Donor body mass index does not predict graft versus host disease following hematopoietic cell transplantation

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Graft versus host disease (GVHD) is a serious complication affecting nearly half of hematopoietic cell transplantation (HCT) recipients.\(^1\) It is characterized by lymphocyte activation and proliferation, a surge in pro-inflammatory cytokines and tissue destruction.\(^2\) GVHD risk factors include degree of donor-recipient human leukocyte antigen (HLA) mismatch, stem cell source, donor-recipient sex matching, donor age, and pre-HCT conditioning regimen intensity.\(^3,4\) More than one-third of HCT donors are obese, and although previous studies have demonstrated either no or minimal effect of recipient body mass index (BMI) on transplant outcomes,\(^5-8\) the impact of donor obesity and donor inflammation on recipient outcomes have not been investigated. Obesity, defined as a BMI $\geq$ 30 kg/m\(^2\), and overweight (BMI 25–29.9 kg/m\(^2\)), are chronic inflammatory states. Most individuals with obesity have increased numbers of circulating monocytes secreting pro-
inflammatory cytokines, including TNF-α, IL-1β and IL-6, similar to the inflammation and cytokine dysregulation that are observed in GVHD. We sought to address the hypothesis that stem cell products from obese donors would result in engrafted hematopoietic cells that are more inflammatory, resulting in increased rates of acute (aGVHD) and chronic GVHD (cGVHD) in transplant recipients.

Data were obtained from the Center for International Blood and Marrow Transplantation Research (CIBMTR). The CIBMTR is a collaboration between the Medical College of Wisconsin and the National Marrow Donor Program/Be the Match. Individuals included in the study had a primary diagnosis of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), or myelodysplastic syndrome (MDS), and underwent their first allogeneic HLA-A, B, C and DRB1-matched (8/8 matched) unrelated peripheral blood stem cell (PBSC) transplant between 2000 to 2013. Individuals who received ex-vivo T-cell depleted or CD34+ selected grafts, transplants from multiple donors, or who had missing donor data were excluded from the analysis. Primary endpoints included incidence of grade II–IV and grade III–IV aGVHD and cGVHD. aGVHD II–IV was graded according to consensus criteria at day 100 with death without aGVHD as a competing risk. cGVHD was reported as cumulative incidence at 6 months, 1 and 2 years post-HCT with death without cGVHD as a competing risk. Secondary outcomes included relapse, disease free survival (DFS), non-relapse mortality (NRM), and overall survival (OS). Relapse was reported as a cumulative incidence with NRM as a competing risk. DFS was defined as time to treatment failure either death or relapse. NRM was defined as death in continuous remission with relapse as a competing risk. Donor BMI category definitions included: underweight (BMI <18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), obese (30–39.9 kg/m²) and morbidly obese (≥40 kg/m²). Other patient-, disease- and transplant-related variables considered included recipient and donor age at HCT, recipient and donor race, donor-recipient sex match, donor and recipient cytomegalovirus (CMV) status, recipient Karnofsky score prior to HCT, disease status at HCT, interval from diagnosis to HCT, HCT conditioning intensity, use of total body irradiation (TBI) in conditioning, CD34+ cell dose, GVHD prophylaxis and use of anti-thymocyte globulin (ATG) or alemtuzumab.

Univariate probabilities of OS and DFS were calculated using the Kaplan-Meier estimator. Cumulative incidences of aGVHD and cGVHD, NRM and relapse were estimated using a cumulative incidence function method. Cox’s proportional hazards models were used to adjust for significant covariates. A stepwise forward model selection was used to identify significant covariates to be included in the models with a threshold of p<0.05 for variable entry and exit. Interactions between donor BMI variables and the significant covariates were tested and no significant interactions were detected. Recipients of grafts from normal weight donors were the reference group for all models. To account for multiple comparisons, p<0.01 was considered as the threshold for significance. P-values are 2-sided. The analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC).

There were 4,412 individuals from 178 centers included in the present analysis. Transplant recipients were 43% female and were a median of 52 years of age (range 0–79 years) at the time of HCT. The indications for transplantation included: AML (54.4%), ALL (14.4%),
CML (7.8%) and MDS (23.4%), and conditioning intensity was myeloablative for 64%, reduced intensity for 28% and non-myeloablative for 8%. Donors were 30% female and were a median of 32 years of age (range 18–62 years). One percent of donors were underweight, 38% were normal weight, 38% were overweight, 21% were obese and 2% were morbidly obese.

Cumulative incidence of grade II–IV and grade III–IV aGVHD at day 100 did not differ based on donor BMI category (p=0.59 and p=0.76, respectively; Table 2). After adjusting for recipient disease, grade II–IV aGVHD was not associated with donor BMI (p=0.51), and for grade III–IV aGVHD, adjusting for donor sex, graft CD34⁺ cell dose, and recipient disease, there was no association with donor BMI (p=0.90) (Figure 1A). Cumulative incidence of cGVHD at one year also did not differ based on donor BMI (p=0.15; Table 2). After adjusting for recipient disease, performance status and donor-recipient sex match, there was not an overall significant association between donor BMI and cGVHD (p=0.03). PBSCs from obese donors were associated with increased risk of cGVHD (hazard ratio [HR]=1.16, 95% CI 1.03–1.30, p=0.01); however, this association was not seen for morbidly obese donors (Figure 1B).

Relapse at 2 years did not differ significantly, as a function of donor BMI (p=0.18; Table 2). In multivariate analysis, adjusting for conditioning intensity, interval from diagnosis to HCT and Karnofsky score, there was no significant effect of donor BMI on relapse (p=0.23). DFS at 2 years did not differ based on donor BMI category (p=0.18; Table 2). After adjusting for recipient age, ATG or alemtuzumab use, CMV status, GVHD prophylaxis, interval from diagnosis to HCT, Karnofsky score and CD34⁺ cell dose, DFS was worse when the donor was overweight compared with a normal weight donor (HR=1.16, 95% CI 1.06–1.28, p=0.002), but this relationship did not hold for obese donors (HR=1.14, 95% CI 1.02–1.28, p=0.02), nor was there an overall significant association with donor BMI category (p=0.02).

Cumulative incidence of NRM at 2 years was not significantly different across donor BMI categories (p=0.04; Table 2). Multivariate analysis, adjusted for recipient age, donor-recipient CMV match, GVHD prophylaxis, interval from diagnosis to HCT, and CD34⁺ cell dose, identified increased risk for NRM in the obese donor group compared with the normal weight donors (HR=1.29, 95% CI 1.08–1.55, p=0.005), but this relationship was not seen consistently across BMI categories (p=0.05). The probability of OS at 2 years did not differ based on donor BMI (p=0.11; Table 2). Multivariate analysis, adjusted for ATG and alemtuzumab exposure, disease, donor-recipient CMV match, GVHD prophylaxis, interval from diagnosis to HCT, and CD34⁺ cell dose, did not reveal a significant effect of donor BMI on OS (p=0.08).

In contrast with our hypothesis, consistent and significant associations were not identified between donor BMI and aGVHD or cGVHD, or relapse, DFS, NRM or OS. Despite identifying inferior DFS and increased risk for NRM in the obese donor group, these relationships were not observed for overweight or morbidly obese donors, nor were significant overall effects of donor BMI observed for any of the outcomes of interest. The lack of significant findings in the morbidly obese group may be due to limited numbers of morbidly obese donors. These results might also reflect a selection bias as donors that were...
suitably healthy to serve as stem cell donors have fewer pro-inflammatory health comorbidities compared with those who may have been excluded as donors, making the donor groups less different than what is observed in the general population. Furthermore, all donors received high-dose granulocyte colony stimulating factor prior to stem cell donation, which may have altered the inflammatory properties of the collected cells, potentially masking differences in inflammation typically observed between obese and normal weight donors. Although data on statin use were not available for this analysis, it is likely that use is more common among obese individuals compared to those of normal weight, and donor statin use has been associated with a decreased risk of grade 3–4 acute GVHD,\(^{(13)}\) potentially influencing the findings of our analysis.

While this study suggests that donor obesity is not a risk factor for GVHD, the concept of whether inflammation is transferrable from donor to recipient remains an outstanding issue not addressed by this study. There are multiple causes for systemic inflammation, beyond increased adipose tissue mass, such as autoimmune conditions, acute infection, and even chronic stress, social isolation, and depression.\(^{(14)}\) Additionally, lifestyle factors such as tobacco or alcohol use may increase systemic inflammation.\(^{(15)}\) These factors may contribute to normal weight or underweight donors having more similar inflammatory profiles to obese donors than we had anticipated.

Based on the present analysis, donor obesity is not associated with increased risk for aGVHD or cGVHD and does not appear to be correlated with other post-HCT adverse outcomes. Further investigation of donor circulating cytokine concentrations or analysis of cytokine producing cells would be an important next step in elucidating the role of donor inflammation in post-HCT outcomes.

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Figure 1.
Acute and chronic GVHD adjusted* hazard ratios, by donor BMI category. Reference group is normal weight donor. A) Acute GVHD, grade 3–4, following HCT. B) Chronic GVHD following HCT.

*Acute GVHD III–IV analysis adjusted for donor sex, graft CD34+ cell dose, conditioning regimen, year of transplant, GVHD prophylaxis, disease stage, disease type, and ATG/Alemtuzumab use; chronic GVHD analysis adjusted for disease type, Karnofsky performance score, donor-recipient sex match, conditioning regimen, year of transplant, and ATG/Alemtuzumab use.

Abbreviations: BMI, body mass index; GVHD, graft versus host disease; HCT, hematopoietic cell transplantation, MOB, morbidly obese; NW, normal weight; OB, obese; OW, overweight; UW, underweight.
Table 1

Univariate analyses of HCT outcomes, based on donor BMI category.

| Outcomes                        | Underweight N | Normal weight N | Overweight N | Obese N | Morbidly Obese N | p-value |
|---------------------------------|---------------|----------------|--------------|---------|------------------|---------|
| Grade 2–4 acute GVHD 100-day    | 43            | 1654           | 1649         | 900     | 99               | 0.59    |
|                                 | 47 (32–61)%   | 44 (42–46)%    | 42 (40–45)%  | 44 (41–48)% | 49 (39–59)%     |         |
|                                 |               |                |              |         |                  |         |
| Grade 3–4 acute GVHD 100-day    | 43            | 1649           | 1648         | 894     | 98               | 0.76    |
|                                 | 16 (7–29)%    | 18 (16–20)%    | 18 (16–20)%  | 17 (15–20)% | 23 (15–32)%     |         |
|                                 |               |                |              |         |                  |         |
| Chronic GVHD 6 months 1-year    | 43            | 1661           | 1646         | 903     | 100              | 0.83    |
|                                 | 23 (12–37)%   | 29 (27–32)%    | 29 (27–32)%  | 29 (26–32)% | 33 (24–43)%     |         |
|                                 |               |                |              |         |                  |         |
|                                 | 47 (32–61)%   | 47 (45–50)%    | 46 (44–48)%  | 51 (48–55)% | 47 (38–57)%     | 0.15    |
|                                 |               |                |              |         |                  |         |
|                                 | 49 (34–64)%   | 53 (51–56)%    | 52 (49–54)%  | 56 (53–60)% | 54 (44–64)%     | 0.28    |
| NRM 1-year                      | 43            | 1650           | 1630         | 898     | 100              | 0.07    |
|                                 | 26 (14–40)%   | 18 (16–20)%    | 21 (20–24)%  | 20 (17–22)% | 16 (10–24)%     |         |
|                                 |               |                |              |         |                  |         |
|                                 | 31 (18–46)%   | 22 (20–24)%    | 26 (24–28)%  | 26 (23–29)% | 19 (12–27)%     | 0.04    |
|                                 |               |                |              |         |                  |         |
|                                 | 34 (20–49)%   | 25 (23–28)%    | 28 (26–30)%  | 29 (26–32)% | 24 (16–32)%     | 0.17    |
|                                 |               |                |              |         |                  |         |
|                                 | 34 (20–49)%   | 29 (27–31)%    | 32 (29–34)%  | 34 (31–38)% | 26 (18–35)%     | 0.07    |
| Relapse 1-year                   | 43            | 1650           | 1630         | 898     | 100              | 0.49    |
|                                 | 21 (10–34)%   | 30 (28–32)%    | 31 (28–33)%  | 29 (26–32)% | 32 (23–41)%     |         |
|                                 |               |                |              |         |                  |         |
|                                 | 21 (10–34)%   | 34 (32–36)%    | 34 (32–36)%  | 33 (30–36)% | 40 (31–50)%     | 0.18    |
|                                 |               |                |              |         |                  |         |
|                                 | 21 (10–34)%   | 35 (33–38)%    | 36 (34–39)%  | 35 (32–39)% | 44 (34–54)%     | 0.08    |
|                                 |               |                |              |         |                  |         |
|                                 | 21 (10–34)%   | 38 (35–40)%    | 38 (35–40)%  | 37 (34–40)% | 46 (36–56)%     | 0.04    |
| DFS 1-year                      | 43            | 1650           | 1630         | 898     | 100              | 0.12    |
|                                 | 53 (39–68)%   | 52 (50–55)%    | 48 (45–50)%  | 52 (49–55)% | 52 (42–62)%     |         |
|                                 |               |                |              |         |                  |         |
|                                 | 48 (33–63)%   | 44 (42–47)%    | 40 (38–43)%  | 41 (38–44)% | 40 (31–50)%     | 0.18    |
|                                 |               |                |              |         |                  |         |
|                                 | 45 (31–61)%   | 39 (37–42)%    | 36 (34–39)%  | 35 (32–39)% | 33 (24–42)%     | 0.17    |
|                                 |               |                |              |         |                  |         |
|                                 | 45 (31–61)%   | 33 (31–36)%    | 31 (28–33)%  | 29 (26–32)% | 28 (19–37)%     | 0.05    |
| Overall survival 1-year         | 43            | 1680           | 1671         | 917     | 101              | 0.22    |
|                                 | 58 (43–72)%   | 60 (58–63)%    | 57 (55–59)%  | 61 (58–64)% | 60 (51–70)%     |         |
|                                 |               |                |              |         |                  |         |
|                                 | 50 (35–65)%   | 50 (48–53)%    | 46 (43–48)%  | 47 (44–51)% | 50 (40–60)%     | 0.11    |
| Outcomes | Underweight |   | Normal weight |   | Overweight |   | Obese |   | Morbidly Obese |   | p-value |
|----------|-------------|---|---------------|---|------------|---|-------|---|----------------|---|---------|
| 3-year   | N           | 48 (33–63)% |   | 44 (42–47)% |   | 41 (39–44)% |   | 40 (37–43)% |   | 43 (33–52)% |   | 0.26    |
| 5-year   | N           | 48 (33–63)% |   | 37 (35–40)% |   | 34 (31–36)% |   | 32 (29–36)% |   | 37 (28–47)% |   | 0.04    |