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

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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

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The full-text version of this article contains a data supplement.
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/m2) 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 (× 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                  | Normal (18.5-24.9) | Overweight (25-29.9) | Obese (30-34.9) | Severely obese (35+) | P     |
|---------------------------------|--------------------|----------------------|------------------|----------------------|-------|
| 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                          | 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)         | 1581 (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.
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/m²), overweight (BMI, 25-29.9 kg/m²), obese (BMI, 30.0-34.9 kg/m²), and severely obese (BMI $\geq 35.0$ kg/m²). 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 χ² 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 1. (continued)

| Characteristic                              | Normal (18.5-24.9) | Overweight (25-29.9) | Obese (30-34.9) | Severely obese (≥ 35) | P     |
|--------------------------------------------|--------------------|----------------------|----------------|-----------------------|-------|
| 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.

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

| Variable                       | BMI, kg/m²                  |
|--------------------------------|-----------------------------|
|                                | Normal (18.5-24.9) | Overweight (25-29.9) | Obese (30-34.9) | Severely obese (≥ 35) | P     |
| 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)             | 28.4 (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$^9$ | 532 (15.0-4677) | 669 (7.9-5967)       | 729 (7.9-4014)  | 756 (52.5-3988)        | <.001 |
| CD34$^+$ cells/L of blood processed, × 10$^9$/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.
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 × CD34⁺ cell concentration in peripheral blood × volume of day 5 product) × 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 × 10⁹/L) and neutrophil counts (3.7 × 10⁹/L), whereas severely obese donors had the highest baseline WBC (7.4 × 10⁹/L) and neutrophil counts (4.6 × 10⁹/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 × 10⁹/L), neutrophil (median, 30.2 × 10⁹/L), and MNC counts (median, 1.7 × 10⁹/L) compared with other BMI categories. The collection yield, expressed as CD34⁺ per liter of blood processed (× 10⁹/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 = 20150). 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).
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 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  |

Table 3. (continued)

| Variable                        | Ratio of means | Lower CL | Upper CL | P     |
|---------------------------------|----------------|----------|----------|-------|
| 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.
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

| 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) | 1.06     | 1.13     | <.001|
| Obese              | 780 (691-840)                                 | 4151| 1.09           | 1.06     | 1.13     | <.001|
| Severe obesity     | 900 (841-930)                                 | 930 | 1.16           | 1.11     | 1.22     | <.001|
| Overweight         | 600 (690)                                     | 116 | Reference (1.00)|          |          | <.001|
| Obese              | 780 (691-840)                                 | 2426| 1.05           | 0.95     | 1.15     | .324 |
| Severe obesity     | 900 (841-930)                                 | 3334| 1.08           | 0.98     | 1.19     | .135 |
| Overweight         | 960 (931-1020)                                | 1239| 1.11           | 1.01     | 1.23     | .037 |
| Obese              | 1080 (1021-1140)                              | 728 | 1.17           | 1.06     | 1.30     | .002 |
| Severe obesity     | 900 (841-930)                                 | 254 | Reference (1.00)|          |          | .520 |
| Overweight         | 960 (931-1020)                                | 918 | 0.98           | 0.92     | 1.06     |      |
| Severe obesity     | 1080 (1021-1140)                              | 704 | 0.98           | 0.91     | 1.06     |      |
| Overweight         | 1200 (1141+)                                  | 1370| 1.01           | 0.94     | 1.09     |      |
| Severe obesity     | 900 (841-930)                                 | 596 | 1.02           | 0.94     | 1.11     |      |
| Overweight         | 960 (931-1020)                                | 170 | 1.06           | 0.94     | 1.20     | .148 |
| Severe obesity     | 1080 (1021-1140)                              | 550 | 1.12           | 1.01     | 1.25     |      |
| Overweight         | 1200 (1141+)                                  | 1293| 1.09           | 0.98     | 1.21     |      |

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 baseline counts. In addition, a higher BMI was associated with baseline counts and morbidly obese donors having the highest changes in the G-CSF dose were not associated with greater pain or toxicities.
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. A study of 2408 PBSC donors between 1999 and 2004 identified female sex and obesity as risk factors for more pericollection pain and toxicities. A more recent prospective study comparing experiences of 2726 unrelated bone marrow vs 6788 PBSC donors who underwent collection between 2004 and 2009 also noted a higher rate of toxicities and pain in overweight and obese donors. 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...
strategy would also reduce pain and acute toxicities should be further studied.

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Authorship

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