

Body Composition After Bone Marrow Transplantation in Childhood

Kathy Ruble, RN, CPNP, AOCN®, PhD, Matthew Hayat, PhD, Kerry J. Stewart, EdD, and Allen Chen, MD, PhD, MHS

Obesity and altered body composition, including central obesity (abdominal obesity), have been identified as complications after treatment of childhood cancer (Garmey et al., 2008; Miller et al., 2010; Nysom et al., 2003; Oeffinger et al., 2003). In addition, obesity in the general population is a growing public health concern; a threefold increase of obesity in children has occurred since 1976, and more than a third of American adults are overweight or obese (Flegal, Carroll, Ogden, & Curtin, 2010; Ogden, Carroll, Curtin, Lamb, & Flegal, 2010). Excess body fat and central obesity in childhood are risk factors for cardiovascular disease, insulin resistance, compromised pulmonary function, musculoskeletal dysfunction, altered gonadal hormone levels, and psychological compromise (Baer, Colditz, Willett, & Dorgan, 2007; Daniels et al., 2005; Eisenmann, DuBose, & Donnelly, 2007; Gonzalez-Barcala et al., 2007; Raitakari, Juonala, & Viikari, 2005; Schiel et al., 2007). Similar complications are seen in adults, where obesity carries an increased mortality rate from cardiovascular and kidney disease, diabetes, and cancers considered obesity-related (Flegal, Graubard, Williamson, & Gail, 2007). Although general and central obesity are significant concerns for the general population, they may have even more harmful consequences for bone marrow transplantation (BMT) survivors who may have preexisting health conditions.

Cranial radiation at higher doses, such as those used to treat brain tumors, is the most common treatment associated with obesity (Garmey et al., 2008; Lustig et al., 2003; Pietilä et al., 2009). Damage to the hypothalamus, including disruption of growth hormone, thyroid, and gonadal function, as well as changes in sensitivity to leptin, ghrelin, and insulin, are mechanisms by which cranial radiation may contribute to obesity (Schwartz, Woods, Porte, Seeley, & Baskin, 2000). Moderate doses of cranial radiation (1,200–2,400 cGy) used to treat childhood acute lymphoblastic leukemia (ALL) have been associated with obesity, including central, liver, and visceral obesity (Janiszewski et al., 2007; Oeffinger et al., 2003).

Purpose/Objectives: To describe the body composition and fat distribution of childhood bone marrow transplantation (BMT) survivors at least one year post-transplantation and examine the ability of the Centers for Disease Control and Prevention criteria to identify survivors with elevated body fat percentage.

Design: Cross-sectional, descriptive.

Setting: Pediatric oncology program at a National Cancer Institute–designated comprehensive cancer center.

Sample: 48 childhood BMT survivors (27 males and 21 females).

Methods: Measurements included dual-energy x-ray absorptiometry scan, height, weight, and physical activity. Descriptive statistics were reported and mixed-model linear regression models were used to describe findings and associations.

Main Research Variables: Total body fat percentage and central obesity (defined as a ratio of central to peripheral fat of 1 or greater).

Findings: Fifty-four percent of survivors had body fat percentages that exceeded recommendations for healthy body composition and 31% qualified as having central obesity. Previous treatment with total body irradiation was associated with higher body fat percentage and central obesity, and graft-versus-host disease was associated with lower body fat percentage. The body mass index (BMI) criteria did not correctly identify the BMT survivors who had elevated body fat percentage.

Conclusions: Survivors of childhood BMT are at risk for obesity and central obesity that is not readily identified with standard BMI criteria.

Implications for Nursing: Nurses caring for BMT survivors should include evaluation of general and central obesity in their assessments. Patient education materials and resources for healthy weight and muscle building should be made available to survivors. Research is needed to develop appropriate interventions.

Energy imbalance, or consuming more calories than burned, is another possible contributor to obesity in childhood cancer survivors, with decreased physical activity documented in this population (Warner, 2008). In ALL survivors, decreased energy expenditure was

associated with increased body fat, which may pertain to obesity development in other survivors who have reduced physical activity levels (Warner, Bell, Webb, & Gregory, 1997).

Less is known about obesity and altered body composition following treatment for childhood cancer, including BMT, but evidence suggests these survivors also may be at risk for obesity (Nysom et al., 2001). Toxicities associated with BMT may appear, progress, and persist long after completion of therapy and include complications that may impact body composition. Cranial radiation often is used as a primary treatment of the underlying disease before BMT or in the preparative regimen as total body irradiation (TBI). In addition, graft-versus-host disease (GVHD) is a common complication of BMT and has been associated with altered body composition, including diminished lean body mass (Kyle et al., 2005).

Identifying obesity and altered body composition in childhood BMT survivors may be challenging. The Centers for Disease Control and Prevention (CDC) body mass index (BMI) criteria are used clinically for identifying overweight and obese individuals, but these recommendations do not consider the relative degree of fat and lean mass, which are important variables in distinguishing healthy versus non-healthy body composition (see Table 1). Studies have shown that BMI is a poor predictor of body fatness in healthy populations and, therefore, may have poor sensitivity in a BMT survivor population where diminished lean mass has been documented (Martarelli, Martarelli, & Pompei, 2008; Nysom et al., 2001; Piers, Soares, Frandsen, & O'Dea, 2000).

The aims of this study are to describe the body composition and fat distribution of survivors who are at least one year postautologous or postallogeneic BMT during childhood and explore the associations with disease and treatment factors. The second aim is to examine the ability of the CDC BMI criteria to accurately classify BMT survivors with healthy body fat percentage.

Methods

Design

A cross-sectional, descriptive design was used to assess the relationship between body composition and demographic and treatment associations for autologous and allogeneic BMT survivors who were at least one year post-transplantation, in remission, and not taking steroids. The study was conducted in a National Institutes of Health–sponsored Clinical Research Unit.

Recruitment

Letters were mailed to the BMT survivors in an institutional database, and face-to-face recruitment occurred during patients' routine survivorship clinic visits. One-

hundred-sixty letters describing the study procedures and eligibility, as well as contact information for the study's principal investigator, were mailed over a six-month period. The protocol was approved by the institutional review board at Johns Hopkins in Baltimore, MD, and informed consent was obtained for all participants. Parental consent and child assent was obtained for those younger than 18 years.

Measurements

Total body fat percentage and central obesity were measured by dual-energy x-ray absorptiometry (DEXA) scan. Based on conservative literature recommendations for healthy body fat percentage in children and young adults, greater than 33% for females and 25% for males were used as thresholds for elevated total body fat percentage (Dwyer & Blizzard, 1996; Gallagher et al., 2000; Williams et al., 1992).

Central obesity was evaluated by calculating a ratio of central to peripheral fat. Survivors with a ratio of 1 or greater were defined as having a central obesity. Weight was measured to the nearest 0.1 kg on an electronic scale (and confirmed by weight measure from DEXA). Height was measured to the nearest centimeter with a stadiometer. BMI was calculated by dividing weight in kilograms by height in centimeters squared.

Physical activity was measured with the **Previous Day Physical Activity Record (PDPAR)**. This self-report instrument asks survivors to report activities and perceived exertion in 30-minute blocks of time from 3 pm to 11:30 pm on the day prior to study participation. The activities and intensities then are converted to metabolic equivalents and were used as a continuous variable in the analysis. Reliability of the instrument has been established by inter-rater reliability ($r = 0.99$, $p < 0.01$) and test-retest correlation ($r = 0.98$, $p < 0.01$) (Weston,

Table 1. Criteria for Weight Status Category by Age

Age: Younger Than 20 Years	
Percentile Range	Weight Category
Less than 5th percentile	Underweight
5th to less than 85th percentile	Healthy weight
85th to less than 95th percentile	Overweight
95th percentile or higher	Obese

Age: 20 Years and Older	
Body Mass Index	Weight Category
Less than 18.5	Underweight
18.5–24.9	Normal
25–29.9	Overweight
30 and higher	Obese

Note. Based on information from Centers for Disease Control and Prevention, 2011.

Petosa, & Pate, 1997). Validity has been established by correlation with pedometer activity counts ($r = 0.88$, $p < 0.01$) and accelerometer counts ($r = 0.77$, $p < 0.01$) (Trost, Ward, McGraw, & Pate, 1999).

Endocrine function was classified using two categories: (a) normal (no endocrinopathy except need for thyroid-stimulating hormone [TSH] suppression therapy), and (b) abnormal (growth hormone and/or gonadal failure on replacement therapy). TSH suppression therapy was categorized as normal because none of the survivors had ever had low T4 levels and, therefore, were not at risk for clinical manifestations of hypothyroidism. A pediatric nurse practitioner collected demographic and disease or treatment data including age, age at time of BMT, years since BMT, diagnosis, central nervous system (CNS) irradiation, TBI, type of BMT, and history of GVHD by medical record review, and pubertal stage was determined by physical examination (i.e., Tanner stages I–V, pubic hair).

Data Analysis

Stata® statistical software (version 10) was used for analysis. Descriptive statistics, including means and standard deviations, were calculated for the outcome variables. Mixed-model multiple linear regression was used to fit predictive models for percent body fat and central obesity. Model selection was performed with backward selection, with an alpha level of 0.2 used for inclusion in the final model. The study variables shown in the literature to affect body composition and/or distribution in healthy and cancer survivor populations considered for the models included age, age at time of BMT, years since BMT, Tanner stage, endocrine function, diagnosis, CNS irradiation, TBI, type of BMT, and history of GVHD (Dwyer & Blizzard, 1996; Gallagher et al., 2000; Williams et al., 1992). An alpha level of 0.05 was used to determine significance of associations with the outcome variables. Using the thresholds described for elevated total body fat percentage, assessment of the CDC BMI criteria's ability to correctly identify survivors as being overweight or obese relative to the DEXA-derived criteria was evaluated with descriptive statistics.

Results

Sample

Forty-eight participants were enrolled in the study during an 18-month period (see Table 2). Twelve survivors were recruited from mailings; the remaining 36 were recruited from clinic visits. Two patients declined participation during face-to-face recruitment because of personal time constraints. All survivors who were categorized as having abnormal endocrine function were on replacement therapy at the time of participation.

Non-malignant diseases (17%) included aplastic anemia and X-linked autoimmune-allergic dysregulation syndrome. No survivors with a history of Fanconi's anemia, Thalassemia, or Down syndrome were enrolled. No participants had active GVHD at the time of participation.

Body Fat Percentage

The mean male body fat percentage was 25% (SD = 10) and the mean female body fat percentage was 35% (SD = 11). Body fat percentages exceeded the thresholds for good health in 54% ($n = 26$) of survivors. Fifty-two percent ($n = 14$ of 21) of males exceeded the body fat percentage threshold of 25%, and 81% ($n = 17$ of 21) of females exceeded the body fat percentage threshold of 33%.

The model for multiple linear regression with backward, stepwise selection resulted in sex, history of GVHD, and preparative regimen with TBI as significant variables (see Table 3). When controlling for other variables in the model, females had an average body fat percentage 11% (95% confidence interval [CI] [5, 17]) higher than males. Survivors with a history of GVHD had an average body fat percentage 10% (95% CI [–19, –1]) lower than those with no GVHD, and those who received TBI had an average body fat percentage 10% (95% CI [2, 17]) higher than those without TBI.

Table 2. Sample Characteristics

Characteristic	\bar{X}	SD
Age (years)	16.9	6.5
Body mass index	20.92	3.9
Age at bone marrow transplantation	8.8	6.5
Years since bone marrow transplantation	7.9	4.7

Characteristic	n
Gender	
Male	27
Female	21
Ethnicity	
Caucasian	40
African American	5
Asian	3
Clinical characteristics	
Allogeneic bone marrow transplantation	30
Hematologic malignancy	26
Abnormal endocrine function	15
Total body irradiation	15
Solid tumor	14
Central nervous system irradiation	8
History of graft-versus-host disease	8
Nonmalignant disease	8
Tanner stage	
I	14
II	4
III	1
IV	4
V	25

N = 48

The mean central obesity ratio was 0.85 (SD = 0.21) for males and 0.88 (SD = 0.21) for females, neither of which qualified for central obesity according the threshold of 1 or greater. At the individual level, however, central obesity was identified in 31% (n = 15) of patients, including 26% (n = 7 of 27) of males and 38% (n = 8 of 21) of females. Only the preparative regimen with TBI was statistically significant in the regression model, although sex was included in the model to control for known differences in fat distributions between males and females. In the multivariable model, while controlling for sex, survivors who received TBI had a central obesity ratio, on average, 0.16 (95% CI [0.03, 0.28]) higher than those without TBI.

The CDC BMI criteria correctly classified 12 survivors as overweight or obese; however 54% (n = 14 of 26) of the survivors with increased body fat were misclassified as normal. Of the 14 survivors with normal BMI and increased body fat, six were female, with a mean BMI of 21.3 (SD = 2.3), and eight were male, with a mean BMI of 20.3 (SD = 2.8).

Discussion

In the acute phase of BMT, the focus is on avoiding inadequate nutrition and, indeed, weight loss can be a treatment-limiting problem in childhood cancer. In contrast, BMT survivors may be at risk for late-occurring toxicities such as cardiovascular dysfunction that may be compounded further by general and central obesity. This study supports previous literature in childhood cancer survivors and found that 54% (n = 26) of the BMT survivors had body fat percentages greater than that considered healthy, and 31% (n = 15) had central obesity.

In clinical practice, BMI commonly is used to identify patients who are overweight or obese. Yet the BMI criteria (i.e., BMI greater than 25, or 85th percentile) failed to identify 54% of the survivors deemed to have an increased body fat percentage by a more precise imaging method (DEXA). Although BMI is a relatively easy-to-use screening tool that may be appropriate for identifying obesity in large epidemiologic studies, consideration should be given when using it in populations with potentially altered body composition. In addition to DEXA, another readily available method for assessing body composition is waist-to-height ratio, which has been shown to be a good predictor of obesity-associated complications in children (Kahn, Imperatore, & Cheng, 2005; Ness-Abramof & Apovian, 2008; Savva et al., 2000). In the childhood cancer survivor population, a waist-to-height ratio greater than 0.5 has been associated with hyperinsulinemia and unfavorable lipid profiles and is proposed as a clinical marker for future health risks (Neville, Cohn, Steinbeck, Johnston, & Walker, 2006). Clinicians need to have reliable methods

Table 3. Results of Stepwise Regression

Response Variable ^a	Coefficient	p	r ²
Body fat percentage covariates	–	–	0.3
Female	11	< 0.001	–
GVHD	–10	0.038	–
Total body irradiation	10	0.011	–
Central obesity (ratio) covariates			0.13
Female	0.34	0.56	–
Total body irradiation	0.16	0.013	–

^aAn alpha of 0.2 was used for inclusion in stepwise, backward model selection.

GVHD—graft-versus-host disease

to diagnose obesity and this study highlights the need to establish standards for fat measurement.

Identifying and addressing obesity in BMT survivors is critical to optimal long-term outcomes. Childhood cancer survivors have a 10.8-fold overall excess mortality rate and an 8.2-fold excess cardiac mortality rate when compared to age- and sex-matched United States data (Mertens et al., 2001). The American Heart Association has classified childhood cancer survivors as “Tier III: At Risk,” indicating the high risk for accelerated atherosclerosis (Kavey et al., 2007). General and central obesity in childhood has been associated with poor vascular health, including decreased endothelial function and increased arterial stiffness, which are precursors to adult cardiovascular disease (Iannuzzi et al., 2006, 2008; Woo et al., 2004). Elevated body fat percentage and central obesity such as that identified in this study may help explain the excess in morbidity and mortality.

Unlike risks such as infertility or second malignancy, which are from therapeutic exposures that are not readily modifiable without compromising survival, general and central obesity may be amenable to interventions. For example, weight training during the BMT period has been shown to preserve or increase muscle mass in adults (Hayes, Davies, Parker, & Bashford, 2003). Few studies have reported the effectiveness of exercise for childhood hematopoietic stem cell transplantation survivors, but preliminary evidence is compelling that improved body composition and fitness are possible (Chamorro-Viña et al., 2010; San Juan et al., 2008).

Reduction of body fat in BMT survivors is a desirable goal, but other considerations are necessary. Diminished bone mineral density (BMD) is a potential complication of BMT, and fat mass has been shown to have a positive association with BMD (Ruble, Hayat, Stewart, & Chen, 2010). In addition, weight loss has been associated with decreasing BMD in other populations (Castro, Lázaro, Pons, Halperin, & Toro, 2000; Rourke, Brehm, Cassell,

& Sethuraman, 2003). Evidence exists that BMD may be maintained during weight loss if fitness and lean mass are increased (Stewart et al., 2005). Interventions aimed at decreasing body fat in BMT survivors should not focus on diet alone but should include aerobic, high-impact, and muscle-building exercises to prevent decreases in BMD.

A unique finding of this study was that survivors with a history of GVHD had lower body fat percentage than those without any history of GVHD. Weight loss in patients with GVHD is well documented and has been attributed to elevated levels of tumor necrosis factor alpha and increased resting metabolic rate (Browning et al., 2006; Remberger, Ringden, & Markling, 1995; Zauner et al., 2001). Other possible mechanisms responsible for weight loss include malabsorption and dysphagia from gastrointestinal involvement with GVHD (Jacobsohn, Margolis, Doherty, Anders, & Vogelsang, 2002). This study indicates that survivors with a history of GVHD may have acceptable levels of body fat even when BMI is low, and suggests that the BMI and body composition changes seen with GVHD may persist even after the disease is controlled. For survivors with a history of GVHD who are underweight, clinicians should consider prescribing interventions to increase muscle mass, such as weights.

In contrast, the current study found that TBI was associated with higher body fat percentage and central fat distribution. Those findings are similar to others who have identified central obesity in survivors treated with TBI (Neville et al., 2006). Growth hormone deficiency is a known complication after TBI and has been associated with decreased insulin sensitivity and increased fat mass after BMT (Frisk, Rössner, Norgren, Arvidson, & Gustafsson, 2011; Shalitin et al., 2006). All of the survivors in the current study who were growth hormone-deficient were receiving replacement hormone therapy. Growth hormone has been shown to blunt final height in BMT survivors and is thought to be related to skeletal abnormalities after TBI (Brauner et al., 1997). No studies have reported the effects of growth hormone on muscle or fat after TBI, but a similar blunting on muscle and fat could be happening and may help explain the obesity seen in the current study population. Additional research examining the effects of growth hormone and replacement after TBI is needed.

No associations between physical activity and body composition were identified in this study. Possible reasons for that finding are that the study population's activity level was lower than required to impact body composition or the PDPAR was not sensitive enough to detect subtle differences in physical activity. Future research should include a more precise device, such as an accelerometer, or include healthy controls for comparison.

Limitations

Limitations exist to the generalizability of this study. The convenience sample was drawn primarily from people who are followed in a survivorship program and may not represent the overall BMT survivor population. The small sample size may have limited the power to detect all the possible associations for general and central obesity in this complex population. Finally, the characteristics of the sample were heterogeneous, which may limit the statistical power and generalizability of the results.

Conclusions

BMT survivors are at risk for increased body fat percentage, which may not be identified with BMI standards for an overweight or obese diagnosis. Survivors with a history of GVHD are at lower risk for elevated body fat percentage and may have healthy body fat percentages, even at lower BMIs. TBI is a risk factor for both higher body fat percentage and central obesity. Additional research, including evaluation of growth hormone effects on fat and muscle tissue after TBI, may be necessary to determine the etiology of that finding. Interventions aimed at decreasing body fat while improving overall fitness and increasing muscle mass may have the best impact on overall long-term health for BMT survivors.

Implications for Nursing Practice

Elevated body fat and central obesity are important health conditions and oncology nurses should become aware of the risks these conditions carry for cancer survivors. Identifying survivors who have elevated body fat percentage or central obesity can present an opportunity for nurses to advocate for healthy lifestyle changes while possibly reducing the risk of long-term complications and improving quality of life. Nurses should not rely on BMI alone to identify survivors with altered body composition and should consider adding measures such as waist-to-height ratio to their assessment. Patient education materials and resources for healthy weight and muscle-building activities should be made available to survivors during follow-up visits. Nurse researchers should focus on studies that better identify the causes of increased body fat and central obesity in this vulnerable population. Finally, developing interventions aimed at decreasing body fat and increasing lean mass should be a priority for nurses caring for survivors.

Kathy Ruble, RN, CPNP, AOCN®, PhD, is the director of the Survivorship Program and an instructor in the School of Medicine, Matthew Hayat, PhD, is an assistant professor in the

School of Nursing, Kerry J. Stewart, EdD, is the director of Exercise and Body Composition Core, Clinical Research Unit, Clinical Translational Science Award, and a professor in the School of Medicine, and Allen Chen, MD, PhD, MHS, is the director of Pediatric Bone Marrow Transplantation and an associate professor in the School of Medicine, all at Johns Hopkins

University in Baltimore, MD. No financial relationships to disclose. Ruble can be reached at rubleka@jhmi.edu, with copy to editor at ONFEditor@ons.org. (Submitted March 2011. Accepted for publication May 2, 2011.)

Digital Object Identifier: 10.1188/12.ONF.186-192

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