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High prevalence of metabolic syndrome after allogeneic hematopoietic cell transplantation

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Abstract

We conducted a cross-sectional study to estimate the prevalence of metabolic syndrome, a clustering of risk factors associated with cardiovascular disease, among 86 adults who had allogeneic hematopoietic-cell transplant (HCT) as compared with 258 age- and gender-matched US population controls selected from the 2005–2006 National Health and Nutrition Examination Survey database. The median age at study enrollment was 50 years (range, 21–71), and patients were at a median of 3 years (range, 1–21) from HCT. The prevalence of metabolic syndrome was 49% (95% confidence intervals (CI), 38–60%) among HCT recipients, a 2.2-fold (95% CI, 1.3–3.6, *P*=0.002) increase compared with controls. The prevalence rates of elevated blood pressure and hypertriglyceridemia were significantly higher among HCT recipients than among controls, but the prevalence rates of abdominal obesity, elevated blood glucose and low high-density lipoprotein cholesterol were not. HCT survivors with metabolic syndrome were more likely to have microalbuminuria (43 vs 10%) and elevated creatinine (31 vs 11%). No patient, donor or transplant characteristics were associated with the diagnosis of metabolic syndrome. We conclude that metabolic syndrome occurs frequently among allogeneic HCT survivors who are seen by transplant physicians. Approaches to screening, prevention and management of metabolic syndrome should be developed for HCT recipients.

Keywords

allogeneic stem cell transplantation; metabolic syndrome; late complications; National Health and Nutrition Examination Survey

Introduction

Metabolic syndrome is a clustering of risk factors for cardiovascular disease characterized by abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance, and a proinflammatory and prothrombotic state.[1-4] Metabolic syndrome has a prevalence of 20–30% among the US adult population.[5,6] Individuals with metabolic syndrome are twice as

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likely to develop atherosclerotic cardiovascular disease than those without metabolic syndrome.[7]

Pediatric and adult cancer survivors have been reported to be at increased risk for developing insulin resistance and metabolic syndrome, and for cardiovascular mortality.[8-15] In a self-reported survey, adult hematopoietic-cell transplant (HCT) recipients were observed to have a higher risk of diabetes and hypertension compared with sibling controls.[16] Allogeneic HCT recipients have also been reported to be at high risk for developing premature arterial vascular disease.[17,18]

Allogeneic HCT recipients may be particularly predisposed to develop metabolic syndrome through several mechanisms, including conditioning regimen-mediated damage to the neurohormonal system and vascular endothelium, and the immunological and inflammatory effects of the allogeneic graft and subsequent GVHD and its therapy. Screening for metabolic syndrome and its individual components could allow for early initiation of risk factor modification therapy that could subsequently reduce the risk of late cardiovascular morbidity and mortality. However, the prevalence and risk factors of metabolic syndrome after allogeneic HCT have not been well established.[15,19] We conducted a cross-sectional study to assess the prevalence of metabolic syndrome among adult survivors with a history of allogeneic HCT.

Patients and methods

Patients and study measurements

Patients who were 18 years or older at HCT and alive without recurrence of the primary disease at least 1 year afterward were eligible for this study, regardless of the presence or absence of active GVHD. Patients were recruited at three centers (Fred Hutchinson Cancer Research Center, University of Minnesota and Vanderbilt University) between July and October 2007 when they returned for scheduled clinic visits. Each participating center obtained Institutional Review Board (IRB) approval.

Metabolic syndrome was defined according to the National Cholesterol Education Program's Adult Treatment Panel III criteria by the presence of at least three of its five defining characteristics: abdominal obesity, elevated blood pressure, raised plasma glucose, raised triglycerides and reduced high-density lipoprotein cholesterol (HDL-C).[1,2]

All patients had measurement of weight, height, waist circumference, blood pressure, fasting blood glucose, fasting blood lipid profile, serum creatinine, serum high-sensitivity C-reactive protein and urine microalbumin. Clinical information was collected using a standardized case report form.

National Health and Nutrition Examination Survey

The National Health and Nutrition Examination Survey consists of a series of population-based surveys and in-person examinations conducted by the National Center for Health Statistics.[20] A complex multistage sampling scheme is used to collect health and nutrition information on a large nationally representative sample of the non-institutionalized US population. Data are collected in 2-year time periods. A structured interview is used to collect information on disease history, health status and diet. A health examination and laboratory measures are completed in the mobile examination center by a trained medical professional. For the current study, we used data from the 2005–2006 questionnaires, examinations and laboratory measures. Fasting laboratory results were collected from 3352 participants, 12 years of age or older, who participated in the mobile examination in the morning. Among this cohort, 731 participants were between 21 and 75 years of age and had complete data available for all variables necessary to ascertain the presence or absence of metabolic syndrome. This

subsample was stratified by 5-year age group and gender and used as the base for the randomly selected comparison group. Details of data collection and laboratory procedures can be found at www.cdc.gov/nchs/nhanes.htm.

Statistical methods

The primary end point was to estimate the overall prevalence of metabolic syndrome among allogeneic HCT survivors. The prevalence of metabolic syndrome and each of its components was compared between HCT recipients and controls. Three to one frequency matching on gender and 5-year age group was used to select a random sample of controls from the National Health and Nutrition Examination survey participants. Given the general population prevalence of 27%,[6] we estimated that a sample size of 85 patients would provide 80% power (α=0.05) to detect an odds ratio (OR) of 1.5 or greater. Frequencies and percentages were compared with χ^2 statistics. Results are reported as OR with 95% confidence intervals (CIs).

We also performed an exploratory analysis to evaluate whether any of the following variables were risk factors for metabolic syndrome or its individual components among HCT recipients: age at enrollment (≤50 vs >50 years), gender (male vs female), donor source (related vs unrelated), conditioning regimen intensity (myeloablative vs non-myeloablative), chronic GVHD (none or resolved vs active) and treatment with corticosteroids (none or remote vs current use) or calcineurin inhibitors or sirolimus (none or remote vs current use) for the management of chronic GVHD. These associations were evaluated in multivariate logistic regression models, further adjusting for time since transplant and transplant center. SAS version 9.1 (Cary, NC, USA) was used for all analyses.

Results

Eighty-six patients were enrolled at three centers (Table 1). The median age at study enrollment was 50 years (range, 21–71) and the median follow-up since transplantation was 3 years (range, 1–21). At the time of study enrollment, 79% of patients had active GVHD, 61% were under treatment with systemic corticosteroids and 51% were taking calcineurin inhibitors or sirolimus.

Two hundred and fifty-eight age- and gender-matched controls were selected from the National Health and Nutrition Examination Survey population. Controls had a median body mass index of 25.7 kg/m^2 (14.7–67.3) compared to 27.0 kg/m^2 (17.3–43.7) among HCT recipients.

The overall prevalence of metabolic syndrome among HCT recipients was 49% (95% CI, 38–60%) (Table 2), a 2.2-fold (95% CI, 1.3–3.6, P=0.002) increase when compared with age- and gender-matched controls. The prevalence rates of elevated blood pressure and hypertriglyceridemia were also statistically significantly higher among HCT recipients, but the prevalence rates of abdominal obesity, elevated blood glucose and low HDL-C were not.

Seventy-eight percentage of the HCT recipients had two or more components of metabolic syndrome. Six patients with untreated diabetes (fasting blood glucose ≥126 mg per 100 ml) and 12 patients with untreated hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) were identified. Also, 30 patients had untreated dyslipidemia (fasting triglycerides >200 mg per 100 ml, HDL-C <40 mg per 100 ml or low-density lipoprotein cholesterol >160 mg per 100 ml) that potentially could have benefited from lifestyle interventions or drug therapy.

The prevalence of metabolic syndrome among patients within 2 years of transplant was comparable to those with follow-up for more than 2 years (57 vs 43%, P=0.20). Similarly, there was no significant difference in the prevalence of each component according to follow-

up less than or more than 2 years. Patients with actively treated and those with no or resolved chronic GVHD also had similar prevalence rates of metabolic syndrome (47 vs 56%, *P*=0.52) and its individual components.

Age, gender, donor source, conditioning regimen intensity, GVHD status, corticosteroid or calcineurin inhibitor use were not significantly associated with metabolic syndrome among HCT recipients (Table 3). Furthermore, we did not observe an association between these risk factors and individual components of metabolic syndrome except for the association of elevated blood pressure with older age (OR 3.7 (95% CI, 1.1–12.0) vs age ≤50 years) and female gender (OR 3.1 (95% CI, 1.0–9.5) vs male gender).

Microalbuminuria (>20 mg/g creatinine) was detected more frequently among HCT recipients with metabolic syndrome than among those without this disorder (43 vs 10%, *P*=0.01). Elevated serum creatinine (>1.5 mg per 100 ml, 31 vs 11%, *P*=0.03) and C-reactive protein (>3 mg/l, 69 vs 46%, *P*=0.04) were also more prevalent among HCT recipients with metabolic syndrome.

Discussion

We report a high prevalence of metabolic syndrome (49%) and elevated triglycerides (58%) and elevated blood pressure (56%) among adult allogeneic HCT survivors compared with general population controls. Although not significantly more common than controls, a large proportion of HCT recipients also had elevated waist circumference (44%), elevated fasting glucose (41%) and reduced HDL-C (41%). For comparison purposes, the general age-adjusted adult US population prevalence of metabolic syndrome has been reported to be 27%; the prevalence of its individual components is 44% for abdominal obesity, 40% for low HDL-C, 39% for elevated blood pressure, 33% for hypertriglyceridemia and 31% for elevated fasting glucose.[6]

A high prevalence of metabolic syndrome among transplant recipients has also been recently reported by Annaloro *et al.*[19] In their cross-sectional study that included 39 allogeneic HCT recipients who had survived for at least 5 years since transplantation and had discontinued all immunosuppressive therapy, 12 (31%) had metabolic syndrome. Hypertriglyceridemia was the most prevalent component of metabolic syndrome, and this was followed in frequency by abdominal obesity, hyperglycemia, high blood pressure and low HDL-C, respectively. Age, insulin resistance, hypogonadism and serum leptin levels were observed to be predictive of metabolic syndrome, whereas a history of GVHD was not.

Taskinen *et al.*[15] studied impaired glucose tolerance and dyslipidemia among 23 pediatric allogeneic HCT recipients (median age 20 years at study enrollment) who had survived for 3–18 years after HCT and compared them to 13 leukemia survivors who did not receive a transplant and 23 healthy controls. HCT survivors had a significantly higher prevalence of hyperinsulinemia (52 vs 31 vs 0%), abnormal glucose metabolism (43 vs 8 vs 0%) and hypertriglyceridemia (39 vs 8 vs 4%). A similar increased prevalence of insulin resistance among 34 pediatric HCT survivors has also been described by Lorini *et al.*[21]

In an analysis from the Bone Marrow Transplant Survivor Study, a retrospective cohort study that compared self-reported late complications between transplant recipients who had survived for 2 years or more and sibling controls, allogeneic HCT recipients were observed to have a significantly higher risk of diabetes and hypertension compared with controls and recipients of autologous HCT.[16] Furthermore, the risks of diabetes and hypertension remained high irrespective of whether patients had received immunosuppressive therapy within the 2 years before study enrollment. A history of chronic GVHD was not found to be associated with an increased risk of either of these two diseases.

As reported by others, we did not find an association between metabolic syndrome or its individual components and GVHD. Also, the use of corticosteroids or calcineurin inhibitors was not associated with the risk of developing metabolic syndrome, although our study was not specifically designed and powered for risk factor analysis. Glucocorticoids have direct effects on the heart and blood vessels, and chronic excessive activation of glucocorticoid receptors induces obesity, insulin resistance, dyslipidemia and hypertension.[22] A high risk of insulin resistance and metabolic syndrome has been reported after solid organ transplantation, especially among kidney allograft recipients.[23-26] Immunosuppression with corticosteroids, calcineurin inhibitors and sirolimus is thought to have an important role in the pathogenesis of insulin resistance and dyslipidemia in this population.[23] Although mixed results have been reported, early withdrawal of corticosteroids might not alter the risks of glucose intolerance, and new-onset diabetes tends to persist after the withdrawal of steroids.[27–29] Further investigation is needed to identify the specific subgroups of HCT recipients at highest risk for developing this syndrome and to study the natural history of these metabolic risk factors after the withdrawal of immunosuppressive treatment. Additional studies should evaluate the prevalence of metabolic syndrome in autologous transplant populations, patients with hematologic malignancies treated with conventional chemotherapy and in solid organ transplant recipients. These populations would shed further light on the potential etiologies for increased rates of metabolic syndrome in the allogeneic HCT population as well as possibly unearth other vulnerable populations that could benefit from heightened attention to the risks of metabolic syndrome.

We also observed an association between C-reactive protein and metabolic syndrome, as has been reported in general population-based studies.[30] Patients with chronic GVHD have also been reported to have high C-reactive protein and leptin levels.[31,32] Future studies of metabolic syndrome among HCT recipients should include other biomarkers such as uric acid, plasminogen activator inhibitor-1, cytokines, adiponectin, leptin and non-esterified fatty acids.[2] Metabolic syndrome has also been identified as an important risk factor for chronic kidney disease,[33,34] and the elevated rates of increased creatinine and microalbuminuria among HCT recipients with the metabolic syndrome need further exploration.

We could not determine why a relatively large proportion of patients had previously undiagnosed or untreated cardiovascular risk factors. Chronic GVHD was very prevalent in our cohort and its active management may have taken priority over identification and treatment of risk factors for cardiovascular disease, which may not manifest till late after transplantation. Also, compared to transplant physicians, diabetes, hypertension and dyslipidemia may be managed more aggressively in HCT survivors who are followed by an internist or within a comprehensive survivorship clinic. More studies are needed to identify the barriers to early recognition and treatment of these risk factors among HCT recipients.

Our cohort was drawn from a sample of patients returning to their transplant center for long-term follow-up. Hence, our study population is enriched with patients with transplant-related problems such as chronic GVHD. On account of this limitation, we are not able to comment on the overall prevalence of metabolic syndrome among all HCT recipients. Nonetheless, several practical implications emerge from the high prevalence of metabolic syndrome observed in our cross-sectional study. First, late effect assessment should include routine screening for this disorder and its individual components, with the expectation that many patients will have abnormal findings. Referral to a comprehensive survivorship clinic or an internist or endocrinologist should be considered for patients in whom these abnormalities are detected. Second, HCT recipients should be offered appropriate prevention and treatment, as has been recommended for the general population to prevent overt cardiovascular disease, diabetes and loss of renal function.[3,7] Physicians may be reluctant to initiate treatment because they believe that diabetes, hypertension and dyslipidemia are transient phenomena that will

resolve with time and withdrawal of immunosuppression. Our data and the literature offer little support for this assumption. Finally, studies are needed to evaluate the safety and efficacy of various management options for transplant recipients and to determine whether long-term morbidity and mortality can be reduced by better recognition and treatment of metabolic syndrome. As we know that transplant survivors are at increased risk for late cardiovascular complications, it behoves physicians to try to mitigate known predisposing conditions as part of a comprehensive approach to survivorship care.

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Table 1

Patient and treatment characteristics

Characteristic	***Patients (N=86)***
Site, N *(%)*	
Fred Hutchinson cancer research center	57 (66)
University of Minnesota	24 (28)
Vanderbilt university	5 (6)
Median age at study enrollment (range), years	50 (21–71)
Median age at transplant (range), years	45 (18–68)
Median time since transplant (range), years	3 (1–21)
Gender, N *(%)*	
Male	55 (64)
Female	31 (26)
Pre-transplant comorbidities, N *(%)*	
Hypertension	8 (9)
Diabetes mellitus	5 (6)
Hyperlipidemia	8 (9)
Diagnosis, N *(%)*	
Acute lymphoblastic leukemia	12 (14)
Acute myeloid leukemia	37 (43)
Chronic myeloid leukemia	10 (12)
Non-Hodgkin's lymphoma	13 (15)
Multiple myeloma	5 (6)
Other	9 (11)
Donor source, N *(%)*	
Related	52 (60)
Unrelated	34 (40)
Graft source, N *(%)*	
Peripheral blood	74 (86)
Bone marrow	7 (8)
Umbilical cord blood	5 (6)
Conditioning regimen, N *(%)*	
Myeloablative	49 (57)
Non-myeloablative	37 (43)
TBI-based conditioning, *N* (%)	66 (77)
GVHD prophylaxis	
CsA+MTX	35 (41)
CsA+mycophenolate mofetil	32 (37)
Other	19 (22)
Chronic GVHD, N *(%)*	
None	13 (15)
Resolved	5 (6)
Active	68 (79)
Treatment with systemic corticosteroids, N *(%)*[a]	
None	15 (17)
Remote	19 (22)
Current	52 (61)
Treatment with calcineurin inhibitors or sirolimus, N *(%)*[a]	
None	16 (19)
Remote	26 (30)
Current	44 (51)
Median body mass index (range), kg/m^2	27.0 (17.3–43.7)

[a] As therapy for chronic GVHD.

Table 2

Prevalence of metabolic syndrome and its individual components among allogeneic HCT and NHANES controls

Component	HCT recipients		NHANES controls		Odds ratio (95% CI)
	N	*Prevalence, % (95% CI)*	N	*Prevalence, % (95% CI)*	
Total subjects	86		258		
Metabolic syndrome	42	49 (38–60)	78	30 (25–36)	2.2 (1.3–3.6)
Individual components of metabolic syndrome[a]					
Elevated triglycerides (≥150 mg per 100 ml or on drug treatment for elevated triglycerides)	50	58 (48–68)	90	35 (29–41)	2.6 (1.6–4.3)
Elevated blood pressure (≥130mmHg SBP or ≥85mmHg DBP or on drug treatment for hypertension)	48	56 (45–66)	101	39 (33–45)	2.0 (1.2–3.2)
Elevated waist circumference (≥102 cm in men or ≥88 cm in women)	38	44 (34–55)	96	37 (31–43)	1.3 (0.8–2.2)
Elevated fasting glucose (≥100 mg per 100 ml or on drug treatment for elevated glucose)	35	41 (31–51)	110	43 (37–49)	0.9 (0.6–1.5)
Reduced HDL-C (<40 mg per 100 ml in men or <50 mg per 100 ml in women or on drug treatment for reduced HDL-C)	35	41 (31–51)	125	48 (42–55)	0.7 (0.4–1.2)

Abbreviations: CI=confidence interval; DBP=diastolic blood pressure; HCT=hematopoietic cell transplantation; HDL-C=high-density lipoprotein cholesterol; NHANES=National Health and Nutrition Examination Survey; SBP=systolic blood pressure.

[a]Presence of any three of five constitutes the metabolic syndrome.

Table 3

Risk factor analysis for metabolic syndrome and its individual components among allogeneic HCT recipients[a]

Risk factor	N	*Metabolic syndrome, OR (95% CI)*	*Elevated waist circumference, OR (95% CI)*	*Elevated blood pressure, OR (95% CI)*	*Elevated fasting glucose, OR (95% CI)*	*Elevated triglycerides, OR (95% CI)*	*Reduced HDL-C, OR (95% CI)*
Age							
≤50 years[b]	44	1.0	1.0	1.0	1.0	1.0	1.0
>50 years	42	0.9 (0.3–2.6)	1.1 (0.4–3.2)	3.7 (1.1–12.0)	1.5 (0.5–4.5)	0.7 (0.2–2.0)	0.4 (0.1–1.3)
Gender							
Male[b]	55	1.0	1.5	1.0	1.0	1.0	1.0
Female	31	1.5 (0.6–4.0)	1.5 (0.6–4.0)	3.1 (1.0–9.5)	0.5 (0.2–1.3)	0.7 (0.2–1.8)	2.6 (1.0–7.1)
Donor							
Related[b]	52	1.0	1.0	1.0	1.0	1.0	1.0
Unrelated	34	2.0 (0.8–5.2)	1.0 (0.4–2.7)	1.3 (0.5–3.5)	1.3 (0.5–3.3)	2.1 (0.8–5.9)	1.1 (0.4–2.8)
Conditioning							
MA[b]	49	1.0	1.0	1.0	1.0	1.0	1.0
NMA	37	0.7 (0.2–2.0)	0.7 (0.2–2.1)	1.0 (0.3–3.6)	0.5 (0.1–1.5)	0.4 (0.1–1.1)	1.3 (0.4–4.2)
GVHD							
No/resolved[b]	18	1.0	1.0	1.0	1.0	1.0	1.0
Active	68	1.7 (0.4–7.2)	2.2 (0.5–10.1)	0.2 (0.1–1.2)	0.4 (0.1–1.7)	0.6 (0.1–2.5)	1.2 (0.3–5.3)
Steroid use							
No/remote[b]	34	1.0	1.0	1.0	1.0	1.0	1.0
Current	52	0.7 (0.2–2.3)	0.4 (0.1–1.5)	2.0 (0.5–8.4)	1.6 (0.5–5.4)	0.6 (0.2–2.4)	2.2 (0.6–7.7)
CsA/FK use							
No/remote[b]	42	1.0	1.0	1.0	1.0	1.0	1.0
Current	44	0.5 (0.2–1.1)	0.7 (0.3–1.6)	1.8 (0.8–3.8)	0.6 (0.2–1.4)	0.5 (0.2–1.2)	1.5 (0.6–3.6)

Abbreviations: CI=confidence interval; FK=tacrolimus; HCT=hematopoietic cell transplantation; HDL-C=high-density lipoprotein cholesterol; OR=Odds ratio; MA=myeloablative; NMA=non-myeloablative.

[a] Adjusted for time since transplant and transplant center.

[b] Reference group.