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Hypertension and Diabetes Mellitus in Adult and Pediatric Survivors of Allogeneic Hematopoietic Cell Transplantation

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Hypertension and diabetes are frequent early complications of allogeneic hematopoietic cell transplantation (HCT); however, their long-term outcomes are not well known. We conducted a retrospective cohort study to describe the risk factors and natural history of post-HCT hypertension and diabetes in 180 consecutive adult (n = 106) and pediatric (n = 74) allogeneic HCT recipients from 2003-2005 who had survived for 1 year post-HCT. The pediatric patients were less likely than the adult patients to have pre-HCT hypertension and diabetes, smoking history, or high-risk disease and more likely to receive myeloablative (MA) conditioning. All patients were followed until at least 2 years post-HCT; of these 1-year survivors, 156 (87%) were alive at 2 years. Acute or chronic graft-versus-host disease (aGVHD, cGVHD) occurred in 118 (66%) patients; of these, 24% received cyclosporine (CsA) for >12 months and 47% received prednisone for >12 months. Within 2 years post-HCT, 126 (70%) had hypertension and 54 (30%) had diabetes. Rates were similar for the adult recipients (hypertension, 68%; diabetes, 30%) and the pediatric recipients (hypertension, 73%; diabetes, 30%). At 2 years post-HCT, in the patients with hypertension, hypertension had not resolved in 34%, and among patients with diabetes, diabetes had not resolved in 32%. On multivariate analyses, exposure to CsA increased the risk of developing hypertension post-HCT (relative risk, 1.6; 95% confidence interval [CI], 1.1-2.5; $P = .03$), but did not affect its persistence at 2 years. Exposure to high-dose corticosteroids (cumulative prednisone dose of > 0.25 mg/kg/day) increased the likelihood of developing diabetes (relative risk, 3.6; 95% CI, 1.7-7.5; $P < .01$) and for having persistent diabetes at 2 years post-HCT (relative risk, 4.1; 95% CI, 1.0-18.2; $P = .05$). Hypertension and diabetes are frequent early complications of allogeneic HCT, but subsequently resolve in a large proportion of recipients in the first 2 years after transplantation. Continued monitoring and treatment of hypertension and diabetes is necessary in allogeneic HCT survivors, especially in those exposed to high doses of corticosteroids.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) can be associated with significant early and late toxicity. Late cardiovascular complications are an important cause of morbidity in this patient population, and both pediatric and adult long-term allogeneic HCT survivors are at risk for developing metabolic syndrome, hypertension, diabetes mellitus, premature arterial cardiovascular events, and congestive heart failure [1-8]. Hypertension and diabetes frequently occur in the early posttransplantation period and have a variable clinical course. Over time, these disorders can improve and even resolve in some patients, but can persist in others. Although they are not life-threatening, they can contribute to the morbidity of transplantation and are potential risk factors for development of cardiovascular late complications. Calcineurin inhibitor and corticosteroid exposure are thought to increase the risk of hypertension and diabetes, but this has not yet been studied systematically. A better understanding of the natural history of post-HCT hypertension and diabetes and of the risk

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factors for their development and long-term persistence is important for developing strategies for their screening, prevention, and early management. We conducted a retrospective cohort study to describe the natural history of early-onset hypertension and diabetes in allogeneic HCT survivors.

METHODS

Patient Selection and Follow-Up

Our single-institution study included consecutive adult (aged ≥ 18 years) and pediatric (aged < 18 years) allogeneic HCT recipients who underwent transplantation between 2003 and 2005 and survived for at least 1 year post-HCT. Because we primarily wanted to study the natural history of post-HCT hypertension and diabetes mellitus along with risk factors for their persistence in long-term HCT survivors, patients who died within the first year post-HCT were excluded. Recipients of both myeloablative (MA) and nonmyeloablative (NMA) preparative regimens were eligible, however, recipients of multiple HCTs (n = 12) were excluded. Patient-, disease-, and transplant-related information was obtained from the University of Minnesota Blood and Marrow Transplant database, which prospectively collects such data for all patients undergoing HCT at our institution. Additional data, including details of hypertension and diabetes, laboratory investigations, and duration and dose of immunosuppressive therapy, were abstracted from our institution's electronic patient medical records. All patients underwent transplantation on protocols approved by our institutional review board.

All patients undergoing HCT at our institution receive post-HCT care exclusively within our Blood and Marrow Transplant Program up to at least day 100. Subsequently, all patients return for follow-up at 6, 9, 12, 18 and 24 months post-HCT. Assessments at these time points include blood pressure and fasting plasma glucose measurements. Patient medications are also reviewed and recorded. Additional follow-up, as clinically indicated (eg, for management of chronic graft-versus-host disease [cGVHD]), is at the discretion of the patient's transplantation physician.

Conditioning Regimens and Supportive Care

The MA and NMA regimens used at our institution have been described previously [9-11]. In brief, the patients undergoing MA related or unrelated donor HCT received a regimen consisting of total body irradiation (TBI) and cyclophosphamide (Cy; n = 30), whereas the recipients of MA umbilical cord blood HCT received TBI, Cy, and fludarabine (Flu; n = 55). The NMA regimen (n = 61), which was common for all donor types, comprised TBI, Cy, and Flu. The preparative regimen for patients with Fanconi anemia (FA; n = 17) included Cy, Flu, and antithymocyte globulin (ATG). Other conditioning regimens were used in the remaining 17 patients (9%).

Our GVHD prophylaxis and treatment regimens also have been described previously [11,12]. All patients received GVHD prophylaxis with Cy (from day −3 to at least day +100), with trough levels maintained at 200-400 ng/mL and either methotrexate (MTX; in MA related and unrelated donor recipients) or mycophenolate mofetil (MMF; in MA umbilical cord blood and all NMA HCT recipients).

Study Definitions

Disease risk was classified as standard risk or high risk. Standard-risk disease included acute leukemia in first complete remission (CR1), chronic myelogenous leukemia (CML) in first chronic phase (CP1), myelodysplastic syndrome (MDS; refractory anemia only), and nonmalignant hematologic disorders. All other diagnoses were categorized as high-risk disease.

Hypertension was defined according to the National Heart, Lung and Blood Institute's Joint National Committee's criteria for adults [13]. Patients with a systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg or receiving treatment for hypertension were classified as having hypertension. For children, the National Heart, Lung and Blood Institute's Working Group on High Blood Pressure in Children and Adolescents, definition for hypertension was used. The diagnosis is based on blood pressure percentile, and hypertension is defined as average systolic and/or diastolic blood pressure ≥95th percentile for sex, age, and height [14]. The American Diabetes Association's criteria were used to define diabetes, and included patients with a fasting plasma glucose level ≥ 126 mg/dL or a casual plasma glucose level ≥ 200 mg/dL or receiving treatment for diabetes mellitus [15].

Patients not receiving active treatment were required to have 2 abnormal evaluations (blood pressure or plasma glucose) before they could be classified as hypertensive or diabetic; the first abnormal evaluation was considered the date of onset. Treatment of hypertension and diabetes was not dictated by specific protocols, and initiation and discontinuation of therapy and choice of therapy was at the discretion of the transplantation physician.

Body mass index (BMI) was calculated using the formula BMI = weight (kg) / [height (m)]^2. Centers for Disease Control and Prevention's criteria were used to categorize BMI [16]. For adults (aged ≥ 20 years), BMI < 18.5 was considered underweight, BMI 18.5-24.9 was normal, BMI 25.0-29.9 was overweight, and BMI ≥ 30.0 was obese. For children (aged 2-19 years), a BMI-for-age growth chart was

used to obtain a percentile ranking; < 5th percentile was underweight, 5th-85th percentile was normal, 85th-95th percentile was overweight, and > 95th percentile was obese.

Cumulative prednisone dose (or the equivalent for other corticosteroids) was estimated by chart review. For this analysis, exposure to prednisone was categorized as none, cumulative dose ≤ 0.25 mg/kg/day, or cumulative dose > 0.25 mg/kg/day. For comparison, a daily prednisone dose of 0.25 mg/kg in an adult weighing 60 kg given for 1 year would correspond to a total cumulative prednisone dose of 5400 mg.

Statistical Analysis

The primary objective of this study was to describe the natural history of hypertension and diabetes among allogeneic HCT survivors who had survived until 1 year post-HCT and to examine risk factors that may predict the persistence of these disorders beyond 2 years post-HCT. We chose the 2-year time point for our analysis because this allowed for complete ascertainment of events (onset or resolution of hypertension and diabetes) in our study cohort. At our transplantation center, all patients are followed for at least 2 years post-HCT.

Patient and transplant characteristics were compared using the χ^2, Fisher exact, or Wilcoxon rank-sum test as appropriate. Overall survival (OS) was determined using the Kaplan-Meier method. Cumulative incidence estimates were obtained where applicable, and death was considered a competing risk. Multivariate logistic regression analysis was performed to evaluate risk factors for development of hypertension and diabetes post-HCT and for their persistence at 2 years post-HCT. The following variables were considered for both analyses: age, sex, BMI (at HCT and at 2 years post-HCT), conditioning regimen intensity, history of hypertension or diabetes before HCT, renal failure (glomerular filtration rate < 60 mL/min/1.73 m^2 at any time within 2 years post-HCT), CsA exposure, and prednisone (or equivalent) exposure. Because prednisone use was highly correlated with aGVHD and cGVHD, the latter were not included in the models. SAS version 9.1 (SAS Institute, Cary, NC) was used for all analyses. All *P* values are 2-sided.

RESULTS

Patients

A total of 180 HCT recipients (106 adult patients and 74 pediatric patients) met the study inclusion criteria. Patient-, disease-, and transplant-related characteristics are summarized in Table 1. The probability of OS at 2 years post-HCT was 83% (95% confidence interval [CI], 78%-88%) for the whole cohort, 76% (95% CI, 68%-84%) for adult recipients, and 92% (95% CI, 86%-98%) for pediatric recipients. In the 24 patients who died between 1 and 2 years post-HCT, the most common cause of death was disease recurrence (50%), followed by GVHD (17%) and infections (17%).

GVHD and Exposure to CsA and Prednisone

Table 2 describes GVHD characteristics and details of exposure to CsA and prednisone within the first 2 years post-HCT. Compared with the pediatric HCT recipients, the adult recipients had a higher frequency of both aGVHD (61% vs 32%; $P < .01$) and cGVHD (44% vs 10%; $P < .01$). Adults were more likely to be exposed to CsA for prophylaxis or treatment of GVHD (98% vs 84%; $P < .01$), but were less likely to have used CsA for an extended period (> 6 months in 49% vs 74%; $P < .01$). However, the proportion receiving CsA therapy at 2 years post-HCT was similar in the adult and pediatric recipients (12% vs 20%; $P = .15$).

Prednisone was used to treat GVHD in 105 patients (58%), who received a median cumulative prednisone dose of 3450 mg (range, 825-12,000 mg). The rate of prednisone use for treating GVHD was comparable in adults and children (63% vs 51%; $P = .11$); however, adult recipients had a longer duration of exposure to prednisone (> 12 months in 36% vs 20%; $P = .02$) and were more likely to continue prednisone beyond 2 years post-HCT (30% vs 16%; $P = .03$). But, pediatric recipients more frequently received a higher cumulative dose (> 0.25 mg/kg/day) of prednisone (34% vs 5%; $P < .01$).

Hypertension after Allogeneic HCT

The overall prevalence of hypertension within the first 2 years post-HCT was 70% (95% CI, 63%-77%) and was similar in adults and children (68% vs 73%; $P = .47$) (Table 3 and Figure 1). The majority of patients with post-HCT hypertension (89%) were receiving drug therapy for hypertension. New-onset hypertension occurred during this period in 61% of patients at a median of 1 month (range, 1-18 months) post-HCT. Of these 109 patients with new-onset hypertension, 88 experienced onset within 4 weeks of initiating CsA therapy. In multivariate analysis, CsA exposure at any time post-HCT was the sole factor predictive for development of new-onset hypertension within the first 2-years post-HCT (relative risk, 1.6; 95% CI, 1.1-2.5; $P = .03$ vs patients who did not receive CsA).

Of the 126 patients with post-HCT hypertension, 109 survived until 2 years post-HCT; among these,

Table 1. Patient, disease, and transplant characteristics

Characteristics	All patients	Adult patients (age ≥ 18 years)	Pediatric patients (age < 18 years)
Total patients, n	180	106	74
Median age, years (range)	27 (0.2-69)	48 (19-69)	8 (0.2-17)
Sex, n (%)			
Male	102 (57%)	62 (59%)	40 (54%)
Female	78 (43%)	44 (42%)	34 (46%)
Hypertension pre-HCT, n (%)	17 (9%)	13 (12%)	4 (5%)
Diabetes mellitus pre-HCT, n (%)	24 (13%)	19(18%)	5 (7%)
History of smoking pre-HCT, n (%)			
Yes	35 (19%)	33 (31%)	2 (3%)
No	83 (46%)	63 (59%)	20 (27%)
Unknown	62 (34%)	10 (9%)	52 (70%)
BMI at HCT, n (%)			
Underweight	7 (4%)	2 (2%)	5 (7%)
Normal weight	75 (42%)	37 (35%)	38 (51%)
Overweight	51 (28%)	38 (36%)	13 (18%)
Obese	34 (19%)	29 (27%)	5 (7%)
Not evaluable (age < 2 years)	13 (7%)	-	13 (18%)
Karnofsky/Lansky score at HCT, n (%)			
90-100	149 (83%)	85 (80%)	64 (86%)
<90	22 (12%)	14 (13%)	8 (11%)
Missing	9 (5%)	7 (6%)	2 (3%)
Diagnosis, n (%)			
Acute myelogenous leukemia	31 (17%)	22 (21%)	9 (12%)
Acute lymphoblastic leukemia	41 (23%)	28 (26%)	13 (18%)
Myelodysplastic syndrome	12 (7%)	9 (9%)	3 (4%)
Chronic myelogenous leukemia	13 (7%)	8 (8%)	5 (7%)
Chronic lymphocytic leukemia	9 (5%)	9 (9%)	0
Non-Hodgkin lymphoma	22 (12%)	21 (20%)	1 (1%)
Fanconi's anemia	17 (9%)	0	17 (23%)
Aplastic anemia	8 (4%)	4 (4%)	4 (5%)
Inherited disorders of metabolism	17 (9%)	0	17 (23%)
Other	10 (6%)	5 (5%)	5 (7%)
Disease risk, n (%)*			
Standard	99 (55%)	45 (43%)	54 (73%)
High	91 (45%)	61 (57%)	20 (27%)
Donor type, n (%)			
Related donor	63 (35%)	45 (43%)	18 (24%)
Unrelated donor	117 (65%)	61 (57%)	56 (76%)
Conditioning regimen, n (%)			
Myeloablative	119 (66%)	49 (46%)	70 (95%)
Nonmyeloablative	61 (33%)	57 (54%)	4 (5%)
Graft source, n (%)			
Bone marrow	35 (19%)	6 (6%)	29 (39%)
Peripheral blood stem cells	50 (28%)	45 (43%)	5 (7%)
Umbilical cord blood			
Single unit	35 (19%)	3 (3%)	32 (43%)
Two units	60 (33%)	52 (49%)	8 (11%)
HLA match status, n (%)†			
6/6	81 (45%)	50 (47%)	31 (42%)
5/6	38 (21%)	8 (8%)	30 (41%)
4/6	61 (33%)	48 (45%)	13 (18%)
CMV serostatus, n (%)			
Positive (donor and/or recipient)	88 (49%)	52 (49%)	36 (49%)
Negative (donor and recipient)	92 (51%)	54 (51%)	38 (51%)
Median follow-up, months (range)	41 (25-61)	43 (25-61)	40 (25-61)
Follow-up status, n (%)			
Alive at 1 year	180 (100%)	106 (100%)	74 (100%)
Alive at 2 years	156 (87%)	86 (81%)	70 (95%)

HCT indicates hematopoietic cell transplantation; BMI, body mass index; CMV, cytomegalovirus.

*Standard risk disease included acute leukemia in first complete remission, chronic myelogenous leukemia in first chronic phase, myelodysplastic syndrome (refractory anemia only), and nonmalignant hematologic disorders; all other diagnoses were categorized as high-risk disease.

†Worst match for double umbilical cord blood transplantation.

37 had persistent hypertension at 2 years (34%)-(Figure 2). Hypertension had resolved in the other 66% of patients. Patients with persistent hypertension were more likely to have had a history of hypertension before undergoing HCT (Table 4). In multivariate analysis, the relative risk of persistent hypertension at 2 years was 3.1 (95% CI, 1.1-8.3; $P = .03$) in patients with pre-HCT hypertension compared with those who were normotensive before HCT.

Table 2. GVHD and its management within the first 2 years post-HCT

	All patients	Adult patients (age ≥ 18 years)	Pediatric patients (age < 18 years)
Total patients, n	180	106	74
Acute GVHD (grade II-IV), n (%)	89 (49%)	65 (61%)	24 (32%)
Median time to onset, days (range)	34 (12-86)	33 (15-86)	35 (12-78)
Chronic GVHD, n (%)	54 (30%)	47 (44%)	7 (10%)
Median time to onset, months (range)	5 (3-22)	5 (3-22)	5 (3-9)
Cyclosporine use, n (%)*	166 (92%)	104 (98%)	62 (84%)
Median duration of use, months (range)	9 (3-24)	6 (3-24)	12 (3-24)
Duration of use, n			
< 6 months	73	54	19
6-12 months	53	27	26
> 12 months	40	23	17
Receiving cyclosporine at 2 years, n	28	13	15
Prednisone use, n (%)†	105 (58%)	67 (63%)	38 (51%)
Median duration of therapy, months (range)	11 (2-24)	13 (4-24)	8 (2-24)
Duration of therapy, n			
≤ 12 months	55	29	23
> 12 months	50	38	15
Receiving prednisone at 2 years, n	44	32	12
Cumulative dose of prednisone			
Median dose, mg/kg/day (range)	0.2 (0.04-3.7)	0.1 (0.04-0.7)	0.4 (0.1-3.7)
Cumulative dose, n			
≤ 0.25 mg/kg/day	75	62	13
> 0.25 mg/kg/day	30	5	25

HCT indicates hematopoietic cell transplantation; GVHD, graft-versus-host disease.
All patients included in this study had survived at for at least 1 year post-HCT.
*For prophylaxis or treatment of GVHD.
†For treatment of acute or chronic GVHD.

Diabetes after Allogeneic HCT

The overall prevalence of diabetes within the first 2 years post-HCT was 30% (95% CI, 23%-37%) (Table 3 and Figure 1). The prevalence was comparable in the adult and pediatric recipients (30% vs 30%; $P = .95$). Some 76% of patients with diabetes had received insulin therapy post-HCT. New-onset diabetes occurred in 17% of patients at a median of 1 month (range, 1-12 months) post-HCT. In these 30 patients with new-onset diabetes, 22 experienced onset within 4 weeks of initiating corticosteroid therapy for GVHD. In multivariate analysis, prednisone exposure was the only risk factor significantly associated with the development of new-onset diabetes within the first 2 years post-HCT. Compared with patients with no prednisone exposure, the relative risk of diabetes was 1.9 (95% CI, 1.0-3.7; $P = .05$) in patients receiving a cumulative prednisone dose ≤ 0.25 mg/kg/day and 3.6 (95% CI, 1.7-7.5; $P < .01$) in patients receiving a cumulative prednisone dose of 0.25 mg/kg/day.

Of the 54 patients with post-HCT diabetes, 47 survived until 2 years post-HCT. Persistent diabetes was present in 15 of these patients (32%), whereas it had resolved in 32 patients (68%) by the 2-year visit (Figure 2). Compared with patients with resolved diabetes, those with persistent diabetes were more

Table 3. Hypertension and diabetes mellitus in the first 2 years post-HCT

	All patients	Adult patients (age ≥ 18 years)	Pediatric patients (age < 18 years)
Total patients, n	180	106	74
Hypertension post-HCT			
Prevalence, n (%)	126 (70%)	72 (68%)	54 (73%)
New-onset hypertension, n (%)	109 (61%)	59 (56%)	50 (68%)
Median time of onset, months (range)*	1 (1-18)	1 (1-18)	1 (1-18)
Hypertension resolved by 2 years, n	87	51	36
Median duration, months (range)†	5 (1-24)	5 (1-20)	5 (2-24)
Diabetes post-HCT			
Prevalence, n (%)	54 (30%)	32 (30%)	22 (30%)
New-onset diabetes, n (%)	30 (17%)	13 (12%)	17 (23%)
Median time of onset, months (range)*	1 (1-12)	1 (1-9)	1 (1-12)
Diabetes resolved by 2 years, n	32	18	14
Median duration, months (range)†	3 (2-17)	3 (2-17)	3 (2-12)

HCT indicates hematopoietic cell transplantation.
All patients included in this study had survived at for at least 1 year post-HCT
*From the date of HCT
†From the date of onset of hypertension or diabetes

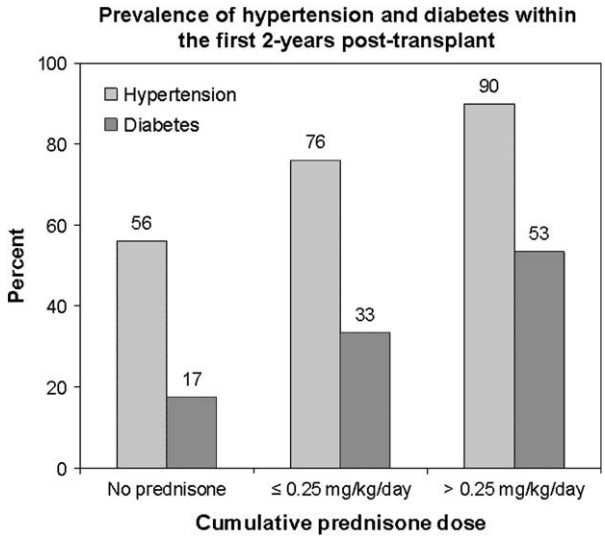

Figure 1. Prevalence of hypertension and diabetes within the first 2 years post-HCT by prednisone (or equivalent) exposure. Our study cohort comprised of patients who had survived for >1 year after transplantation.

likely to have a history of pre-HCT diabetes and exposure to higher cumulative doses of prednisone (Table 4). Both of these factors also significantly influenced the risk of persistent diabetes at 2 years in multivariate analysis; the relative risk was 5.7 (95% CI, 1.5-21.2; $P = .01$ vs no history) in patients with a history of pre-HCT diabetes and 4.1 (95% CI, 1.0-18.2; $P = .05$ vs no prednisone) in patients receiving a cumulative prednisone dose of > 0.25 mg/kg/day. Exposure to a cumulative prednisone dose ≤ 0.25 mg/kg/day did not increase these risks (relative risk, 1.3; 95% CI, 0.3-5.8; $P = .76$).

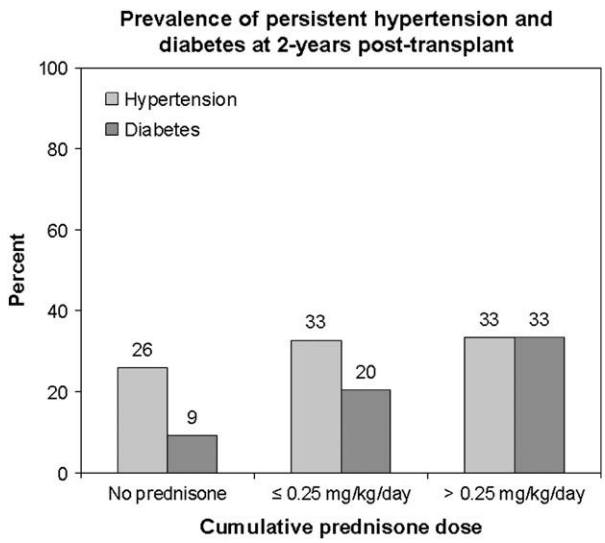

Figure 2. Prevalence of persistent hypertension and diabetes at 2-years post-HCT by prednisone (or equivalent) exposure. Our study cohort comprised of patients who had survived for >1 year after transplantation.

DISCUSSION

Our data provide important insights into the natural history of early-onset hypertension and diabetes in allogeneic HCT recipients. Both diseases are highly prevalent (hypertension, 70%; diabetes, 30%) in the first 2 years post-HCT. In patients with incident hypertension and diabetes, onset typically occurs very early post-HCT (median time to onset, 1 month for both disorders). Onset of hypertension usually corresponds to initiation of CsA therapy, and onset of diabetes frequently occurs soon after initiation of corticosteroid therapy for GVHD. Both hypertension and diabetes subsequently resolve in a large proportion of HCT recipients, and their overall duration is typically short in these patients (median duration, 5 months for hypertension and 3 months for diabetes). As can be expected, a history of hypertension and diabetes before HCT increases the risk after HCT, and both disorders are less likely to resolve with long-term follow-up in these patients. Exposure to CsA is associated with post-HCT hypertension. Exposure to high-dose prednisone (or equivalent) is associated with post-HCT diabetes and its persistence through 2 years post-HCT.

The prevalence of early hypertension and diabetes in allogeneic HCT recipients has been reported, particularly in clinical trials comparing the use of tacrolimus and CsA for GVHD prophylaxis. But, these studies could not address the clinical course post-HCT, especially given that some of the risk factors for their development may change and even resolve over time. Hypertension has been reported in 21%-63% of patients; hyperglycemia requiring treatment, in 10%-70% [17-20]. At least one study reported a significantly lower risk of hypertension with tacrolimus [19], although this was not confirmed in other studies. Although the risk factors and natural history of hypertension and diabetes occurring in the early post-HCT period among HCT recipients have not yet been well described, certain generalizations can be extrapolated from experience in solid organ transplant recipients. Calcineurin inhibitor–induced hypertension occurs very frequently in recipients of heart, lung, liver, and kidney transplantation, with reported prevalences ranging from 65% to 100% [21-23]. Its origin is most likely multifactorial, including renal vasoconstriction, increased systemic vascular resistance, increased sympathetic nervous tone, and activation of the renin-angiotensin system. Hypertension is seen more frequently in patients receiving CsA-based immunosuppression compared with those receiving tacrolimus-based regimens. In general, corticosteroids are not considered a risk factor for hypertension, although high-dose corticosteroid therapy can temporarily increase this risk [21,24]. Sirolimus and MMF have not been observed to have a hypertensive effect. In contrast to solid organ transplant recipients,

Table 4. Comparison of patients with persistent and resolved hypertension or diabetes at 2 years post-HCT

	Hypertension at 2 years*			Diabetes at 2 years†		
	Resolved	Persistent	P‡	Resolved	Persistent	P‡
Total patients, n	72	37		28	19	
Median age, years (range)	23 (0.6-68)	21 (1-59)	.69	23 (1-57)	22 (2-59)	.51
Male, n (%)	40 (56%)	23 (62%)	.51	18 (64%)	10 (53%)	.42
Pre-HCT hypertension, n (%)	4 (6%)	7 (19%)	.02	6 (21%)	9 (47%)	.06
Pre-HCT diabetes, n (%)	11 (15%)	5 (14%)	.81	1 (4%)	6 (32%)	< .01
Myeloablative conditioning, n (%)	54 (75%)	26 (70%)	.60	23 (82%)	14 (74%)	.49
Renal failure post-HCT, n (%)§	27 (38%)	20 (54%)	.09	13 (46%)	12 (63%)	.26
Cyclosporine use > 12 months, n (%)	13 (18%)	8 (22%)	.65	12 (43%)	13 (68%)	.08
Cumulative prednisone dose > 0.25 mg/kg/day, n (%)	17 (24%)	7 (19%)	.58	5 (18%)	9 (47%)	.02

HCT indicates hematopoietic cell transplantation.

All patients included in this study had survived at for at least 1 year post-HCT.

*Excludes 17 patients (15 resolved, 2 persistent) with prevalent hypertension who died before the 2-year post-HCT anniversary time point.

†Excludes 7 patients (4 resolved, 3 persistent) with prevalent diabetes who died before the 2-year post-HCT anniversary time point.

‡Using the χ^2 test, Fisher's exact test, or Wilcoxon's rank-sum test, as appropriate.

§Defined as calculated glomerular filtration rate <60 mL/min/1.73 m^2 at any time within the first 2 years post-HCT.

HCT recipients discontinue immunosuppression if they do not have active GVHD. Although there are no data on the long-term effects of calcineurin inhibitors, we speculate that these inhibitors' effects on the renovascular system are reversible, given the large number of patients in our study who were able to discontinue therapy for hypertension.

As with hypertension, we have only limited knowledge of the risk factors, natural history, and impact of hyperglycemia and diabetes occurring early post-HCT. One study found that hyperglycemia was commonly associated with the use of total parenteral nutrition in HCT recipients and was a risk factor for infections, blood product support, and delayed granulocyte and platelet engraftment [25]. In a recent retrospective analysis by Hammer et al. [26], at least 1 episode of hyperglycemia (defined as blood glucose >150 mg/dL) occurred in 93% of 1175 adult allogeneic HCT recipients within the first 100 days after transplantation. Hyperglycemia and increased glucose variability led to a significantly higher risk of infection and nonrelapse mortality (NRM). In solid organ transplant recipients, tacrolimus has been reported to be a major risk factor for new-onset diabetes, with CsA-containing immunosuppressive regimens associated with lower risk [27-29]. Other important risk factors for impaired glucose tolerance in this population include older recipient age, obesity, and preexisting diabetes [28]. The risk of post-HCT diabetes after solid organ transplantation also is increased by exposure to higher doses of corticosteroids, and glucose tolerance usually improves with tapering of corticosteroid dose [30-32]. In our cohort of HCT recipients, we also identified exposure to higher doses of prednisone as one of the most important risk factors for the development and persistence of diabetes.

Our study has the usual limitations of a retrospective cohort study design. To minimize misclassification, definitions of hypertension and diabetes were established a priori, and patients were required to have at least 2 abnormal measurements. There were no specific guidelines for management; in particular, patients with hypertension may have continued therapy despite its resolution. Nonetheless, our observations are very relevant, because they reflect routine clinical practice. We did not examine the persistence of hypertension and diabetes beyond 2 years post-HCT. Because patients without cGVHD are discharged to their referring physicians at 2 years, follow-up beyond this time point would have led to a disproportionate number of patients with cGVHD in the cohort, and then we would have not been able to identify those patients without GVHD in whom hypertension and diabetes had resolved. The duration of hypertension and diabetes was relatively short (< 6 months) in patients in whom these disorders improved, and those patients with persistent hypertension and diabetes at 2 years post-HCT can be expected to have a low likelihood of subsequent resolution. Finally, we had no information regarding pre-HCT treatment exposures, which also may contribute to the risk of post-HCT hypertension and diabetes.

In conclusion, hypertension and diabetes are common early complications in both adult and pediatric HCT recipients. Exposure to CsA increases the risk of hypertension, whereas exposure to high-dose corticosteroids increases the risk of diabetes. That both hypertension and diabetes resolve in the majority of HCT survivors is reassuring; however, hypertension and diabetes can persist long term in some HCT survivors, and aggressive screening and treatment strategies may be needed to prevent late cardiovascular complications in these patients. Further studies are needed to address some important unanswered questions, including the impact of limited-duration hypertension and glucose intolerance on the risk of cardiac and renal late effects and the optimal therapy for these complications.

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