REGULAR ARTICLE

blood advances

Weighty choices: selecting optimal G-CSF doses for stem cell mobilization to optimize yield

Nosha Farhadfar,[1] Jack W. Hsu,[1] Brent R. Logan,[2,3] Jennifer A. Sees,[4] Pintip Chitphakdithai,[4] Michele W. Sugrue,[1] Hisham Abdel-Azim,[5] Paolo N. Anderlini,[6] Christopher Bredeson,[7] Saurabh Chhabra,[8] Miguel Angel Diaz,[9] Siddhartha Ganguly,[10] Peiman Hematti,[11] Rammurti T. Kamble,[12] Kimberly A. Kasow,[13] Hillard M. Lazarus,[14] Debra Kelly Lynch,[1] Hemant S. Murthy,[1] Richard F. Olsson,[15,16] Mona Papari,[17] Donna Przepiorka,[18] Bipin N. Savani,[19] Raquel Schears,[20] Sachiko Seo,[21] Melhem M. Solh,[22] Thomas Spitzer,[23] Jean A. Yared,[24] Michael A. Pulsipher,[25] Nirali N. Shah,[26] Galen E. Switzer,[27] Dennis L. Confer,[4,28] Bronwen E. Shaw,[2] and John R. Wingard[1]

[1]Division of Hematology and Oncology, Department of Medicine, Shands HealthCare and University of Florida, Gainesville, FL; [2]Center for International Blood and Marrow Transplant Research (CIBMTR), Department of Medicine, and [3]Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, WI; [4]CIBMTR, National Marrow Donor Program/Be The Match, Minneapolis, MN; [5]Children's Hospital of Los Angeles, Los Angeles, CA; [6]Department of Stem Cell Transplantation and Cellular Therapy, University of Texas MD Anderson Cancer Center, Houston, TX; [7]Ottawa Hospital Blood and Marrow Transplant Program and Ottawa Hospital Research Institute, Ottawa, ON, Canada; [8]Division of Hematology/Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI; [9]Department of Hematology/Oncology, Hospital Infantil Universitario Nino Jesus, Madrid, Spain; [10]Division of Hematological Malignancy and Cellular Therapeutics, University of Kansas Health System, Kansas City, KS; [11]Division of Hematology/Oncology/Bone Marrow Transplantation, Department of Medicine, University of Wisconsin Hospital and Clinics, Madison, WI; [12]Division of Hematology and Oncology, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX; [13]Pediatric Hematology Oncology Program, University of North Carolina, Chapel Hill, NC; [14]Seidman Cancer Center, University Hospitals Cleveland Medical Center, Cleveland, OH; [15]Division of Therapeutic Immunology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden; [16]Centre for Clinical Research Sormland, Uppsala University, Uppsala, Sweden; [17]ITxM Clinical Services Cord Blood Laboratory, Rosemont, IL; [18]Center for Biologic Evaluation and Research, US Food and Drug Administration, North Potomac, MD; [19]Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN; [20]Department of Emergency Medicine, Mayo Medical School, Rochester, MN; [21]Department of Hematology and Oncology, Dokkyo Medical University, Tochigi, Japan; [22]Blood and Marrow Transplant Program, Northside Hospital, Atlanta, GA; [23]Massachusetts General Hospital, Boston, MA; [24]Blood and Marrow Transplantation Program, Division of Hematology/Oncology, Department of Medicine, Greenebaum Cancer Center, University of Maryland, Baltimore, MD; [25]Division of Hematology, Oncology, and Blood and Marrow Transplantation, Children's Hospital Los Angeles, USC Keck School of Medicine, Los Angeles, CA; [26]Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; [27]Department of Medicine, University of Pittsburgh, Pittsburgh, PA; and [28]National Marrow Donor Program/Be The Match, Minneapolis, MN

Key Points

- Higher donor BMI predicts better PBSC mobilization response to G-CSF.
- There is a maximum effective G-CSF dose for PBSC mobilization in obese and severely obese donors, above which higher doses add no benefit.

There are limited data on the effect of donor body mass index (BMI) on peripheral blood stem cell (PBSC) mobilization response to granulocyte colony-stimulating factor (G-CSF), especially in unrelated donors. Obesity has been associated with persistent leukocytosis, elevated circulating progenitor cells, and enhanced stem cell mobilization. Therefore, we hypothesized that adequate collection of $CD34^+$ cells may be achieved with lower doses (per kilogram of body weight) of G-CSF in donors with higher BMI compared with donors with lower BMI. Using the Center for International Blood and Marrow Transplant Research database, we evaluated the impact of donor BMI on G-CSF–mobilized PBSC yield in healthy unrelated donors. We examined 20 884 PBSC donations collected at National Marrow Donor Program centers between 2006 and 2016. We found significantly higher collection yields in obese and severely obese donors compared with normal and overweight donors. An increase in average daily G-CSF dose was associated with an increase in stem cell yield in donors with normal or overweight BMI. In contrast, an increase in average daily G-CSF dose beyond 780 μg per day in obese and 900 μg per day in severely obese donors did not increase

Submitted 4 September 2019; accepted 6 January 2020; published online 24 February 2020. DOI 10.1182/bloodadvances.2019000923.

Presented at the 60th annual meeting of the American Society of Hematology, San Diego, CA, 1-4 December 2018.

The Center for International Blood and Marrow Transplant Research (CIBMTR) supports accessibility of research in accord with the National Institutes of Health Data Sharing Policy and the National Cancer Institute Cancer Moonshot Public Access and Data Sharing Policy. These policies hold that data that correspond to and support publications should be made as widely and freely available as possible while safeguarding the privacy of participants and protecting confidential and proprietary data. As of 1 January 2020, and in accordance with journal embargo policy and international data sharing requirements, CIBMTR will make available on its public Web site (https://www.cibmtr.org) deidentified analysis data sets and corresponding data dictionaries.

The full-text version of this article contains a data supplement.

cell yield. Pain and toxicities were assessed at baseline, during G-CSF administration, and postcollection. Obesity was associated with higher levels of self-reported donation-related pain and toxicities in the pericollection and early postdonation recovery periods. This study suggests a maximum effective G-CSF dose for PBSC mobilization in obese and severely obese donors, beyond which higher doses of G-CSF add no increased yield.

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is used to treat a wide variety of malignant and nonmalignant hematologic diseases. In the United States, peripheral blood stem cells (PBSCs) remain the most common hematopoietic stem cell (HSC) graft source, accounting for 89% of related and 87% unrelated adult donor HSC grafts in 2015.[1] Increased use of PBSCs over the past few decades has been mainly attributed to donor and provider convenience, donor safety because of avoidance of general anesthesia and surgical complications, and faster engraftment in recipients.[2-4]

PBSC collection yield relies on effective mobilization of hematopoietic precursors from the bone marrow. Granulocyte colony-stimulating factor (G-CSF) is the most commonly used mobilizing agent in PBSC donors. There is wide interindividual variation in mobilization response to G-CSF, even in healthy volunteer donors. Several factors have been identified that influence collection efficacy in healthy volunteer donors, including G-CSF dose and schedule, use of central venous catheter (CVC), and donor sex, age, body mass index (BMI), and race.[5-8]

Previous studies evaluating the impact of BMI on PBSC yield in related and unrelated donors were mostly single-center studies limited by small numbers of donors. BMI was not observed to have an impact on PBSC yield in some studies,[9,10] although a positive correlation was suggested by others.[11-13] Thus, the relationship between BMI and PBSC yield efficacy remains uncertain. The prevalence of obesity has increased in the United States over the past few decades. Currently, nearly 70% of otherwise healthy adults are either obese or overweight.[14-16] Therefore, better understanding of the impact of obesity on mobilization is necessary to optimize collection yield and improve donor health and safety in this growing population.

Obesity is associated with a state of chronic low-grade inflammation resulting from chronic activation of the innate immune system.[17,18] In both rodent models and humans, obesity-induced proinflammatory cytokines have been associated with persistent leukocytosis and an increase in the number of circulating progenitor cells.[19-23] Hypercholesterolemia, which is mostly seen in obese individuals, has also been associated with enhanced stem cell mobilization.[24] Therefore, we hypothesized that adequate collection of $CD34^+$ cells may be achieved by lower doses of G-CSF (per kilogram of body weight) in donors with higher BMI compared with donors with lower BMI. The purpose of this study was to examine the impact of BMI on PBSC mobilization in a large cohort of adult unrelated donors.

Methods

Study population

The study population consisted of unrelated donors from the United States whose G-CSF–mobilized PBSC donation was facilitated by the National Marrow Donor Program (NMDP) between 2006 and 2016. G-CSF agent used for stem cell collection was filgrastim. Only first-time donors for whom data were available from baseline to the first day of apheresis were included. Because of small numbers (n = 149), underweight (BMI <18.5 kg/m^2) donors were excluded. Data on donor and donation characteristics were collected using standard NMDP forms. All donors provided written informed consent for participation in Center for International Blood and Marrow Transplant Research studies approved by the NMDP Institutional Review Board (IRB). A total of 20 844 donors were eligible for inclusion.

PBSC donation

PBSC collection was performed according to the NMDP-sponsored and IRB-approved research protocol for manufacturing PBSC products, under an Investigational New Drug (IND) application with the US Food and Drug Administration (#F00815). G-CSF was dosed according to the IND-specified NMDP algorithm (supplemental Table 1) and administered subcutaneously for 5 consecutive days at a daily dose of approximately 10 μg of the donor's actual body weight rounded to the nearest commercial vial dose (300 and 480 μg), with the total daily dose ranging from 600 to 1200 μg per day. PBSCs were collected by apheresis over 1 or 2 days. The total volume of blood processed by the apheresis procedure was targeted to be between 12 and 24 L, determined by donor body weight. Apheresis was performed via CVC only if PBSCs could not be collected using peripheral veins.

Data collection

Data collection started at the donor's medical evaluation and continued throughout the time of donation and 1 week after collection.

End points

The primary outcome of this study was collection yield, defined as the $CD34^+$ cell count per liter of blood processed ($\times 10^6$/L) on the first day of apheresis (day 5 of G-CSF administration). Because significant variability exists among apheresis centers in number of days of collection and volume of blood processed per day, $CD34^+$ cell counts normalized by volume of blood processed only on the first day of collection were analyzed.

Secondary outcomes included donor symptoms associated with PBSC mobilization and collection. Donor toxicities were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). These symptoms included the incidence of grade 2 to 4 or grade 3 to 4 skeletal pain and the highest toxicity level across selected body symptoms at 24 hours after the first G-CSF dose and peak toxicity between days 1 to 5 of G-CSF administration and 2 days and 1 week postcollection. Skeletal pain was defined as pain in at least 1 site including back, bone, headache, hip, limb, joint, or neck. The severity of skeletal pain was defined as the maximum grade of pain among these sites.

Table 1. Characteristics of unrelated PBSC donors facilitated by NMDP between 2006 and 2016 (N = 20 884)

Characteristic	BMI, kg/m²				P
	Normal (18.5-24.9)	Overweight (25-29.9)	Obese (30-34.9)	Severely obese (35+)	
No. of donors	6965	7897	3873	2149	
No. of centers	101	100	98	96	
Sex					<.001
Female	3221 (46)	2068 (26)	1206 (31)	940 (44)	
Male	3744 (54)	5829 (74)	2667 (69)	1209 (56)	
Donor age at donation, y					<.001
18-29	4193 (60)	3557 (45)	1339 (35)	795 (37)	
30-39	1508 (22)	2153 (27)	1172 (30)	627 (29)	
40-49	871 (13)	1552 (20)	910 (23)	514 (24)	
≥50	393 (6)	635 (8)	452 (12)	213 (10)	
Median	28	31	35	35	<.001
Range	18-62	18-61	19-61	19-61	
Race					<.001
White	5225 (75)	5843 (74)	2750 (71)	1424 (66)	
Hispanic	454 (7)	659 (8)	422 (11)	294 (14)	
Black/African American	148 (2)	289 (4)	225 (6)	165 (8)	
Asian/Pacific Islander	536 (8)	394 (5)	109 (3)	47 (2)	
American Indian/Alaska Native	35 (1)	70 (1)	39 (1)	29 (1)	
Other/multiple races	474 (7)	549 (7)	281 (7)	174 (8)	
Decline/unknown	93 (1)	93 (1)	47 (1)	16 (1)	
Weight at baseline, kg					<.001
≤45	18 (< 1)	0 (0)	0 (0)	0 (0)	
45-60	1701 (24)	45 (1)	0 (0)	0 (0)	
61-78	4199 (60)	2300 (29)	183 (5)	7 (<1)	
79-90	993 (14)	3458 (44)	931 (24)	81 (4)	
91-96	44 (1)	1243 (16)	694 (18)	152 (7)	
97-108	10 (< 1)	805 (10)	1428 (37)	528 (25)	
>108	0	46 (1)	637 (16)	1381 (64)	
Median	67	84	98	114	<.001
Range	41-103	52-123	68-136	70-179	
Baseline WBC, × 10^9/L					<.001
Median	6.0	6.2	6.7	7.4	
Range	2.3-29.9	0.4-18.9	2.4-16.0	2.7-17.6	
Baseline neutrophils, × 10^9/L					<.001
Median	3.7	3.8	4.1	4.6	
Range	0.9-28.7	0.2-15.2	1.1-12.4	1.3-13.2	
Baseline platelets, × 10^9/L					<.001
Median	236	238	246	262	
Range	106-467	100-509	100-585	113-562	
Baseline MNCs, × 10^9/L					<.001
Median	2.2	2.3	2.5	2.6	
Range	0.7-5.8	0.2-6.9	0.9-8.7	1.0-5.9	
Use of CVC					<.001
No	6418 (92)	7432 (94)	3512 (91)	1804 (84)	
Yes	547 (8)	465 (6)	360 (9)	344 (16)	
Unknown	0 (NA)	0 (NA)	1 (NA)	1 (NA)	

Values are n (%) unless otherwise indicated.
NA, not applicable.

Table 1. (continued)

Characteristic	BMI, kg/m^2				P
	Normal (18.5-24.9)	Overweight (25-29.9)	Obese (30-34.9)	Severely obese (35+)	
Average daily G-CSF dose d 1-5, μg					<.001
Median	780	900	1044	1200	
Range	360-1200	492-1440	540-1344	600-1296	
Average daily G-CSF dose per donor weight d 1-5, μg					<.001
Median	11.1	10.5	10.4	10.1	
Range	6.1-18.7	5.6-18.2	6.4-13.9	5.5-12.3	
2-d collection					<.001
No	5994 (86)	7161 (91)	3534 (91)	1981 (92)	
Yes	971 (14)	736 (9)	339 (9)	168 (8)	
Volume of whole blood processed d 5, L					<.001
0 ≤ blood volume < 12	436 (6)	380 (5)	225 (6)	143 (7)	
12 ≤ blood volume < 18	2220 (32)	2333 (30)	1133 (29)	705 (33)	
18 ≤ blood volume	4308 (62)	5182 (66)	2513 (65)	1301 (61)	
Unknown	1 (NA)	2 (NA)	2 (NA)	0 (NA)	
Median	18	19	19	19	
Range	1-35	3-30	2-30	3-35	
Collection year					<.001
2006-2009	1604 (23)	2185 (28)	1138 (29)	577 (27)	
2010-2013	2975 (43)	3177 (40)	1512 (39)	837 (39)	
2014-2016	2386 (34)	2535 (32)	1223 (32)	735 (34)	

Values are n (%) unless otherwise indicated.
NA, not applicable.

Toxicity was defined as fever in the absence of signs of infection, fatigue, skin rash, local reactions, nausea, vomiting, anorexia, dizziness, syncope, and insomnia.

Statistical analysis

Donors were divided into 4 groups based on BMI category, according to World Health Organization definitions: normal (BMI, 18.5-24.9 kg/m^2), overweight (BMI, 25-29.9 kg/m^2), obese (BMI, 30.0-34.9 kg/m^2), and severely obese (BMI ≥35.0 kg/m^2). G-CSF dose groups were based on average daily doses using the IND-specified NMDP algorithm (2018 National Donor Program Document #F00825; supplemental Table 1). Donor and procedure characteristics, including donor sex, age at donation, race, weight at baseline, use of a central line, volume of whole blood processed, collection year, baseline white blood cell (WBC) count, platelet, neutrophil, and mononuclear cell (MNC) values, and G-CSF dosage were described. The change in WBC, platelet, neutrophil, and mononuclear cell values from baseline to postcollection was calculated, and the CD34$^+$ cell yield was tabulated. The Pearson χ^2 test was used for comparing categorical characteristics; the Kruskal-Wallis test was used for comparing continuous values.

Log transformations were applied to the collection yield outcome (CD34$^+$ cells per liter of blood processed) to induce normality. Multiple linear regression was used to model log collection yield as

Table 2. Donor response after 5 d of G-CSF administration

Variable	BMI, kg/m^2				P
	Normal (18.5-24.9)	Overweight (25-29.9)	Obese (30-34.9)	Severely obese (≥ 35)	
No. of donors	6965	7897	3873	2149	
No. of apheresis centers	101	100	98	96	
Change in WBC, × 10^9/L	29.9 (0.2-73.4)	29.4 (2.2-84.1)	29.7 (−0.5 to 100)	30.7 (3.9-84.7)	<.001
Change in neutrophils, × 10^9/L	29.6 (0.9-74.3)	28.9 (0.4-82.5)	29.5 (1.9-98.3)	30.2 (2.3-91.2)	<.001
Change in platelets, × 10^9/L	−124 (−350 to 98)	−120 (−34 to 186)	−122 (−479 to 156)	−123 (−391 to 119)	<.001
Change in MNCs, × 10^9/L	1.4 (−2.9 to 54.7)	1.4 (−2.5 to 50.5)	1.5 (−3.6 to 46.1)	1.7 (−2.5 to 36.5)	<.001
Total CD34$^+$ collected, × 10^6	532 (15.0-4677)	659 (7.9-5967)	729 (7.9-4014)	756 (52.5-3985)	<.001
CD34$^+$ cells/L of blood processed, × 10^6/L	29.6 (1.6-333)	36.4 (0.6-316)	40.8 (0.4-511)	42.9 (2.5-432)	<.001

Values are median (range) unless otherwise indicated.

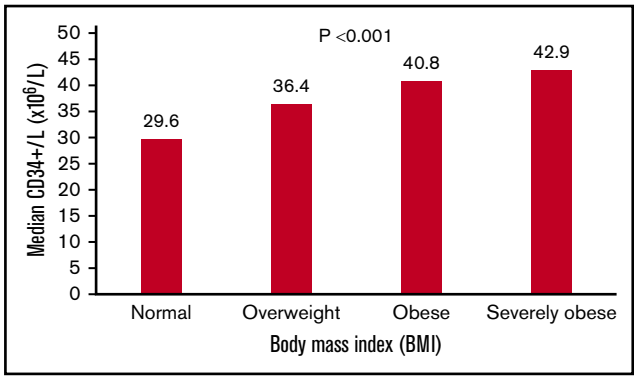

Figure 1. Association between donor BMI and collection yield. Collection yield ($CD34^+$ per liter of blood processed on day 5 of G-CSF administration) was positively correlated with donor BMI.

a function of the primary variables of interest (BMI group and G-CSF dosage) as well as donor characteristics. Stepwise variable selection was used to add variables to the model; BMI group and G-CSF dose were forced into the final model as the variables of interest. The resulting effect of each variable was summarized as a ratio of means, where 1.0 indicated no effect. Because of concerns about confounding between BMI and the average daily G-CSF dose, the model was constructed 3 ways for each outcome. First, average daily G-CSF dose was omitted from the model; second, an adjustment for average daily G-CSF dose was forced into the model; finally, subgroup analyses of the effect of G-CSF dose were performed separately for each BMI group.

To enhance the understanding of mobilization effectiveness vs collection efficiency (CE), the impact of donor BMI on $CD34^+$ CE was also evaluated using multiple linear regression. Other factors considered in this analysis were donor race, donor sex, volume of blood processed, baseline neutrophils, and preapheresis WBC, platelet, and neutrophil counts. The following formula was used to calculate the $CD34^+$ CE: ($CD34^+$ cell count in day 5 product)/(WBC count preapheresis day 5 $\times$ $CD34^+$ cell concentration in peripheral blood $\times$ volume of day 5 product) $\times$ 100.

Stepwise logistic regression was performed on grade 2 to 4 pain and grade 2 to 4 toxicities at various time points, in the same manner as described. G-CSF dosing for analysis of pain and toxicities was based on days 1 to 4, because pain and toxicities on day 5 were evaluated before day 5 G-CSF administration.

Results

Characteristics of PBSC donors

A total of 20 884 PBSC donors mobilized by G-CSF between 2006 and 2016 were examined in this study. The baseline demographic and collection characteristics are summarized in Table 1. The largest cohort of donors was the overweight group (37.8%). The normal BMI category comprised the second largest group, at 33.3%, followed by obese (18.5%) and severely obese (10.3%). Donors in the obese and morbidly obese groups were older (median age, 35 years) compared with donors with normal BMI (median age, 28 years). There were more male donors in the overweight and obese groups (74% male and 69% female, respectively), whereas male/female ratios were similar in the normal and severely obese groups (54% male and 56% male, respectively). Donors with normal BMI had the lowest median baseline WBC (6.0 $\times$ 10^9/L) and neutrophil counts (3.7 $\times$ 10^9/L), whereas severely obese donors had the highest baseline WBC (7.4 $\times$ 10^9/L) and neutrophil counts (4.6 $\times$ 10^9/L). There was a significant difference in CVC use, with severely obese donors having the highest use (16%) compared with other groups. Although severely obese donors received higher total average daily G-CSF dose because of greater weight, there were no notable differences between BMI categories with regard to total average daily G-CSF dose per kilogram of donor weight. The average daily G-CSF dose per kilogram of donor weight was 11.1, 10.5, 10.4, and 10.1 μg/kg in normal, overweight, obese, and severely obese donors, respectively (Table 1).

Response to G-CSF and collection yield

The $CD34^+$ cell yields and cell count changes after 5 days of G-CSF administration in each BMI category are shown in Table 2. After 5 days of G-CSF administration, severely obese donors had the largest increase in WBC (median, 30.7 $\times$ 10^9/L), neutrophil (median, 30.2 $\times$ 10^9/L), and MNC counts (median, 1.7 $\times$ 10^9/L) compared with other BMI categories. The collection yield, expressed as $CD34^+$ per liter of blood processed ($\times$ 10^6/L) on day 5 of G-CSF administration, was 29.6, 36.4, 40.8, and 42.9 in normal, overweight, obese, and severely obese donors, respectively ($P < .001$; Figure 1).

In multivariate analysis, higher BMI correlated with greater cell yield (Table 3). To evaluate whether an increase in collection yield was due to higher CE or better mobilization response to G-CSF, $CD34^+$ CE was calculated for those with available data (n = 20 150). In a multivariate analysis of factors influencing CE, BMI of the donor did not have an impact on CE ($P = .782$), indicating mobilization response to G-CSF as the main factor influencing collection yield.

Other factors that were independently associated with an increase in the stem cell collection yield were male sex, African American race, younger age of the donor, and higher baseline and precollection platelet, neutrophil, and MNC counts. Increased volume of blood processed on day 5 was associated with lower stem cell collection yield. The volume of blood processed on day 5 of G-CSF administration was also correlated with CE. Compared with low volume apheresis (<12 L), apheresis volumes of 12 to 18 L were associated with an average 6% decline in CE, whereas volumes >18 L were associated with an average 10% decline in collection efficiency ($P < .001$).

Multivariate analysis of the impact of G-CSF dose on collection yield within each BMI category after adjusting for donor and collection characteristics is shown in Table 4. An increase in the average daily G-CSF dose was associated with an increase in PBSC collection yield in donors in the normal and overweight BMI groups, as illustrated by an increase in the ratio of means of 16% for donors with normal BMI and 17% for donors with overweight BMI, in those with the highest daily dose compared with those with the lowest daily dose ($P < .001$ and $P = .002$, respectively). In contrast, an increase in the average daily G-CSF dose above a targeted dose of 780 μg per day in obese donors and a targeted dose of 900 μg per day in severely obese donors did not translate to a statistically significant increase in PBSC collection yield ($P = .520$ and $P = .148$, respectively).

Table 3. Multivariate analysis of factors influencing peripheral blood collection yield in unrelated donors

Variable	Ratio of means	Lower CL	Upper CL	*P*
Donor BMI				
Normal	Reference (1.00)			
Overweight	1.16	1.14	1.18	<.001
Obese	1.28	1.26	1.31	<.001
Morbidly obese	1.32	1.29	1.35	<.001
Donor race				
White	Reference (1.00)			
Hispanic	1.00	0.97	1.02	.696
African/African American	1.17	1.13	1.22	<.001
Asian/Pacific Islander	1.01	0.98	1.04	.588
Native American	1.02	0.95	1.11	.530
Multiple	1.05	1.02	1.08	<.001
Unknown	1.07	1.00	1.14	.052
Donor sex				
Male	Reference (1.00)			
Female	0.70	0.69	0.71	<.001
Donor age, y				
18-29	Reference (1.00)			
30-39	0.96	0.94	0.97	<.001
40-49	0.87	0.86	0.89	<.001
>50	0.77	0.75	0.79	<.001
Volume of blood processed on day 5, L				
<12	Reference (1.00)			
12-18	0.79	0.77	0.82	<.001
>18	0.69	0.67	0.71	<.001
Baseline neutrophils, quartile				
1	Reference (1.00)			
2	1.05	1.03	1.07	<.001
3	1.06	1.03	1.08	<.001
4	1.06	1.04	1.08	<.001
Baseline platelets, quartile				
1	Reference (1.00)			
2	1.03	1.01	1.05	.013
3	1.07	1.04	1.09	<.001
4	1.08	1.05	1.11	<.001
Baseline MNCs, quartile				
1	Reference (1.00)			
2	1.04	1.01	1.06	.001
3	1.05	1.03	1.07	<.001
4	1.06	1.04	1.08	<.001
Unknown	1.15	1.03	1.28	.015
WBC count (pre–day 5 of G-CSF administration), quartile				
1	Reference (1.00)			
2	1.09	1.06	1.13	<.001
3	1.18	1.13	1.23	<.001
4	1.33	1.27	1.40	<.001
Neutrophil count (pre–day 5 of G-CSF administration), quartile				
1	Reference (1.00)			
2	1.09	1.06	1.13	<.001
3	1.12	1.07	1.16	<.001
4	1.16	1.11	1.22	<.001
Unknown	1.08	0.92	1.25	.345
Platelet count (pre–day 5 of G-CSF administration), quartile				
1	Reference (1.00)			
2	1.03	1.01	1.05	.004
3	1.03	1.00	1.05	.026
4	1.07	1.04	1.10	<.001

CL, confidence limit.

Pain and toxicity experiences in PBSC donors

Figure 2 shows the time course and extent of pain and toxicities experienced by PBSC donors in different BMI groups. At baseline, before administration of G-CSF, skeletal pain and toxicities were comparable among the BMI groups. However, differences were noted in the severity of pain and toxicities at both the pericollection and early postdonation recovery periods. Obese and severely obese donors were more likely to experience grade 2 pain and toxicities compared with normal and overweight donors between days 1 and 5 of G-CSF administration and 2 days after donation. Grade 3 to 4 pain and toxicities were infrequently experienced in all BMI groups, but obese and severely obese donors had a slightly higher percentage of reported grade 3 to 4 skeletal pain and toxicities on days 1 to 5 of G-CSF administration. One week after donation, most pain and toxicities had abated, and there were no differences noted based on BMI.

In multivariate analysis, in addition to BMI, other donor characteristics, including age and sex, were also associated with different risks of toxicities and pain (supplemental Tables 2-9). Women were more likely to experience pain and other toxicities compared with men in both the pericollection timeframe and early postdonation recovery period. Older donors were at less risk of grade 2 to 4 pain and toxicities in the pericollection period, but they were more likely to have persistent pain and toxicities at 2 days after collection. In addition, older donors were at a higher risk for grade 2 to 4 toxicities at 1 week after collection. One other factor that was independently associated with an increase in toxicities and pain in the

Table 4. Multivariate analysis of impact of G-CSF dose on collection yields within each BMI category

BMI group	Average daily G-CSF day 1-5 target (range), μg	n	Ratio of means	Lower CL	Upper CL	*P*
Normal	600 (≤690)	1815	Reference (1.00)			<.001
	780 (691-840)	4151	1.09	1.06	1.13	<.001
	900 (841-930)	930	1.16	1.11	1.22	<.001
Overweight	600 (≤690)	116	Reference (1.00)			<.001
	780 (691-840)	2426	1.05	0.95	1.15	.324
	900 (841-930)	3334	1.08	0.98	1.19	.135
	960 (931-1020)	1239	1.11	1.01	1.23	.037
	1080 (1021-1140)	728	1.17	1.06	1.30	.002
Obese	780 (691-840)	254	Reference (1.00)			.520
	900 (841-930)	918	0.98	0.92	1.06	
	960 (931-1020)	704	0.98	0.91	1.06	
	1080 (1021-1140)	1370	1.01	0.94	1.09	
	1200 (1141+)	596	1.02	0.94	1.11	
Severely obese	900 (841-930)	106	Reference (1.00)			.148
	960 (931-1020)	170	1.06	0.94	1.20	
	1080 (1021-1140)	550	1.12	1.01	1.25	
	1200 (1141+)	1293	1.09	0.98	1.21	

pericollection period was a higher baseline MNC count. Use of CVC was associated with a higher risk of grade 2 to 4 pain 1 week after collection and with donation-associated toxicities 2 days and 1 week after collection.

To evaluate whether a G-CSF dose threshold exists above which donors may experience a significant increase in acute pain and toxicities from mobilization, the impact of different G-CSF dosing subgroups was analyzed for each BMI category (Table 5). A significant increase in pain and toxicities was not observed in obese or severely obese donors who received higher doses of G-CSF ($P = .586$ and $P = .300$, respectively). Thus, within each BMI group, incremental increases in the G-CSF dose were not associated with greater pain or toxicities.

Discussion

This is the largest study to date investigating the association of BMI with PBSC mobilization yield in unrelated healthy donors. We found significant differences in baseline leukocyte counts based on BMI, with normal BMI donors having the lowest baseline counts and morbidly obese donors having the highest baseline counts. In addition, a higher BMI was associated with the largest change (increase) in WBC, neutrophil, and MNC counts, which may suggest a better mobilization response to G-CSF. Previously, higher donor age had been associated with a negative effect on $CD34^+$ mobilization response.[25,26] Interestingly, in this study, better mobilization responses in donors with higher BMI were seen, despite older median ages of obese and severely obese donors compared with normal and overweight donors.

To determine if the increase in cell yield was due only to higher average daily G-CSF doses secondary to higher weights of donors with larger BMI, we evaluated stem cell collection yields in different G-CSF dose subgroups at each BMI category. We found a positive correlation between the average daily G-CSF dose and the $CD34^+$ cell yield in normal and overweight donors. However, in obese and severely obese donor groups, there was no increase in the $CD34^+$ yield with average daily G-CSF doses >780 and 900 μg per day, respectively. These data suggest that higher BMI predicts a better HSC mobilization response to G-CSF and identify a dose threshold above which there is no appreciable increase in progenitor cell yield in obese and severely obese healthy unrelated donors. In addition, our results suggest that the higher PBSC collection yield observed in obese donors is not solely due to a relatively higher average daily G-CSF dose but also may be influenced by some intrinsic factor associated with obesity.

The exact mechanism by which obesity affects PBSC mobilization responses to G-CSF in humans remains to be elucidated. The interaction between BMI and stem cell collection yield has been attributed to altered pharmacokinetics of G-CSF in donors with higher BMI.[27,28] Hypercholesterolemia, which is commonly seen in obese individuals, has also been shown to have an impact on the bone marrow microenvironment regulating HSC mobilization. Hypercholesterolemia-induced expression of adhesion molecules and the release of proinflammatory cytokines lead to leukocyte recruitment and chronic mild leukocytosis.[29-31] Hypercholesterinemia-associated chronic proinflammatory states also interfere with the chemokine stromal cell–derived factor-1 (SDF1)/CXCR4 signaling axis, which is a critical pathway in homing and retention of hematopoietic progenitor cells in the bone marrow.[20,32-34] Perturbation of the SDF1/CXCR4 signaling pathway by increasing SDF1 in peripheral blood results in hematopoietic progenitor cell mobilization. In the prior study, hypercholesterolemia was also associated with higher hematopoietic progenitor cell yields in patients receiving cyclophosphamide and G-CSF for mobilization before autologous transplantation.[24] Because NMDP does not prohibit stem cell donation in individuals with obesity-related health issues, including well-controlled diabetes by diet or medications (other

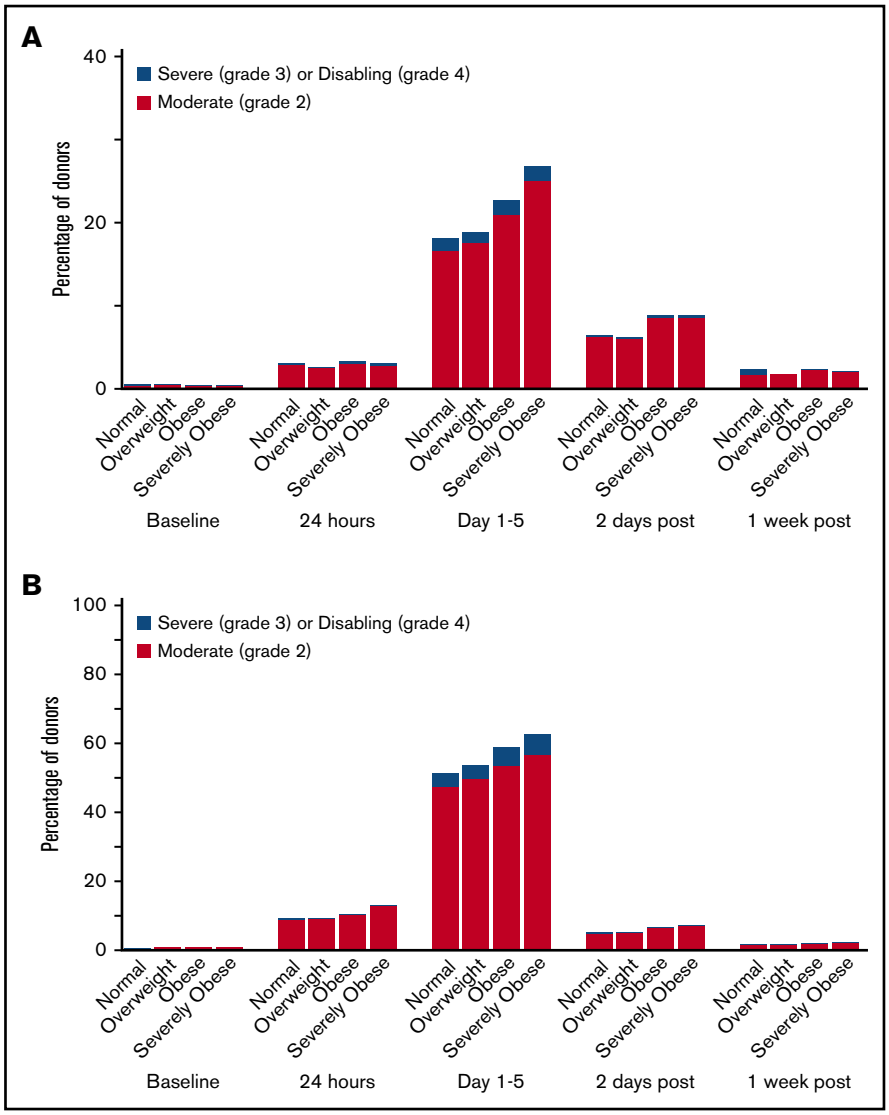

Figure 2. Donor skeletal pain and toxicities. Highest toxicity level of key symptoms (fever in the absence of signs of infection, fatigue, skin rash, local reactions, nausea, vomiting, anorexia, insomnia, dizziness, and syncope) (A) and highest skeletal pain level (B) experienced by PBSC adult donors at baseline, 24 hours after first dose of G-CSF, between days 1 to 5 of G-CSF administration, and after donation.

than insulin) and hypercholesteremia, the prevalence of hyperlipidemia may have been higher in obese and severely obese donors in this study. Unfortunately, data regarding donor lipid profiles were not available in our study.

Previous studies in unrelated donors have identified higher BMI as a risk factor in developing toxicities with apheresis.[35-37] A study of 2408 PBSC donors between 1999 and 2004 identified female sex and obesity as risk factors for more pericollection pain and toxicities.[36] A more recent prospective study comparing experiences of 2726 unrelated bone marrow vs 6768 PBSC donors who underwent collection between 2004 and 2009 also noted a higher rate of toxicities and pain in overweight and obese donors.[37] The results of our study are consistent with prior literature, where we also found an increased incidence of moderate to severe skeletal pain and toxicities in obese and severely obese donors compared with normal and overweight donors. However, we found that average daily G-CSF doses of >780 and 900 μg per day in obese and severely obese donors, respectively, did not correlate with a greater incidence of bone pain or toxicities, implying there are other intrinsic factors associated with obesity that contribute to the development of symptoms.

There were several limitations to this study. Information regarding the type of cell separator used to perform the apheresis procedure and details of procedural factors that may have affected the collection were not available. Although a cost analysis was not performed in this study, limiting the doses of G-CSF in obese and severely obese donors will reduce direct costs of stem cell mobilization.

In conclusion, we have demonstrated that in unrelated donors, there is a correlation between higher BMI and apheresis yields, consistent with previously published findings. More importantly, the increased apheresis yields of $CD34^+$ cells in obese and severely obese donors are not completely explained by higher G-CSF doses, and there is a threshold above which additional doses of G-CSF have no appreciable effect. In addition, capping G-CSF doses in obese and severely obese donors may achieve adequate collection yields at a lower cost. Whether this dosing

Table 5. Multivariate analysis of grade 2 to 4 skeletal pain between days 1 and day 5 of G-CSF administration

BMI group	Average daily G-CSF day 1-5 target (range), μg	n	Ratio of means	Lower CL	Upper CL	P
Normal	Overall					.137
	600 (≤690)	1788	Reference (1.00)			
	780 (691-840)	4136	1.10	0.96	1.25	
	900 (841-930)	926	1.22	1.0	1.48	
Overweight	Overall					.135
	600 (≤690)	104	Reference (1.00)			
	780 (691-840)	2411	0.77	0.51	1.17	
	900 (841-930)	3320	0.76	0.50	1.16	
	960 (931-1020)	1230	0.85	0.55	1.31	
	1080 (1021-1140)	726	0.89	0.57	1.39	
Obese	Overall					.586
	780 (691-840)	251	Reference (1.00)			
	900 (841-930)	915	1.05	0.78	1.40	
	960 (931-1020)	702	1.14	0.83	1.57	
	1080 (1021-1140)	1362	1.01	0.74	1.38	
	1200 (1141+)	593	1.15	0.81	1.62	
Severely obese	Overall					.175
	900 (841-930)	104	Reference (1.00)			
	960 (931-1020)	169	1.07	0.65	1.78	
	1080 (1021-1140)	544	1.21	0.78	1.87	
	1200 (1141+)	1288	1.43	0.93	2.21	

Adjusted for donor race, age, sex, year of collection, and baseline MNC counts.

strategy would also reduce pain and acute toxicities should be further studied.

Acknowledgments

The Center for International Blood and Marrow Transplant Research is supported primarily by Public Health Service Grant/Cooperative Agreement #5U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases, National Institutes of Health; Grant/Cooperative Agreement #1U24HL138660 from NHLBI and NCI; Contract #HHSH250201700006C with Health Resources and Services Administration; Grants #N00014-17-1-2388, #N00014-17-1-2850, and #N00014-18-1-2045 from the Office of Naval Research; grants from Adaptive Biotechnologies, an anonymous donation to the Medical College of Wisconsin, Astellas Pharma US, Atara Biotherapeutics Inc., Be The Match Foundation, Fred Hutchinson Cancer Research Center, Gamida Cell Ltd, Gilead Sciences Inc., HistoGenetics Inc., Immucor, Janssen Scientific Affairs LLC, Karius Inc., Karyopharm Therapeutics Inc., Medac GmbH, Medical College of Wisconsin, MesoScale Diagnostics Inc., Millennium, Takeda Oncology Co., Mundipharma EDO, National Marrow Donor Program, Novartis Pharmaceuticals Corp., Patient-Centered Outcomes Research Institute, PIRCHE AG, Shire, Spectrum Pharmaceuticals Inc., St Baldrick's Foundation, Swedish Orphan Biovitrum Inc., and University of Minnesota; and grants from corporate members Amgen Inc., bluebird bio Inc., Bristol-Myers Squibb Oncology, Celgene Corp., Chimerix Inc., CytoSen Therapeutics Inc., Incyte Corp., Jazz Pharmaceuticals Inc., Kite Pharma Inc., Mediware, Merck & Co. Inc., Mesoblast, Miltenyi Biotec Inc., Pfizer Inc., Pharmacyclics LLC, Sanofi Genzyme, Seattle Genetics, and Takeda Oncology.

The views expressed in this article do not reflect the official policy or position of the National Institutes of Health, the Department of the Navy, the Department of Defense, the Health Resources and Services Administration, or any other agency of the US Government.

Authorship

Contribution: N.F., J.W.H., J.R.W., and B.E.S. designed the study, developed the protocol, interpreted the data, and wrote the manuscript; B.R.L., J.A.S., and P.C. designed the study, analyzed and interpreted the data, and generated the figures; M.W.S., H.A.-A., P.N.A., C.B., S.C., M.A.D., S.G., P.H., R.T.K., K.A.K., H.M.L., D.K.L., H.S.M., R.F.O., M.P., D.P., B.N.S., R.S., S.S., M.M.S., T.S., J.A.Y., M.A.P., N.N.S., G.E.S., and D.L.C. participated in the design of the study and edited the final manuscript; and the final manuscript was reviewed and approved by all authors.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: P.C., 0000-0002-0792-1764; S.C., 0000-0001-9117-8696; M.A.D., 0000-0001-5286-1329; K.A.K., 0000-0002-0651-8666; H.M.L., 0000-0002-1159-5607; H.S.M., 0000-0003-4534-4248; R.F.O., 0000-0001-5970-2128; J.A.Y., 0000-0002-5346-6299; M.A.P., 0000-0003-3030-8420.

Correspondence: Bronwen E. Shaw, CIBMTR, 9200 W Wisconsin Ave, Suite C5500, Milwaukee, WI 53226; e-mail: beshaw@mcw.edu.

References

1. D'Souza A, Lee S, Zhu X, Pasquini M. Current use and trends in hematopoietic cell transplantation in the united states. *Biol Blood Marrow Transplant*. 2017;23(9):1417-1421.
2. Anasetti C, Logan BR, Lee SJ, et al; Blood and Marrow Transplant Clinical Trials Network. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med*. 2012;367(16):1487-1496.
3. Couban S, Simpson DR, Barnett MJ, et al; Canadian Bone Marrow Transplant Group. A randomized multicenter comparison of bone marrow and peripheral blood in recipients of matched sibling allogeneic transplants for myeloid malignancies. *Blood*. 2002;100(5):1525-1531.
4. Bensinger WI, Martin PJ, Storer B, et al. Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers. *N Engl J Med*. 2001;344(3):175-181.
5. Suzuya H, Watanabe T, Nakagawa R, et al. Factors associated with granulocyte colony-stimulating factor-induced peripheral blood stem cell yield in healthy donors. *Vox Sang*. 2005;89(4):229-235.
6. Ings SJ, Balsa C, Leverett D, Mackinnon S, Linch DC, Watts MJ. Peripheral blood stem cell yield in 400 normal donors mobilised with granulocyte colony-stimulating factor (G-CSF): impact of age, sex, donor weight and type of G-CSF used. *Br J Haematol*. 2006;134(5):517-525.
7. Hsu JW, Wingard JR, Logan BR, et al. Race and ethnicity influences collection of granulocyte colony-stimulating factor-mobilized peripheral blood progenitor cells from unrelated donors, a Center for International Blood and Marrow Transplant Research analysis. *Biol Blood Marrow Transplant*. 2015; 21(1):165-171.
8. Wang T-F, Wen S-H, Chen R-L, et al. Factors associated with peripheral blood stem cell yield in volunteer donors mobilized with granulocyte colony-stimulating factors: the impact of donor characteristics and procedural settings. *Biol Blood Marrow Transplant*. 2008;14(11):1305-1311.
9. Tabilio A, Falzetti F, Giannoni C, et al. Stem cell mobilization in normal donors. *J Hematother*. 1997;6(3):227-234.
10. Grigg AP, Roberts AW, Raunow H, et al. Optimizing dose and scheduling of filgrastim (granulocyte colony-stimulating factor) for mobilization and collection of peripheral blood progenitor cells in normal volunteers. *Blood*. 1995;86(12):4437-4445.
11. Chen J, Burns KM, Babic A, et al. Donor body mass index is an important factor that affects peripheral blood progenitor cell yield in healthy donors after mobilization with granulocyte-colony-stimulating factor. *Transfusion*. 2014;54(1):203-210.
12. Stroncek DF, Clay ME, Smith J, et al. Composition of peripheral blood progenitor cell components collected from healthy donors. *Transfusion*. 1997; 37(4):411-417.
13. Basak GW, Wiktor-Jedrzejczak W, Apperley JF, et al. Higher BMI is not a barrier to stem cell mobilization with standard doses of plerixafor and G-CSF. *Bone Marrow Transplant*. 2012;47(7):1003-1005.
14. Hruby A, Hu FB. The epidemiology of obesity: a big picture. *Pharmacoeconomics*. 2015;33(7):673-689.
15. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007-2008 to 2015-2016. *JAMA*. 2018;319(16):1723-1725.
16. Ogden CL, Carroll MD, Fryar CD, Flegal KM. Prevalence of obesity among adults and youth: United States, 2011-2014. *NCHS Data Brief*. 2015;(219): 1-8.
17. Kanneganti TD, Dixit VD. Immunological complications of obesity. *Nat Immunol*. 2012;13(8):707-712.
18. Lumeng CN. Innate immune activation in obesity. *Mol Aspects Med*. 2013;34(1):12-29.
19. do Carmo LS, Rogero MM, Paredes-Gamero EJ, et al. A high-fat diet increases interleukin-3 and granulocyte colony-stimulating factor production by bone marrow cells and triggers bone marrow hyperplasia and neutrophilia in Wistar rats. *Exp Biol Med (Maywood)*. 2013;238(4):375-384.
20. Lévesque J-P, Hendy J, Takamatsu Y, Simmons PJ, Bendall LJ. Disruption of the CXCR4/CXCL12 chemotactic interaction during hematopoietic stem cell mobilization induced by GCSF or cyclophosphamide. *J Clin Invest*. 2003;111(2):187-196.
21. Bellows CF, Zhang Y, Simmons PJ, Khalsa AS, Kolonin MG. Influence of BMI on level of circulating progenitor cells. *Obesity (Silver Spring)*. 2011;19(8): 1722-1726.
22. Herishanu Y, Rogowski O, Polliack A, Marilus R. Leukocytosis in obese individuals: possible link in patients with unexplained persistent neutrophilia. *Eur J Haematol*. 2006;76(6):516-520.
23. Cohen KS, Cheng S, Larson MG, et al. Circulating CD34(+) progenitor cell frequency is associated with clinical and genetic factors. *Blood*. 2013; 121(8):e50-e56.
24. Crysandt M, Hilgers RD, von Hobe S, et al. Hypercholesterolemia and its association with enhanced stem cell mobilization and harvest after high-dose cyclophosphamide+G-CSF. *Bone Marrow Transplant*. 2011;46(11):1426-1429.
25. Vasu S, Leitman SF, Tisdale JF, et al. Donor demographic and laboratory predictors of allogeneic peripheral blood stem cell mobilization in an ethnically diverse population. *Blood*. 2008;112(5):2092-2100.
26. Teipel R, Schetelig J, Kramer M, et al. Prediction of hematopoietic stem cell yield after mobilization with granulocyte-colony-stimulating factor in healthy unrelated donors. *Transfusion*. 2015;55(12):2855-2863.
27. Waples JM, Moreb JS, Sugrue M, et al. Comparison of autologous peripheral blood stem cell dosing by ideal vs actual body weight. *Bone Marrow Transplant*. 1999;23(9):867-873.
28. Cetin T, Arpaci F, Ozet A, et al. Stem cell mobilization by G-CSF in solid and hematological malignancies: single daily dose is better than split dose in obese patients. *J Clin Apher*. 2003;18(3):120-124.

29. Han KH, Han KO, Green SR, Quehenberger O. Expression of the monocyte chemoattractant protein-1 receptor CCR2 is increased in hypercholesterolemia. Differential effects of plasma lipoproteins on monocyte function. *J Lipid Res*. 1999;40(6):1053-1063.

30. Bobryshev YV. Monocyte recruitment and foam cell formation in atherosclerosis. *Micron*. 2006;37(3):208-222.

31. Coller BS. Leukocytosis and ischemic vascular disease morbidity and mortality: is it time to intervene? *Arterioscler Thromb Vasc Biol*. 2005;25(4): 658-670.

32. Gomes AL, Carvalho T, Serpa J, Torre C, Dias S. Hypercholesterolemia promotes bone marrow cell mobilization by perturbing the SDF-1:CXCR4 axis. *Blood*. 2010;115(19):3886-3894.

33. Feng Y, Schouteden S, Geenens R, et al. Hematopoietic stem/progenitor cell proliferation and differentiation is differentially regulated by high-density and low-density lipoproteins in mice. *PLoS One*. 2012;7(11):e47286.

34. Cimato TR, Palka BA, Lang JK, Young RF. LDL cholesterol modulates human CD34+ HSPCs through effects on proliferation and the IL-17 G-CSF axis. *PLoS One*. 2013;8(8):e73861.

35. Miller JP, Perry EH, Price TH, et al. Recovery and safety profiles of marrow and PBSC donors: experience of the National Marrow Donor Program. *Biol Blood Marrow Transplant*. 2008;14(9 suppl):29-36.

36. Pulsipher MA, Chitphakdithai P, Miller JP, et al. Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. *Blood*. 2009;113(15):3604-3611.

37. Pulsipher MA, Chitphakdithai P, Logan BR, et al. Acute toxicities of unrelated bone marrow versus peripheral blood stem cell donation: results of a prospective trial from the National Marrow Donor Program. *Blood*. 2013;121(1):197-206.