prognostic method as reported previously, however, it is not sensitive when it is measured six months after the transplant. Considering the importance of muscle mass as an essential body component to prevent mortality related to infectious and non-infectious diseases and the malnutrition intrinsic to FA, the results of this study open perspectives for more studies focused on muscle mass loss and mortality risk in FA patients.

This study presented some limitations including: the size of the population regarding the subgroup stratification, absence of phase angle stratified by BMI reference values for the Brazilian population resulting in the use of reference values for the German population and absence of a sexual maturity assessment, which would be beneficial to assess the development of children and adolescents as well as the cross-sectional characteristic of the study that did not allow paired comparisons especially related to body composition analysis before and after HSCT. Moreover, the lack of studies performed exclusively with FA patients limited the possibility of comparing the results.

Conclusion

All groups of FA patients had low muscle stores, being under-weight was common among adults diagnosed with FA, and short stature was common in children and adolescents. This study showed that the longer after the HSCT, the higher the tendency of reaching a normal weight according to the patient’s BMI. Regular nutritional assistance is highly recommended, as well as monitoring body composition, food intake and gastrointestinal complications in order to control the weight and optimize growth. More studies are needed to address the association between muscle mass loss and risk of mortality/morbidity among FA patients.

Conflicts of interests

The authors declare no conflicts of interest.

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