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Role of Nutrition and Physical Therapy in Maintaining Fat Free Mass and Muscle Strength During Hematopoietic Stem Cell Transplantation

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ROLE OF NUTRITION AND PHYSICAL THERAPY IN MAINTAINING FAT FREE MASS AND MUSCLE STRENGTH DURING HEMATOPOIETIC STEM CELL TRANSPLANTATION

by

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ABSTRACT

Hematopoietic stem cell transplantation (HSCT) is a pediatric cancer treatment, but malnutrition and fat free mass (FFM) loss during the process induce negative outcomes. Tracking changes in body composition, physical activity, and handgrip strength (HGS) may determine the effectiveness of current nutrition and physical therapy in maintaining FFM. This prospective quality improvement study of 9 participants receiving first-time HSCT considered bioelectrical impedance analysis (BIA) and HGS data at intake and discharge with nutrition, physical activity, medication administration, and incidence of graft versus host disease (GVHD) throughout admission. An overall loss of weight, FFM, and right and left HGS ($p=0.009$; $p=0.020$) and increased fat mass and body fat percentage were observed. Most participants discharged with worsened nutrition diagnoses. No participant experienced GVHD. No relationships were found between participant characteristics, steroid administration, appetite stimulant administration, or nutrition route. A small sample set precluded conclusive observations and necessitates further research in this area.

TABLE OF CONTENTS

LIST OF TABLES

Table

CHAPTER 1

INTRODUCTION

Cancer affects nearly 10,500 children younger than age 15 and over 5,300 adolescents aged 15 to 19 each year,[1] and is the top disease-related killer of children below the age of 15.[2] Hematopoietic stem cell transplant (HSCT) is a viable treatment option for pediatric cancers and can be performed as an autologous transplant or an allogeneic transplant. The former describes a technique in which bone marrow is harvested from and returned to a patient after the patient is treated with radiotherapy or chemotherapy or both. The latter is a technique by which a patient receives marrow from a donor; this option is complicated by the challenge of finding histocompatibility of the HLA-genotype between donor and patient.[3]

Proper nutrition is a significant concern for children and adolescents undergoing HSCT. Suboptimal nutrition status may or may not exist before transplant, but nutrition status is negatively impacted by several procedure-related factors during the entire transplant admission, such as graft-versus-host disease (GVHD), a complication that may occur in allogeneic transplant patients and can cause severe gastrointestinal disturbances.[3,4] Increased metabolic needs due to stress, increased muscle catabolism, decreased nutrient intake, and the effects of cancer-associated therapy often lead to malnutrition and can impair normal growth and development in these children and adolescents.[4-6] Many of the aforementioned factors also compromise physical functioning and result in declines in fat free mass after transplant; however, physical therapy regimen help maintain muscle strength.[7]

Malnutrition, which can occur in underweight populations as well as overweight and obese populations, has been found to adversely affect disease outcome,[4] lead to longer hospital stays,[8] compromise quality of life,[9] delay engraftment,[4] and yield lower overall survival rates.[10]

Pretransplant body composition and weight change during the transplant inpatient period are also factors to consider, as relapse rate and risk of mortality, among other outcomes, have been associated with individuals of unhealthy weight, including underweight, overweight, and obese individuals.[10-13] An effective and efficient tool that accurately evaluates nutrition status and body composition during the transplant process would help identify risk factors and direct the provision of adequate nutrition.

Although several tools for assessing body composition exist, the validity of their use has not been confirmed in healthy populations and even less focus has been given to studying the use of these tools in unhealthy populations. The sensitivity of body mass index (BMI) to low lean body mass is controversial and dual x-ray absorptiometry (DEXA) is expensive.[14,15] Bioelectrical impedance analysis (BIA) is a less expensive and less time-consuming tool that provides more sensitivity to changes in body composition after HSCT than changes in body mass as measured by BMI.[16] Handgrip strength (HGS) assessed by handgrip dynamometry effectively identifies changes in physical function[7] and is a strong predictor of morbidity and mortality in health-compromised individuals.[17-20] Assessing body composition may help prevent nutrient deficits during the transplant process and promote advances in nutrition therapy for children and adolescents undergoing HSCT.

The primary aim of this quality improvement (QI) study was to determine if current nutrition and physical therapy interventions are effective in maintaining fat free mass (FFM) and muscle strength during a child's or adolescent's first HSCT admission. This was done by looking at the relationship between changes in FFM and HGS in relation to the nutrition diagnosis, dose and type of corticosteroids and appetite stimulants administered, and acute GVHD (aGVHD) grade and duration unique to each patient during the initial HSCT admission.

CHAPTER 2

LITERATURE REVIEW

Pediatric cancers devastate families across the nation and around the world. Fortunately, science and technology have found ways to combat these diseases and drastically reduce the number of deaths from childhood and adolescent cancers that occur each year. Hematopoietic stem cell transplantation (HSCT) is a viable treatment modality for several of these cancers. Since body composition and nutritional status are highly related to cancer and the associated treatments, several tools have been created, tested, and analyzed to find the most effective and accurate technique of assessing body composition and nutrition. It is critical to track changes in body composition and nutrition both before and after HSCT, as this can have significant implications on treatment outcome and survival.

Prevalence of Childhood and Adolescent Cancer

Nearly 10,500 children younger than age 15 and over 5,300 adolescents aged 15 to 19 are diagnosed with cancer yearly.[1,21] Although pediatric cancer is rare, it is the top disease-related killer of children 14 years of age and younger.[2] The most common cancers afflicting these children are acute lymphoblastic leukemia, central nervous system cancers, neuroblastoma, and Non-Hodgkin's lymphoma, whereas adolescents tend to experience Hodgkin's disease, central nervous system cancers, and germ cell tumors. The latter also have higher rates of melanoma, thyroid cancer, non-rhabdomyosarcoma soft tissue sarcoma, osteosarcoma, and Ewing's sarcoma compared to children younger than 15 years of age.[2] Pediatric cancers of all ages are often treated with hematopoietic stem cell transplantation, which is subdivided into allogeneic and autologous transplants.

Allogeneic Bone Marrow Transplantation

During allogeneic HSCT, a patient receives marrow from a donor. The histocompatibility of the human leukocyte antigen (HLA)-genotype is an extremely important factor to consider when choosing a donor.[3,4] Only about 30% of patients find such a match from a sibling.[22] In an effort to create the most accepting environment for the new marrow, a patient matched with a donor must first receive intense doses of radiotherapy or chemotherapy or both; this destroys cancer cells and immunologically active cells in the host.[22] It is crucial that the conditioning regimen is strong enough to induce immunosuppression of the recipient so as to inhibit rejection of the graft without reaching a toxic level.[3]

Because a donor's marrow has no malignant cells, the possibility that a graft might provide anticancer benefits by attacking a recipient's cancerous cells, via the graft versus tumor effect, is a significant advantage of allogeneic HSCT.[22] However, when immunocompetent graft cells instead attack cell antigens of the recipient after an allogeneic transplant, the resulting complication known as graft-versus-host disease (GVHD) has a variety of harmful consequences; physical manifestations most commonly appear in the skin, gastrointestinal tract, liver, and lungs.[3,23] GVHD can be deadly in the most severe of cases[22] and, in fact, is the leading cause of death unrelated to the original cancer diagnosis in HSCT recipients.[24]

Autologous Bone Marrow Transplantation

Autologous HSCT involves returning to a patient marrow that was originally harvested from the patient in an attempt to regenerate normal cell function after having been treated with intensive chemotherapy.[3,22] Patients receiving autologous HSCT need not rely on a donor match; their own marrow is readily available. Benefits of this procedure are lower costs and decreased rates of morbidity and mortality.[23,25,26] The disadvantage of autologous HSCT is the possibility

that tumor cells may still exist within a treated graft and without the potential for a therapeutic donor graft versus tumor effect, the risk of relapse is much higher than with allogeneic HSCT.[25,26] Nutrition is of utmost concern for any form of stem cell transplantation, as it may significantly impact disease outcome.

Malnutrition

Cancer alters metabolism and body composition in complex ways not yet fully understood. Proper nutrition is crucial during times of intense stress on the body, but it is often very difficult for cancer patients to consume and utilize the nutrition they so desperately need due to a plethora of complications.[4] This is an especially significant concern in the pediatric oncology population because children and adolescents need to meet nutrition requirements in order to achieve proper growth and development.[4] Oral nutritional intake is lowest during the week immediately following transplant[27] and appears to correlate with the occurrence of severe GVHD in those receiving allogeneic HSCT.[28] Malnutrition is a major complication of cancer treatment associated with several adverse outcomes,[4] including a reduction in body mass,[29] increased length of hospitalization,[30] compromised quality of life,[9] and lower overall survival rates.[4,10,31]

Fortunately, patients are generally not afflicted with malnutrition during the pre-HSCT stage.[8,15] Nutritional status upon admission does not appear to correlate with survival, mortality, or engraftment, but the proper metabolism of chemotherapeutic treatments may be compromised by poor nutrition.[32] Likewise, conditioning regimens exacerbate nutrition concerns because they often cause patients to develop an array of complications such as oroesophageal mucositis, gastrointestinal toxicity, febrile neutropenia, nausea, vomiting, diarrhea or constipation, changes in taste and smell, decreased oral intake, and decreased nutrient absorption.[4,6,22,27,32,33] As a

result of the nutrient depletion that occurs with cancer, patients are more susceptible to infections, which in turn facilitates further catabolism and increased energy needs that may progress to malnutrition without appropriate care.[11]

The relatively immediate manifestations of cancer are not the only concern; pediatric cancer survivors have an increased risk of developing diabetes mellitus and cardiovascular diseases, which can progress to a lifelong diagnosis of metabolic syndrome.[34] Because malnutrition can have both short- and long-term implication on cancer outcome and survival, it is critical that an understanding of nutrition and body composition is applied to the treatment of childhood and adolescent cancer.[35,36] However, limited data in the pediatric HSCT population exists regarding the impact of nutrition on cancer outcome, implying a need for further studies in this area.

The Implications of Low Body Mass Index and Fat Free Mass

The loss of body mass, particularly fat free mass - which includes all body materials except fat - may have significant implications on cancer outcome. Steroid therapy causes losses in fat free body mass, which includes both muscle and bone.[15,37] Several consequences have been associated with low BMI. As fat free body mass decreases, instances of febrile neutropenia, mucositis, cardiotoxicity, emesis, and hyperglycemia increase.[32] Individuals with low body weight are more susceptible to infections and septicemia.[10,11] It is possible that patients who are underweight are at more risk of drug toxicity as a result of overdose.[11,12] While Campos and colleagues[8] did not find a correlation between GVHD and weight loss, others have found that patients with low fat free body mass, when measured by dual x-ray absorptiometry (DXA), were at a higher risk of developing chronic GVHD, independent of body fat.[15,31] Losses in muscle mass may be reduced or prevented with effective and timely interventions.[31]

Underweight pediatric cancer patients experience lower survival rates but in fact, the same consequence has been observed for overweight and obese pediatric patients.[10,12,13]

The Implications of Overweight and Obesity

Just as obesity is a concern in the general public, it is a concern for HSCT patients with even more consequences.[14] Overweight patients may not receive enough treatment since their doses are calculated using adjusted or ideal body weight.[11,38] Overweight and obese patients are also at higher risk of acquiring certain infections compared to normal weight patients during early treatment.[10]

Research does not agree about the implications of overweight and obesity on HSCT outcomes. In the adult population, obese patients may be more likely to suffer relapse than non-obese patients and also may have a higher mortality rate.[39] The risk for treatment-related toxicity seems to be higher in obese individuals than those who are non-obese.[40] Lower overall survival rates are correlated with overweight and obesity in children and adolescents with leukemia.[10,12,41]

These findings are contradicted by studies showing a lack of connection between BMI and nutrition status or time to engraftment and in fact support a higher likelihood of survival for obese patients compared to patients of normal or underweight.[42] To further compound the complexity of the issue, it may be that obesity does not have the same negative effects on HSCT outcome in the pediatric population when compared to adult cancer patients.[39] This is an area that would benefit from further research because the implications of body composition and nutritional status can extend far into the future.

Body Weight in the Long Term

The implications of cancer, cancer-related treatment, nutrition, and physical activity habits after discharge may have lasting effects on the health of a patient. In many patients,

weight and fat free body mass remain severely below normal levels for months after transplant.[8,31] Conversely, it may be that survival after HSCT predisposes an individual to obesity later in life.[14] Kyle and colleagues[15] found instances of overweight in 15% of patients six months after transplant, reaching a rate of 50% of patients after six years.

The achievement of adequate nutrition and a healthy body weight is critical for quality of life; children with weight loss are likely to experience muscle weakness and compromised performance in social situations and children with weight gain are more likely to experience emotional and cognitive struggles.[9] Although childhood cancer survivors are at an increased risk of developing components of metabolic syndrome, the insulin resistance and central obesity related to this condition are two factors whose courses could be influenced during and long after the HSCT process with appropriate monitoring and interventions.[43] In order to accurately evaluate the nutritional status and body composition of patients, it is critical that an effective, efficient, and readily accessible tool be validated.

Body Mass Index as a Tool for Measurement

Body mass index has long been a tool for anthropometric assessment of the body due to its simple calculation and ease of access. However, its sensitivity to both healthy and cancer-stricken populations has been questioned.[44-46] Low fat free mass and excess fat is not detected well by BMI and this flaw is emphasized when compared to precise measurements obtained by a DEXA, the gold standard in body composition assessment.[14,15] BMI is a significantly flawed screening tool and cannot therefore be effective in accurately identifying nutritional status.[47]

Despite the poor quality of BMI, the parameter has been investigated for its correlation to HSCT outcomes. Certain studies have not identified correlations between BMI and pretransplant nutritional status, mortality, fat free muscle mass, or fat mass.[24,48] These findings are supported

by other studies that refute the correlation between low BMI and poor survival, identifying no association between poor body composition and disease duration, disease remission, or the reduction of components of fat free mass, such as bone matter, as seen in sarcopenia.[49,50]

Others have contradicted these findings by showing that BMI was, in fact, correlated with time to engraftment and survival;[51] specifically that a BMI greater than 25, before transplantation, was indicative of better chances of survival and those with a low BMI.[11] In light of these results, a tool that can more accurately qualify nutrition status of pediatric cancer patients would have significant implications on treatments and interventions.

Bioelectrical Impedance Analysis as a Prognostic Tool

The increased need for a more efficient, accurate, inexpensive, and non-invasive technique has given rise to studies evaluating the validity of bioelectrical impedance analysis (BIA).[52] BIA provides information about cell membrane properties and body water distribution by measuring the resistance (R) and reactance (Xc) of an electrical current that is sent through a body.[53,54] The relationship between R and Xc is known as phase angle (PA). Positive PA values are associated with healthy individuals, whereas low or negative PA values may be indicative of compromised membrane permeability, cell death, losses in muscle mass, displaced body water, or any combination of these characteristics.[49,53,55] PA was also found to positively correlate with nutrition status.[56] Since all of these attributes may be influenced by metabolic rate and nutrition, BIA has been considered an effective prognostic tool for the assessment of nutritional status and disease.[16,53,57] Because PA values can be transformed into standardized z-scores based on sex-, age-, and BMI-, population-, ethnicity- and disease-specific equations, its predictive power may make it a more useful tool than others that currently exist.[16,49,52,58]

There is a significant positive correlation between BIA-derived PA, and other standard measurements, including triceps skinfold, arm circumference, and arm muscle circumference.[16] BIA-derived PA better detects the severity of malnutrition when compared to BMI and severity of disease when compared to the Standardized Global Assessment.[16,58] When compared to DEXA, BIA accurately reports changes in body composition, over a period of time, in children who are either normal weight or overweight.[59] In addition, several studies have supported the reliability and accuracy of BIA,[60] such that any change in fat free mass greater than 5% can be detected, and there is little disagreement between measured and calculated values for BIA.[61]

Patients with low PA more often experience compromised nutrition and functional status, longer hospital stays, lower quality of life, a higher risk of relapse mortality for allogeneic HSCT recipients,[49] a higher risk of mortality, and shorter survival.[16,58] BIA values, but not BMI values, decrease 180 days after patients receive allogeneic HSCT, indicating that BIA is sensitive to changes in cell structure before these changes are identified by BMI.[16]

However, the validity of BIA is not entirely accepted; BIA may generally underestimate fat free mass and total body water.[54] There have been several instances in which fat mass and fat free mass were not accurately reported by BIA.[60] Further studies are necessary to strongly indicate or contradict the use of BIA, as current evidence is contradictory. The combination of these findings and the fact that most BIA studies have focused on the adult population makes it imperative that a study should focus on using BIA to assess children and adolescents before and after HSCT for the possibility that changes in body composition and nutrition status may be identified.

Two types of BIA exist: single-frequency and multiple-frequency. Multi-frequency BIA measures intracellular and extracellular fluid in addition to FFM.[57] Because this study did not require the differentiation of TBW compartments, the single-frequency model was sufficient.

Handgrip Dynamometry as a Concomitant Assessment

Due to the controversy surrounding the validity of BIA assessment, a concomitant measurement can be used for comparison of fat free mass stores. Handgrip dynamometry is an efficient, effective, and inexpensive tool to assess fat free body mass. Height, fat free body mass, and nutritional status are positively correlated with handgrip strength (HGS),[62] whereas a negative relationship exists between HGS and mortality.[7] It is desirable that all people maintain proper muscle function throughout their lifespan in order to perform daily activities of living; it is even more important that health-compromised individuals such as pediatric oncology patients maintain muscle function since it is a strong predictor of mortality.[18,20] Low muscle strength, as assessed by handgrip dynamometry, was found to be more predictive of postoperative morbidity in individuals receiving surgery after gastric cancer than calculating the amount of fat free body mass in those individuals,[17] and therefore has significant implications on determining the risk of morbidities after cancer treatments. Using hand grip strength as an indicator of fat free body mass provides another means of assessing changes in body composition of pediatric oncology patients who undergo HSCT.

CHAPTER 3

METHODS

Participants

This QI project followed 9 pediatric oncology participants, including 4 females and 5 males, who were scheduled for either allogeneic or autologous HSCT at St. Jude Children's Research Hospital between 1/1/2016 and 6/30/2016. Eligible participants were between 7 and 21 years of age. Inclusion criteria required that participants had no limb amputations, could bear weight equally on both feet, could hold the BIA handgrips in both hands, and could speak English. Participants receiving IV fluids above maintenance and those identified as having edema per visual examination of hands, feet, face, and body were not eligible to participate.

Procedure

BIA assessment and HGS assessments were performed at two time points: once within +/- 3 days of intake for transplant and once at discharge after marrow infusion within +/- 3 days. Additional factors were recorded through the entire HSCT admission.

Measures

Treatment Intensity. One-time classification of treatment intensity was performed at admission. All participants were categorized using the Intensity of Treatment Rating (ITR)-3 from the Children's Hospital of Philadelphia at the time of admission.[63]

Bio Impedance Analyzer. The BC-418 Tanita® Body Composition Analyzer (Tokyo, Japan) was used for this procedure. This device has a reported validity, reliability, and error range of +/- 5% in comparison to the DEXA when measuring body composition, as reported by the company. The device was calibrated before each use by a Clinical Nutrition Service member according to manufacturer protocol. All attempts were made to test participants under ideal

conditions: ≥ 12 hours after vigorous exercise, ≥ 3 hours after waking, and ≥ 3 hours after a meal. The participant emptied their bladder and removed any jewelry before testing began. The team member input the appropriate information regarding the participant's gender, body type, age, and height. A standard value of one kilogram was used for all participants' clothing weight. The participant stood on the BC-418 Tanita® Body Composition Analyzer electrodes with bare feet and without bending the knees. The participant held the grips with both hands, at which time the impedance measure began. Once the body composition and impedance measurements were completed, the participant measurements were printed from the machine and body fat percentage, body fat mass, and FFM were recorded. Intake BIA data was compared to discharge BIA data to determine if change had occurred.

Nutrition Diagnosis. Nutrition diagnosis including the problem, etiology, and signs and symptoms (PES) statement per the electronic Nutrition Care Process Terminology Reference Manual (eNCPT)[64] from the Academy of Nutrition and Dietetics (AND) was collected from the registered dietitian nutritionist's assessment at the point of intake and at the point of discharge for each patient. The sub-classification of malnutrition was diagnosed using the Academy of Nutrition and Dietetics (AND) and the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines. The primary indicators for malnutrition are listed in Table 1.

Table 1. Indicators of Malnutrition

	Mild Malnutrition	Moderate Malnutrition	Severe Malnutrition
Weight-for-height z-score	-1 to -1.9	-2 to -2.9	-3 or greater
BMI-for-age z-score	-1 to -1.9	-2 to -2.9	-3 or greater
Length/height-for-age z-score	No data	No data	No data

Table 1. Indicators of Malnutrition

	Mild Malnutrition	Moderate Malnutrition	Severe Malnutrition
Weight gain velocity	Less than 75% of the norm for expected weight gain	Less than 50% of the norm for expected weight gain	Less than 25% of the norm for expected weight gain
Weight loss	5% usual body weight	7.5% usual body weight	10% usual body weight
Deceleration in weight for length/height z-score	Decline of 1 z-score	Decline of 2 z-scores	Decline of 3 z-scores

Becker P, Carney LN, Corkins MR, Monczka J, Smith E, Smith SE, Spear BA, White JV, Academy of Nutrition and Dietetics, American Society for Parenteral and Enteral Nutrition (2015). Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: indicators recommended for the identification and documentation of pediatric malnutrition (undernutrition). *Nutr Clin Pract.* 2015;30(1):147-161

Handgrip Strength Assessment. HGS in kilograms was assessed by an inpatient physical therapist (PT), using a Jamar Hydraulic Hand Dynamometer (Patterson Medical, Atlanta, GA), at the point of intake and discharge. Strength data was compared to HGS norms for ages 6-19 (B&L Engineering, 1986). Participants were seated with the shoulder at 0-10° and the elbow in 90° of flexion. The forearm was in neutral position. Each participant completed three trials and the average was used for analysis.[65,66] Strength at intake was compared to strength at discharge to determine if change had occurred.

Nutrition Intake and Requirements. Averages of kilocalorie and protein intake including parenteral and enteral routes were obtained during the entire HSCT admission and expressed as an overall percentage of estimated needs: percentage of kilocalorie needs met (PKNM) and percentage of protein needs met (PPNM). Oral nutrition intake was analyzed using Nutritionist Pro software v. 6.2 (Axxya Systems, Stafford, TN) or obtained from the calculated values in the nutritionist's note. Kilocalorie and protein intakes from total parenteral nutrition (TPN) and enteral nutrition (EN) routes were obtained from the metabolic infusion support service notes in

the electronic medical records. Estimated energy requirements were calculated using the World Health Organization (WHO) equation with a factor of 1.2 to 1.4 to determine total kilocalorie requirements. Protein requirements were calculated using a 200-total kilocalorie: nitrogen ratio. PKNM and PPNM were compared to changes in FFM and HGS measured from time of intake to time of discharge.

Symptoms. Acute GVHD was diagnosed, staged, and graded according to the *COG Stem Cell Committee Consensus Guidelines for Establishing Organ Stage and Overall Grade of Acute GVHD, Appendix 4 BMTCT SOP*.[67] Duration and stage of aGVHD was recorded and evaluated for comparison to changes in FFM and strength. Nutrition-related adverse events rated greater than 3, according to the Common Terminology Criteria for Adverse Events (CTCAE) per the National Institutes of Health (NIH) and National Cancer Institute (NCI), were collected if the conditions presented.[68] The nutrition-related adverse events that were recorded include: diarrhea, malabsorption, mucositis, nausea, vomiting, and anorexia. The type of adverse event and total number of days present were evaluated for comparison with changes in FFM and HGS.

Medication Dosage. Corticosteroid administration was obtained from the medical record. Type, cumulative dose, indication for usage, and total number of days provided were recorded and compared with changes in FFM and HGS. In addition, type, average dose of appetite stimulant, and total number of days provided were recorded and compared with changes in FFM and HGS.

Physical Activity Duration. Duration of physical activity, in minutes, was collected from the PT note as well as from self-report of activity by the participant and/or the family of the participant. Average time spent doing physical activity was analyzed for comparison to changes in FFM and HGS.

Data Analysis and Statistics

This was a quality improvement project with an aim to determine if current nutrition and physical therapy interventions were effective in maintaining FFM and muscle strength during the initial HSCT admission. We enrolled 9 patients for either allogeneic or autologous HSCT.

To determine if current nutrition and physical therapy interventions are effective in maintaining FFM and HGS during the initial admission. We evaluated the kilocalories and protein as an overall percentage of estimated needs and the average number of minutes spent doing physical activity from the time of intake to the time of discharge. The paired one-sample t-test or Wilcoxon signed rank test was used to test if there was significant difference in change in FFM and HGS, from intake to discharge, depending on the normality of the data tested by Shapiro-Wilk test. The SAS 9.4 software package was used for the statistical analysis. A p-value of 0.05 was considered significant. Summary statistics including mean, standard deviation, median and range for continuous variables and the number and percentage for categorical variables are provided.

To explore the relationship between changes in FFM and HGS based on cumulative steroid dose, appetite stimulant type, duration and grade of aGVHD. Descriptive and raw data are provided to show trends.

CHAPTER 4

RESULTS

Characteristics of the Participants

A total of 9 pediatric oncology participants scheduled to receive their first of either an allogeneic (66.6%) or autologous (33.3%) HSCT were included in the study (Table 2). Allogeneic HSCT were either haploidentical (n=3), matched-sibling donor (n=1), or matched-unrelated donor (n=2) transplants. The majority of participants (55.6%) were male and their median age was 15 years (8-19). The diagnoses of the participants that precipitated a need for HSCT included acute leukemia (33.3%), Hodgkin's lymphoma (33.3%), and solid tumor malignancies (33.3%). The majority of the participants were white (66.7%). All participants met the criteria for level 4 of the ITR-3 rating system; therefore this data is not presented in a table.

Table 2. Characteristics of the participants at intake.

Characteristics		Number (n = 0)
Sex	female (%)	4 (44.4)
	male (%)	5 (55.6)
Median age (range)		15 (8-19)
Diagnosis	Acute Leukemia	3 (33.3)
	Hodgkin's Lymphoma	3 (33.3)
	Solid Tumors	3 (33.3)
Race	Asian	1 (11.1)
	Black	1 (11.1)
	Other	1 (11.1)
	White	6 (66.7)
Type of Transplant	Allo (Haplo)	3 (33.3)
	Allo (MSD)	1 (11.1)
	Allo (MUD)	2 (22.2)
	Auto	3 (33.3)

Allo, allogeneic; Haplo, haploidentical; MSD, matched sibling donor; MUD, matched unrelated donor; Auto, autologous

Nutrition Diagnosis at Intake and Discharge

Six participants were diagnosed with predicted suboptimal nutrient intake; of those, only two improved by discharge as evidenced by receiving no nutrition diagnosis (Table 3). The only other participant that improved to no nutrition diagnosis by discharge had been admitted with a nutrition diagnosis of inadequate oral intake. Three participants were discharged with inadequate oral intake and one was diagnosed with mild malnutrition; this last participant was the youngest and had been admitted with a diagnosis of predicted suboptimal intake, indicating significant nutrient depletion had occurred during HSCT admission. No other trend was observed between type of transplant, age, or nutrition diagnoses for either intake or discharge.

Table 3. Nutrition diagnosis (PES statement) of the participants at intake and discharge related to age, sex, and type of transplant

P	Age	Sex	Transplant Type	Intake PES statement	Discharge PES statement
1	15	F	Allo (MSD)	Predicted suboptimal nutrient intake related to planned allogenic HSCT (MSD) per NPTP protocol as evidenced by history of marginal/suboptimal energy intake.	No nutritional diagnosis at this time.
2	15	M	Allo (Haplo)	Altered nutrition-related laboratory values related to cancer directed therapy/endocrine dysfunction as evidenced by low vitamin D level.	Inadequate oral intake and swallowing difficulty related to inability to consume sufficient energy as evidenced by sore throat, inability to swallow food/pills, and nasogastric tube (NGT) for medications.
3	15	M	Allo (Haplo)	Inadequate oral intake related to decreased ability to consume sufficient energy as evidenced by 6% or 3 kg weight loss over past 4 months but stable over past month; need for oral supplementation with Boost nutritional drink.	Inadequate oral intake related to decreased ability to consume sufficient energy as evidenced by sore throat, diet history, and recent weight loss since discharge.
4	8	M	Auto	Predicted suboptimal nutrient intake related to inability to consume sufficient energy as evidenced by history of suboptimal energy intake, upcoming HSCT.	Malnutrition (mild) related to decreased ability to consume sufficient energy as evidenced by BMI for age Z score of -1.81 but PO intake improving.
5	19	F	Allo (MUD)	Predicted suboptimal nutrient intake related to planned allogenic HSCT (MUD) as evidenced by previous history of marginal/suboptimal energy intake.	Inadequate oral intake related to decreased ability to consume sufficient energy as evidenced by diet history; met only 31% of estimated needs with PO intake yesterday and continued need for parenteral nutrition (PN).
6	12	F	Auto	Predicted suboptimal nutrient intake related to planned autologous HSCT therapy as evidenced by previous history of suboptimal energy intake.	Inadequate oral intake related to decreased ability to consume sufficient energy as evidenced by diet history and need for continuous nasogastric tube (NGT) feeds.
7	13	F	Allo (MUD)	Predicted suboptimal nutrient intake related to upcoming HSCT as evidenced by known side effects.	No nutritional diagnosis at this time.
8	13	M	Auto	Inadequate oral intake related to decreased ability to consume sufficient energy due to relapsed Hodgkin's Lymphoma as evidenced by poor PO intake, need for oral supplement, and 9.2% weight loss over past 20 days (9.1kg).	No nutritional diagnosis at this time.
9	17	M	Allo (Haplo)	Predicted suboptimal nutrient intake related to upcoming HSCT as evidenced by known side effects.	Inadequate oral intake related to decreased ability to consume sufficient energy as evidenced by diet history resulting in a 6.4% or 3.4% weight loss over the past month.

P, participant; PES, problem, etiology, signs and symptoms; Allo, allogenic; MSD, matched sibling donor; Haplo, haploidentical; Auto, autologous; MUD, matched unrelated donor.

Changes in Body Measurements

Due to a small sample size, no significant p-values were identified after statistical analysis with the exception of those related to HGS; however, several insignificant trends in the data were observed. During HSCT admission, more participants lost weight (n=5) than gained weight (n=4). Overall, there an average weight loss of 0.4 kilogram. The majority of participants lost FFM (n=5) as well as FM (n=5). While there was an average FFM loss of 0.4 kilogram, there was an average gain of 0.1 kilogram of FM during HSCT admission. Body fat percent was increased in the majority of the participants (n=5) and the average overall body fat percent gain was 0.1%. All but one participant lost HGS on both right and left sides; one participant gained muscle strength, as assessed by right upper extremity (RUE) HGS, and a different participant gained muscle strength, as assessed by left upper extremity (LUE) HGS. An average of 3.1 kilograms worth of strength were lost on the right side (p=0.009) and 2.4 kilograms of strength were lost on the left side (p=0.020) (Table 4). No relationships were observed between age or type of transplant with magnitude of change in FFM, FM, body fat percent, or grip strength.

Table 4. Changes in body measurements of the participants from intake to discharge.

P	Transplant Type	Weight (kg)			Fat Free Mass (kg)			Fat Mass (kg)			% Body Fat			HGS RUE (kg)			HGS LUE (kg)		
		In	Dc	CHG	In	Dc	CHG	In	DC	CHG	In	Dc	CHG	In	Dc	CHG	In	Dc	CHG
1	Allo (MSD)	43.4	43.6	0.2	32.9	31.9	-1.0	10.5	11.7	1.2	24.2	26.8	2.6	14.2	11.3	-2.9	10.3	9.0	-1.3
2	Allo (Haplo)	60.8	63.3	2.5	52.0	53.5	1.5	8.8	9.8	1.0	14.5	15.5	1.0	29.0	22.7	-6.3	22.6	17.7	-4.9
4	Allo (Haplo)	47.1	44.0	-3.1	40.1	37.3	-2.8	7.0	6.7	-0.3	14.9	15.3	0.4	19.9	20.4	0.5	17.2	17.0	-0.2
4	Auto	22.2	21.5	-0.7	18.7	18.8	0.1	3.5	2.7	-0.8	15.8	12.4	-3.4	10.3	10	-0.3	10.0	8.3	-1.7
5	Allo (MUD)	59.3	60.2	0.9	39.1	42.0	2.9	20.2	18.2	-2.0	34.0	30.3	-3.7	18.7	13	-5.7	14.7	10.4	-4.3
6	Auto	35.4	35.9	0.5	28.5	27.8	-0.7	6.9	8.1	1.2	19.5	22.6	3.1	11.7	10.6	-1.1	4.7	4.3	-0.4
7	Allo (MUD)	46.4	45.6	-0.8	35.6	36.0	0.4	9.7	9.6	-0.1	21.5	21.1	-0.4	20.0	17.3	-2.7	18.6	13.7	-4.9
8	Auto	91.0	90.9	-0.1	63.1	61.4	-1.7	27.9	29.5	1.6	30.7	32.5	1.8	29.0	26.7	-2.3	24.0	25.3	1.3
9	Allo (Haplo)	67.5	64.5	-3.0	55.3	53.2	-2.1	12.2	11.3	-0.9	18.1	17.5	-0.6	41.3	34.0	-7.3	34.0	28.7	-5.3
Mean (SD)			-0.4(1.79)			-0.4(1.18)			0.1(1.22)			0.1(2.41)			-3.1(2.75)			-2.4(2.48)	
Median (Range)			-0.1(-3.1~2.5)			-0.7(-2.8~2.9)			-0.1(-2.0~1.6)			0.4(-3.7~3.1)			-2.7 (-7.3~0.5)			-1.7 (-5.3~1.3)	
P-Value			0.52			0.54			0.81			0.91			0.009			0.02	

P, participant; In, intake; Dc, discharge; CHG, change; kg, kilograms; Allo, allogenic; MSD, matched sibling donor; Haplo, haploidentical; Auto, autologous; MUD, matched unrelated donor; HGS, hand grip strength; RUE, right upper extremity; LUE, left upper extremity.

Factors Impacting Nutrition Status

Nutrition supportive techniques were used in four of the nine participants, two of which required only EN; the other two required both EN and TPN. None (n=0) of the participants consumed enough nutrition by any route during HSCT admission to meet their estimated energy or protein needs (Table 5). No relationships were observed between route of nutrition with magnitude of change in FFM, FM, body fat percent, or grip strength.

The majority (n=6) of participants received steroids at some point during HSCT admission. The most common types, hydrocortisone and methylprednisolone, were most often administered in preparation for protocol-specific therapy. Other indications included Engraftment Syndrome, preparation for blood transfusion, and allergic drug reaction. Most (n=5) of the participants also received appetite stimulants at some point during their HSCT admission. Dronabinol was most commonly used, but one participant received cyproheptadine. Not all participants who received steroids also received appetite stimulants; the opposite is true as well. Participants who did not receive steroids (n=3) saw an increase in weight, fat mass, and percent body fat along with a loss in muscle strength on both right and left sides. Participants who received appetite stimulants (n=5) lost muscle strength with the exception of one participant, who gained strength on the left side. Participants 1, 8, and 9 had the least amount of physical activity per day, all of whom (n=3) lost FFM and generally lost muscle strength. Only one participant self-reported minutes of physical activity; therefore, only physical activity as reported by the physical therapist is reflected in the data. None (n=0) of the participants presented with GVHD.

Table 5. Variables affecting nutrition status of the participants during the transplant admission.

			Nutrition					Steroid Administration				AS Administration				
				PKNM (%)		PPNM (%)										
Participant	Transplant Type	LOS (days)	Route	RS	Total	RS	Total	# Days	Total (mg)	Type	Indication	# Days	Total (mg)	Type	# Mins PA/day	GVHD
1	Allo (MSD)	23	PO	61	61	95	95	0	0	None		3	13	Dronabinol	6.52	No
2	Allo (Haplo)	32	PO	6	72	7	82	0	0	None		0	0	None	10.28	No
			EN	1		1										
			TPN	65		74										
3	Allo (Haplo)	31	PO	52	69	77	94	4	600	Hydrocortisone	Pre-med for Alemtuzumab	0	0	None	16.84	No
			EN	17		17										
4	Auto	21	PO	54	54	67	67	1	30	Hydrocortisone	Pre-med for blood transfusion	3	15	Dronabinol	13.24	N/A
5	Allo (MUD)	32	PO	23	62	20	81	8	1795	Hydrocortisone	Pre-med for Thymoglobulin (1200mg); Engraftment Syndrome (595mg)	4	10	Cypro-heptadine	11.91	No
			EN	6		8		4	500	Methyl-prednisolone	Pre-med for Thymoglobulin					
			TPN	34		53										
6	Auto	22	PO	45	53	44	51	0	0	None		0	0	None	13.64	N/A
			EN	7		7										
7	Allo (MUD)	30	PO	79	79	75	75	3	699	Hydrocortisone	Pre-med for Thymoglobulin	29	285	Dronabinol	14.77	No
								3	279	Methyl-prednisolone	Pre-med for Thymoglobulin					
8	Auto	20	PO	71	71	53	53	6	550	Hydrocortisone	Allergic drug reaction	6	30	Dronabinol	8.50	N/A
9	Allo (Haplo)	28	PO	55	55	76	76	5	545	Hydrocortisone	Engraftment Syndrome	0	0	None	8.39	No

LOS, length of stay; PKNM, percentage of kilocalorie needs met; PPNM, percentage of protein needs met; RS, route-specific; AS, appetite stimulant; PA, physical activity; GVHD, graft-versus-host disease; PO, per os (by mouth); EN, enteral nutrition; TPN, total parental nutrition.

CHAPTER 5

DISCUSSION

This is the first study to consider the impact of nutrition intake, physical therapy, steroid administration, appetite stimulant administration, and incidence of GVHD on changes in body mass assessed by BIA and HGS during the initial HSCT admission to treat pediatric cancer. While the small sample size precluded the identification of significance except for changes in HGS, the participants in this study appeared to experience an overall, but insignificant, fat mass increase, body fat percentage increase, and weight loss. FFM loss was reflected by a significant decrease in HGS.

Nutrition Diagnosis at Intake and Discharge

Nutrition is essential in the pediatric population for its role in growth and development[4] and particularly significant when affected by cancer. In this study, the majority of participants at intake received a nutrition diagnosis predictive of suboptimal nutrient intake. The remaining participants were diagnosed with pre-existing poor nutrition status; similar results were reported by White and colleagues,[35] who suggested that many children already have suboptimal nutrition even before undergoing HSCT.

While pre-HSCT nutrition status may not influence survival,[32] any decline in nutrition status during HSCT admission can compromise recovery.[69] Low oral intake and compromised gastrointestinal dysfunction are expected due to disease- and treatment-related side effects,[4,6,22,27,32,33] rendering a patient unable to meet nutrient requirements.[69] Nutrient depletion predisposes patients to infections,[10] increased catabolism, and risk of malnutrition.[11] Suboptimal nutrition during the course of cancer and treatment[70] has significant implications on a number of outcomes including quality of life and survival.[11,71]

Changes in Body Measurements

The change in body mass during HSCT is a phenomenon that demands attention. The majority of the participants in this study lost weight during HSCT and of those, most also experienced a loss of fat free mass accompanied by a reduction in HGS. Similar losses in lean mass were reported by Inaba and colleagues,[31] after a longitudinal study at St. Jude Children's Research Hospital that followed 179 cancer survivors who received HSCT. While lean mass stores were considerably lower in these individuals, fat mass stores were maintained. Medications like glucocorticoids and appetite stimulants can raise body adiposity,[72] but do not have a positive effect on fat free mass. A study by den Hoed et al[73] showed that weight loss during pediatric cancer treatment is characterized mostly by lean mass loss, which has been associated with hyperglycemia, cardiotoxicity,[32] relapse, and decreased survival;[73] therefore understanding the role of nutrition intervention in maintaining healthy body mass stores is essential.[74]

BMI has long been used for anthropometric assessment, but its sensitivity to both healthy and cancer-stricken populations is questioned,[44-46] prompting a need for a more effective marker of health status. In this study, we measured HGS as a concomitant measurement to BIA data because reductions in HGS have been associated with loss of lean and fat mass.[19] Several studies have also suggested that HGS is independently and positively associated with nutrition status, aside from body mass data.[62,75,76] Despite the small sample size of this study, HGS measurements indicate the participants experienced a significant loss of muscle strength, and therefore FFM stores, during the HSCT admission.

Factors Impacting Nutrition Status

It was not possible to identify associations between nutrition support and changes in body composition in this study. Baumgartner and colleagues[74] reported that engraftment occurs more quickly in children who receive parenteral nutrition after undergoing HSCT. Nutrition support and vigilant attention to signs of undernutrition are key components in identifying and combating malnutrition after HSCT.[51]

As mentioned previously, malnutrition has been associated with length of stay. However, in this study it was observed that participants with the shortest lengths of stay also had some of the lowest percent-needs-met; one such participant was ultimately diagnosed with mild malnutrition at discharge. Unlike those with short lengths of stay that tended to consume nutrition only orally, the majority of those with the longest lengths of stay received nutrition support in some form. Nutrition support can prolong a hospital admission due to the need for monitoring and the requirement to achieve a baseline status before receiving approval for discharge from the hospital. This is corroborated by Espinoza and colleagues,[77] who found that TPN was correlated with length of stay in patients receiving HSCT. Of note, those who received nutrition support in this study also had some of the highest PPNM and PKNM, suggesting that despite longer hospital stays, better nutrition status may be achieved through the artificial provision of nutrients. Murphy and colleagues[36] have also suggested that nutrition support be employed as a means to achieve better short- and long-terms outcomes in childhood cancer. Limited data in the pediatric HSCT population exists regarding nutrition status during HSCT admission and the impact of nutrition on cancer outcome, demonstrating a need for continued studies in this area.

Limitations of this study include a small sample size that prevented the finding of significant data, with the exception of HGS. Measurement error was also an issue; any trends in weight and body mass could be falsely interpreted because the changes recorded in the data are not large enough to overcome the percent error of the BIA machine. It is impossible to know if the changes observed are measurement error or actual body mass fluctuations. It was also very difficult to capture an accurate measurement of physical activity; records of scheduled activity within PT notes were readily accessible on the patient database used by the institution, but the tool used for self-report of physical activity was neglected by all but one participant, demonstrating the need for a better technique to accurately report this factor. In future studies, it will be pertinent not only to develop this tool, but also to include physical activity minutes performed while participating in occupational therapy. A more advanced version of the BIA scale used in this study would permit the assessment of children younger than 7 years of age, thus increasing the participant pool from which data could be collected.

Conclusion

This study suggests that pediatric oncology patients undergoing HSCT for the first time may experience an overall weight loss characterized by an increase in fat mass and body fat percentage with a concomitant reduction in fat free mass, as evidenced by significantly decreased HGS. All patients were diagnosed at intake with pre-existing suboptimal nutrition or were expected to become poorly nourished and most were discharged with diagnoses indicating continued suboptimal nutrition. None consumed sufficient nutrients to meet their estimated needs for either energy or protein. Improved identification of nutrition status and provision of nutrients during HSCT admission may combat negative changes in body composition and have a profound impact on outcomes both short- and long-term.

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Institutional Review Board #29
FWA00004775

NR15-141

December 11, 2015

St. Jude Children's Research Hospital

This is to certify that, on 12/11/2015, the
New Quality Assurance application with project description
submitted to the Institutional Review Board for consideration was evaluated by an IRB member/ OHSP staff member for non-research determination

IRB Review Status:

The activity has been determined to not meet the definition of research, as defined in 45CFR46.102 (d):

Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

This determination also is based on the Office for Human Research Protections' (OHRP) *Quality Improvement Activities Frequently Asked Questions*, found at the following Web link: http://www.hhs.gov/ohrp/qualityfaq.html

IRB Determination Protocol#3992

January 14, 2016

University of Memphis

Dear Dr. Williams-Hooker and Courtney Nordhus,
From the information provided on your Determination form for the study "Pilot Study to Evaluate the Effectiveness of Nutrition and Physical Therapy Interventions in Maintaining Fat Free Mass During Hematopoietic Stem Cell Transplantation", your activity does not meet the Office of Human Subjects Research Protections definition of human subjects research and 45 CFR part 46 does not apply.

This research does not require IRB approval nor review.

With best regards,

Beverly Jacobik
Associate Director of Research Compliance
Research and Sponsored Programs