Impact of obesity and visceral fat on mortality in Hematopoietic Stem Cell Transplantation (HSCT)

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Clinical Relevancy Statement:

Body composition is an important tool to evaluate muscle and adipose tissue in cancer patients, however there are not a lot of studies in patients who have undergone Hematopoietic Stem Cell Transplant. Ultrasound is a highly accurate and

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jpen.2048.

precise method when in the hands of an experienced technician. Furthermore, it is a tool which is portable, capable of regional and segmental measurements, noninvasive, of rapid procedure, besides having no ionizing radiation. In these patients, ultrasound can be a useful tool for measuring muscle and fat thickness in addition to visceral fat.

Abstract:

Rationale: Many studies have shown the importance of body composition parameters, muscle and fat mass, evaluated by several methods in HSCT outcomes. Ultrasound (US) is an efficient and low-cost method to evaluate body composition, even though there have not been many studies in HSCT. **Objectives:** To investigate the muscle, visceral fat (VF) and echogenicity before HSCT and after engraftment, evaluated by US and its association with outcomes. **Methods:** All adult patients with hematological malignances admitted for HSCT autologous and allogeneic to Hospital Israelita Albert Einstein between 2016 and 2017 were eligible to enter this prospective study. Their thigh muscle thickness, VF and echogenicity were evaluated by US, on the first day of hospitalization (baseline) and after engraftment (15-25 days post-HSCT). **Results:** We evaluated 50 patients, 42% were male and 58% had undergone allogeneic HSCT. Most patients were < 55 years-old (68%) and had normal body mass index (50%). We found a significant reduction of right and left muscle thickness(p<0,001) and echogenicity (p=0,002) after engraftment compared to baseline. Our elderly patients had a significant bigger right thigh muscle thickness (p=0,02) and more VF (p=0,009). The following data were higher in obese patients: right and left muscle thickness (p<0,001); VF (p=0,003) and echogenicity (p=0,04). Death in the first 100 days had a positive association with obesity (p=0,001) and visceral fat (p=0,002). VF was the only variable independent of HSCT type and age in mortality risk. **Conclusion:** Obesity and VF had an important impact in mortality. US could be a useful tool and strategy for evaluating body composition in HSCT patients.

Key words:

Nutrition; Ultrasound; Hematopoietic Cell Transplant; Muscle mass; Lean mass; Fat mass; Visceral fat

Introduction:

Hematopoietic Stem Cell Transplantation (HSCT) is associated with reduction of lean mass and increased fat mass, which are poor outcomes due to infections, engraft-versus-host-disease (GVHD), corticosteroids and immunosuppressive therapy.(1) Besides, malnutrition and obesity have been attributed with a negative effect on survival. (2,3)

Although weight and body mass index (BMI) have been considered a practical nutritional method to evaluate these patients, they do not offer information about lean and fat mass. It explains conflicting literature results for HSCT outcomes when only either BMI or weight has been taken into consideration. (4–6)

In the last years many studies have shown the importance of body composition parameters, muscle and fat mass, evaluated by bioelectrical impedance analysis (BIA), dual energy x-ray absorptiometry (DXA) and computerized tomography (CT) in HSCT outcomes, as mortality and GVHD. (7–11) In HSCT patients there are not many studies using ultrasound (US) to evaluate body composition.

In medical practice, US has been used since the early 1950s. (12) It is based on the transmission of ultrasound waves of the skin to a tissue interface (for example, subcutaneous skin fat, adipose muscle and muscle bone) and partially returning to the transducer, according to the density of the evaluated structures.(13)

US is a good method to evaluate body composition, both muscle and fat mass, whose advantages are the lack of technical limitations related to the size and weight of patients; the lowest associated financial cost among all available techniques, except for skinfold; high accuracy and precision in the hands of an experienced technician; it is portable; also capable of regional and segmental measurements; it is noninvasive and there is no ionizing radiation; besides being such a rapid procedure. (14–20) On the other hand, its disadvantages include requiring experienced technician with considerable skill; measurement procedures and techniques which are not yet standardized; inherent artifacts; its interpretation is more difficult and subjective due to the lack of standardized procedure and measurements. (13–20) Moreover, US allows us to measure muscle thickness, visceral fat and echogenicity. (15,21,22)

In our study, we aimed to investigate the muscle and fat mass before HSCT and after engraftment, which was evaluated by US and its association with mortality, engraftment and GVHD.

Methods:

Patients

The study enrolled adult patients (n = 67) with hematological malignances admitted for HSCT autologous and allogeneic to Hospital Israelita Albert Einstein between June 2016 and September 2017. From those, 50 patients were eligible to enter this prospective study, considering the inclusion criteria of ≥18 years who had anthropometric and ultrasound measurements evaluated on the first day of hospitalization (baseline) and after engraftment (15-25 days post-HSCT) and also data regarding the outcomes, such as acute and chronic GVHD, and death in the first 100 days.

The study protocol was approved by Ethics Committee and all patients provided informed consent.

Anthropometric measurements

In order to determine the height (m), a stadiometer (with total height of 2.0 m and precision of 1.0 mm) was used duly posted on the wall with the patient standing barefoot with their heels together their back straight and arms outstretched at the sides of the body. The measurement of weight (kg) was performed by a properly calibrated scale, with the patient standing in the center of the scale base barefoot and wearing light clothing. All of measurements, which were used only once each, were evaluated by a single examiner.

Body mass index (BMI) was calculated as weight (kg) divided by the squared height (m). (23,24) BMI was used to classify nutritional status of the adult patients as: (23) < 16 kg/m2: malnutrition grade III; 16 – 16,9 kg/m2: malnutrition grade II; 17 – 18,4 kg/m2: malnutrition grade I; 18,5 – 24,9 kg/m2: normal; 25 – 29,9 kg/m2: overweight;30 – 34,9 kg/m2: obesity grade I; 35 – 39,9 kg/m2: obesity grade II; ≥ 40 kg/m2: obesity grade III.

Ultrasound (US)

All patients were examined using the Philips ® Envisor CHD ultrasound machine, using the 5.0-MHz linear transducer of the quadriceps femoris in the lower extremity. This muscle was chosen because of its large motor use and the ease of performing the ultrasound technique on it. For the ultrasound measurements, the probe was placed at the position of maximum circumference. Additionally, the thickness of the muscle was measured by the distance between the muscle fascia and the underlying bones (femur) (mm). (Figure 1)

Muscle measurements were performed 15 cm from the superior pole of the patella in the proximal direction on the quadriceps muscle on the ventral midline of the thigh. (15)

Visceral fat was evaluated with a convex transducer (3.5 MHz) which was used to assess the distance between the internal surface of the straight muscle of the abdomen (rectus abdominis) and the rear wall of the aorta.(16) The transducer was placed next to the umbilicus along the xypho-umbilical line, and the subjects were breathing out gently, in inspiration time. (Figure 2)

Echogenicity was analyzed using a computer assisted grey-scale analysis (Pixel Health®, Uezima, Brazil). The thigh image was selected in the transverse ultrasound image in each muscle without any bone or surrounding fascia. The mean echo intensity of this region was calculated.

All of measurements were evaluated by a single examiner, an experienced ultrasound radiologist, who calculated the mean of the three ultrasound measurements performed at the same site in the longitudinal and transverse planes. The majority of our intraclass correlation coefficient was 0.9 and the reproducibility was 0.12 for all measurements.

Data Analysis

Quantitative variables were described as mean, standard deviation, median, interquartile range and extreme values. In addition, the variables were evaluated for their distribution through quantile, histogram and boxplot plots, as well as the Shapiro-Wilk test, and those in which we did not reject the assumption of normality had the mean and standard deviation measures highlighted. Qualitative variables were described by absolute frequency and percentage.(25)

In order to compare body composition measurements between the moments, baseline and after engraftment mixed linear models were adjusted with the measures as outcomes and the moment as an explanatory variable, considering the dependence between the measurements of the same individual.

Association between engraftment, age, survivorship, acute and chronic GVHD, BMI and body composition measurements and the difference between measurements studied at baseline and after engraftment was assessed by multiple linear models with time to take as an outcome and measurements as an explanatory variable in conjunction with transplant type, elderly ((≥55 years) and obesity(BMI≥ 30).

Kaplan-Meier analysis was applied to calculate survival considering obese and non-obese patients. Multi-variate regression analysis was used related to visceral fat and obesity with age and HSCT type.

For the analyzes we used the R statistical package (26), as well as the lme4 package (27) for the mixed linear and *nlme* models linear.(28) The adopted significance level was 5%.

Results:

We evaluated 50 patients, 42% were male and 58% had undergone allogeneic HSCT. 17 patients were excluded because they were not evaluated by ultrasound on the first day of hospitalization. Most patients were < 55 years-old (68%) and had normal BMI (50%). Less than 2% were malnourished. Also note that out of the 50 people, 21 (42%) are considered elderly for HSCT (≥55 years). Engraftment was shorter in autologous patients (p=0.009). We did not find other significant differences between autologous and allogeneic patients. Table 1 presents the description of the characteristics of individuals.

Table 2 describes the differences between before HSCT and after engraftment (2 patients died before it) in relation to anthropometry and body composition.

We found a significant reduction of right and left muscle thickness (p<0,001) and echogenicity (p=0,002) after engraftment compared to baseline.

Our elderly patients had a significant bigger right thigh muscle thickness (p=0,02) and more visceral fat (p=0,009).

Considering obese and non-obese patients, we found some significant differences, all of them were higher in obese patients: right and left muscle thickness (p<0,001); visceral fat (p=0,003); echogenicity (p=0,04).

Death in the first 100 days, occurred only in allogeneic HSCT patients, which had a positive association with obesity (p=0,001) (Graphic 1) and visceral fat(p=0,002). (Table 3) (Graphic 2) Visceral fat was the only variable independent of HSCT type and age in mortality risk. Allogeneic HSCT and older patients had higher death risk.

We did not find any significant difference related to engraftment, acute and chronic GVHD and body composition parameter.

Discussion:

Our prospective study, which used US to evaluate body composition, showed visceral fat was associated with death in the first 100 days and obesity was a risk factor for mortality in patients undergoing HSCT. There was reduction of muscle thickness and echogenicity between baseline and post engraftment in these patients, however it was not associated with risk factors.

Unlike other studies, in which there is a greater number of malnourished patients, we found 32% of overweight patients, 16% with obesity and only 2% with malnutrition. (1,29) However, both malnutrition and obesity, classified by BMI, are known to be factors of poor prognosis in HSCT. (3,29)

In the baseline our obese patients had higher muscle thickness, in which case our observation agreed with others reports. (30–32) Nevertheless, there are studies using computed tomography to evaluate the muscle area and muscular quality of obese sarcopenic and non-sarcopenic patients, whereas there are no studies using echogenicity in HSCT patients. (33–35) Echogenicity was higher in our obese patients who showed more fibrous or fat infiltration in their muscle.

Our finding suggested that visceral fat, for which measurement US is a validated method, may have a positive relationship with cardiovascular risk, lower insulin sensitivity and higher circulating triglyceride levels (16,36–39), was associated with death in the first 100 days in patients undergoing HSCT independent of known risk factors. There were no studies about HSCT patients and visceral fat, however in cancer patients it is associated with adverse outcomes and progression due to increased insulin resistance and its influence on levels of endocrine hormonal secretion. (39,40) Besides, there is a positive association between visceral fat and all-cause mortality in adults. (41)

According to other studies, obesity was a risk factor for mortality due to the fact that higher doses of chemotherapy contribute to the induction of cytokine storms, which leads to severe acute GVHD; the different immune status in obesity affects the functional status of immune cells after allogeneic HSCT; the number of adipose tissue-resident immune cells, such as macrophages, CD8+ T cells and IFN-γ Th1+ cells, is increased, and the number of regulatory T cells is decreased; obesity-induced shift in adipose tissue-resident immune cells might increase the alloimmune reaction after allogeneic HSCT. (42) Even though our finding did not show association between obesity and GVHD as found in other studies(42), it could be explained by our small sample.

Our patients had a reduction of muscle thickness, it was different from other studies that used BIA to evaluate HSCT, nonetheless, it was similar to CT results. (8,9,11) Our study showed a femoris quadriceps reduction, which is observed in our clinical practice and in critical patients.(43)

Additionally, echogenicity or muscle density were reduced between baseline and post engraftment. (44,45) In general, a healthy young muscle has low echogenicity (darker images at US), on the other hand, an old or unhealthy muscle, which has adipose tissue and fibrosis infiltration, has high echogenicity (whiter images at US). (46)

Several studies using ultrasound echogenicity and computed tomography density to evaluate muscle in different ages found more fat and less muscle fiber in elderly. (44,45,47–49) However, our elderly patients did not have different echogenicity compared to non-elderly patients, probably because our prevalence of malnutrition was low (2%), therefore our elderly and non-elderly did not have myofibers and disruption of muscle architecture. (43)

US has lower cost, higher spatial resolution, real-time evaluation, ability to compare to the contralateral site, and it is also a non-invasive, portable, safe and easy-to-use imaging method.(13,15,21,50) Although there were few studies about this method to evaluate body composition in HSCT patients, it could be useful, practical and have a high cost-benefit.

The present study had limitations, such as the small number of patients in the same way most of prospective studies about body composition in HSCT patients. Also, BMI alone does not capture the severity of malnutrition due to its inherent limitations. We have only 2% of malnutrition patients, therefore we did not have sufficient sample, nor methodology, to evaluate severity of malnutrition. It is important to emphasize that the body composition evaluation by US has to be performed by a specialist to be actually useful. For this study we assured that all the exams were done by the same researcher with experience in body composition by US. Another important point is that our sample is prevenient from a private sector of health assistance which might guarantee a better nutritional status in terms of less obesity and better muscle mass as it has been shown in literature. (3)

Conclusion:

In our study visceral fat and obesity, measured by ultrasound, had an important impact in increasing mortality. Body composition in HSCT patients could help in predicting undesired outcomes and be useful in defining preventive and treatment strategies.

The impact of body composition on HSCT outcome should be investigated in further studies to standardize procedure and measurements by ultrasound.

Statement of Authorship:

Andrea Pereira, Bianca de Almeida Pitito and **Nelson Hamerschlak** equally contributed to the conception and design of the research, and interpretation of the data**; Gisele Cristine Eugenio** and **Rogério Ruscitto do Prado** contributed to the analysis of the data; **Cinthya Correa Silva** contributed to the acquisition of the data. **All authors** drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

In this study we had no financial support and no author had a conflict of interest.

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Table 1: Description of patients'characteristics

Variable (N=50)	Total	Autologus	Alogenic	p
Age(years)				0,592
Mean (Standard deviation)	49(15)	50,5 (16)	48 (15)	
Gender				0.493
Male(%)	58	52	62	
Female(%)	42	48	38	
Weight(kg)				0.174
Mean (Standard deviation)	75(14.5)	72(14)	77(14.5)	
Body Mass Index (kg/m²)				0,505
Mean (Standard deviation)	25,5 (4)	25 (5)	26 (4)	
Elderly (>55 years) (%)				0,917
No	29 (58)	12 (57)	17 (59)	
Yes	21 (42)	9 (43)	12 (41)	
Body Mass Index Classification (%)				
Normal	25 (50)	9 (43)	16 (55)	
Overwight	16 (32)	7 (33)	9 (31)	
Obesity	8 (16)	4 (19)	4 (13)	
Malnutrition	1 (2)	1 (5)	0 (0)	
Engraftment (days)				**0,009**
Mean (Standard deviation)	14 (5)	12 (4)	16 (5)	

Table 2: Description of variables before HSCT and after engraftment

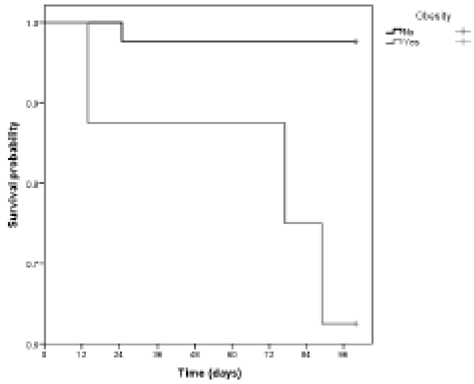
	Before HSCT(n:50)		After HSCT(n:48)		p		
Variables Mean (SD)	**Autologus(n:21)**	**Alogenic(n:29)**	**Autologus(n:21)**	**Alogenic(n:27)**	**moment**	**HSCT**	**interaction**
Weight (kg)	72 (14)	78 (14,5)	69 (14)	71 (12)	**0.010**	0.223	0.426
BMI (kg/m²)	25 (5)	26 (4)	24 (5)	23 (3)	**0.003**	0.969	0.411
UMTRT (cm)	1,7 (0,3)	1,6 (0,4)	1,5 (0,3)	1,5 (0,3)	**<0,001**	0.640	0.091
UMTLT (cm)	1,7 (0,4)	1,7 (0,3)	1,5 (0,4)	1,5 (0,3)	**0.003**	0.726	0.527
UFTRT (cm)	0,8(0,4)	0,7 (0,3)	0,9 (0,5)	0,7 (0,3)	0.498	0.180	0.084
UFTLT (cm)	0,8 (0,4)	0,7 (0,3)	0,8 (0,5)	0,7 (0,3)	0.782	0.308	0.734
VF (cm)	4,6 (1,6)	5,0 (1,6)	4,2 (1,6)	4,7 (1,6)	0.281	0.506	0.727
Echogenicity	6242 (4126)	5654 (5024)	3611 (2337)	2990 (2084)	**0.001**	0.502	0.878

SD – standard deviation; HSCT-Hematopoietic Stem Cell Transplant; BMI-Body Mass Index; UMTRT-ultrasound muscle transversal right thigh; UMTLT- ultrasound muscle transversal left thigh; UFTRT- ultrasound fat transversal right thigh; UFTLT- ultrasound fat transversal left thigh; VF – visceral fat

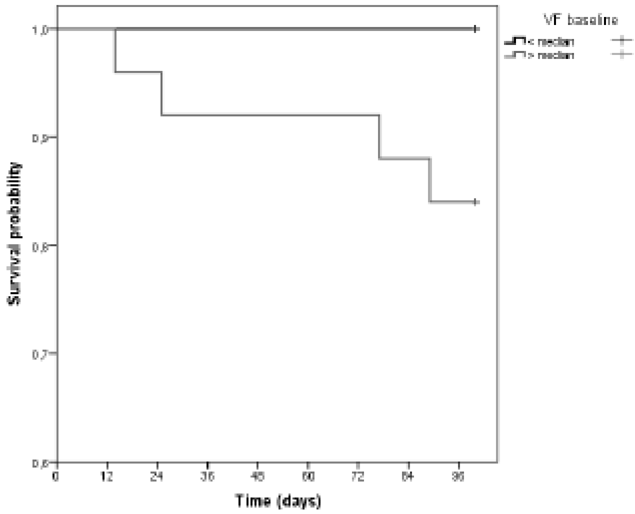
Table 3: Association between Mortality (first 100 days) and Obesity and Visceral Fat

Variable	**HR**	**95% CI**		**p**
		Lower	Upper	
Obesity	17.92	1.86	172.56	0.01
Visceral Fat	1.80	1.08	3.02	0.02

Bivariate Cox regression



Graphic 1: Survivorship curve for obese and non-obese patients undergone HSCT (p:0.01)



Graphic 2: Survivorship curve for visceral fat of patients undergone HSCT (p:0.02)