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New-Onset Post-Transplant Diabetes Mellitus after Allogeneic Hematopoietic Cell Transplant Is Initiated by Insulin Resistance, Not Immunosuppressive Medications



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A B S T R A C T

New-onset post-transplant diabetes mellitus (PTDM) occurs frequently after allogeneic hematopoietic cell transplant (HCT). Although calcineurin inhibitors and corticosteroids are assumed to be the cause for hyperglycemia, patients developing PTDM have elevated fasting C-peptide levels before HCT and before immunosuppressive medications. To determine if PTDM results from established insulin resistance present before transplant, we performed oral glucose tolerance tests (OGTTs) and measured whole body, peripheral, and hepatic insulin sensitivity with euglycemic hyperinsulinemic clamps before and 90 days after HLA-identical sibling donor HCT in 20 patients without pretransplant diabetes. HCT recipients were prospectively followed for the development of new-onset PTDM defined as a weekly fasting blood glucose ≥ 126 mg/dL or random blood glucose ≥ 200 mg/dL. During the first 100 days all patients received calcineurin inhibitors, and 11 individuals (55%) were prospectively diagnosed with new-onset PTDM. PTDM diagnosis preceded corticosteroid treatment. During the pretransplant OGTT, elevated fasting (87 mg/dL versus 101 mg/dL; $P = .005$) but not 2-hour postprandial glucose levels predicted PTDM diagnosis ($P = .648$). In response to insulin infusion during the euglycemic hyperinsulinemic clamp, patients developing PTDM had lower whole body glucose utilization ($P = .047$) and decreased peripheral/skeletal muscle uptake ($P = .031$) before and after transplant, respectively, when compared with non-PTDM patients. Hepatic insulin sensitivity did not differ. Survival was decreased in PTDM patients (2-year estimate, 55% versus 100%; $P = .039$). Insulin resistance before HCT is a risk factor for PTDM independent of immunosuppression. Fasting pretransplant glucose levels identified PTDM susceptibility, and peripheral insulin resistance could be targeted for prevention and treatment of PTDM after HCT.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is an effective therapy for patients with high-risk hematologic malignancies; however, its efficacy can be diminished by treatment-related complications. The mortality risk increases 3-fold for the 50% of patients developing new-onset post-transplant diabetes mellitus (PTDM) after HCT [1,2]. Despite the

clinical burden of this disease PTDM physiology remains poorly understood, and recommendations for screening are negligible. Current dogma suggests that PTDM is merely a side effect of diabetogenic immunosuppressive medications. Contrary to this belief, we have shown that elevated fasting C-peptide levels before transplant (ie, before immunosuppression or alloractivity) predict both PTDM and mortality [1]. Although our C-peptide data indirectly support the role of established insulin resistance in PTDM development, independent of immunosuppression, formal techniques are available to directly measure insulin sensitivity *in vivo*, including the oral glucose tolerance test (OGTT) and the euglycemic hyperinsulinemic clamp.

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Insulin resistance and β -cell failure are the major determinants of diabetes progression. Insulin resistance is categorized broadly as hepatic or peripheral [3]. In the setting of insulin resistance, hyperglycemia results from insulin's failure to adequately suppress hepatic glucose production and/or increase glucose uptake by skeletal muscle. During a euglycemic hyperinsulinemic clamp, patients receive a fixed dose of i.v. insulin continuously while plasma glucose is held constant at 90 to 100 mg/dL (defined as euglycemia) using a variable infusion of 20% dextrose. Insulin's action *in vivo* can be calculated by quantifying the amount of dextrose infused to maintain steady-state euglycemia. The greater the insulin sensitivity, the more dextrose required to maintain euglycemia because of insulin's regulatory effects on liver glucose production and glucose disposal by skeletal muscle. The euglycemic hyperinsulinemic clamp is considered the gold standard for determining insulin sensitivity, and when combined with a radiolabeled glucose tracer infusion it can quantify both hepatic and peripheral/skeletal muscle insulin resistance [4–6].

In this study we performed a hyperinsulinemic clamp and an OGTT on HCT recipients to determine if new-onset PTDM develops from established insulin resistance and whether plasma glucose levels during a standard oral glucose challenge can predict PTDM diagnosis. These results could be used to identify high-risk patients before HCT or find therapeutic targets for the prevention of new-onset PTDM.

METHODS

Patients and Study Protocol

From November 2014 to February 2017, 79 HCT candidates were screened: 35 individuals provided consent, and 15 were excluded (Figure 1). In total, 20 euglycemic patients (≥ 18 years old) with hematologic malignancies undergoing myeloablative or reduced-intensity conditioning followed by a related, HLA-identical, unmanipulated peripheral blood HCT were accrued into an institutional review board–approved study. No patients received thymoglobulin or total body irradiation.

Patients with a history of diabetes mellitus, diabetes therapy within 6 months of enrollment, fasting blood glucose ≥ 126 mg/dL at screening, a 2-hour postprandial blood glucose ≥ 200 mg/dL during the pretransplant OGTT, and chronic/continuous corticosteroid treatment at evaluation (>10 mg/day of prednisone or prednisone equivalent) were excluded. Patients previously treated with intermittent/pulsed corticosteroids were permitted. Baseline OGTT and hyperinsulinemic clamps were obtained before the start of conditioning, chemotherapy, and/or immunosuppressive medications and were repeated 90 days after HCT.

Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus and either methotrexate or mycophenolate mofetil. Acute and chronic GVHD were assessed using consensus criteria [7,8]. From day 0 to day +100, fasting blood glucose levels were monitored weekly and random blood glucose levels were assessed daily until neutrophil engraftment and then at least 2 to 3 times a week thereafter.

During the first 100 days of transplant, HCT recipients were monitored for GVHD, corticosteroid treatment for any reason, and new-onset PTDM defined as a weekly fasting blood glucose ≥ 126 mg/dL, any random blood glucose ≥ 200 mg/dL, or a 2-hour postprandial glucose ≥ 200 mg/dL during an OGTT [1,9]. All HCT recipients were monitored prospectively for PTDM; however, 1 patient did not undergo a hyperinsulinemic clamp because of a lack of peripheral i.v. access, and 2 patients were unable to complete the second hyperinsulinemic clamp because of logistical considerations and malignancy relapse after HCT.

Study Procedures

HCT patients completed OGTT and hyperinsulinemic clamp at the Vanderbilt Clinical Research Center on separate days before starting chemotherapy/immunosuppression and not more than 14 days before transplant. These baseline studies measured insulin sensitivity without confounding by alloreactivity, immunosuppression, or other features of the transplant. The procedures were repeated 90 days post-HCT. Additional information on the conduct of OGTTs/hyperinsulinemic clamps, calculations of insulin sensitivity, and statistical analysis are available in the Supplemental Methods.

Study Approval

The protocol was approved by the Vanderbilt University Medical Center Institutional Review Board. All subjects gave written informed consent and were treated in accordance with the Declaration of Helsinki.

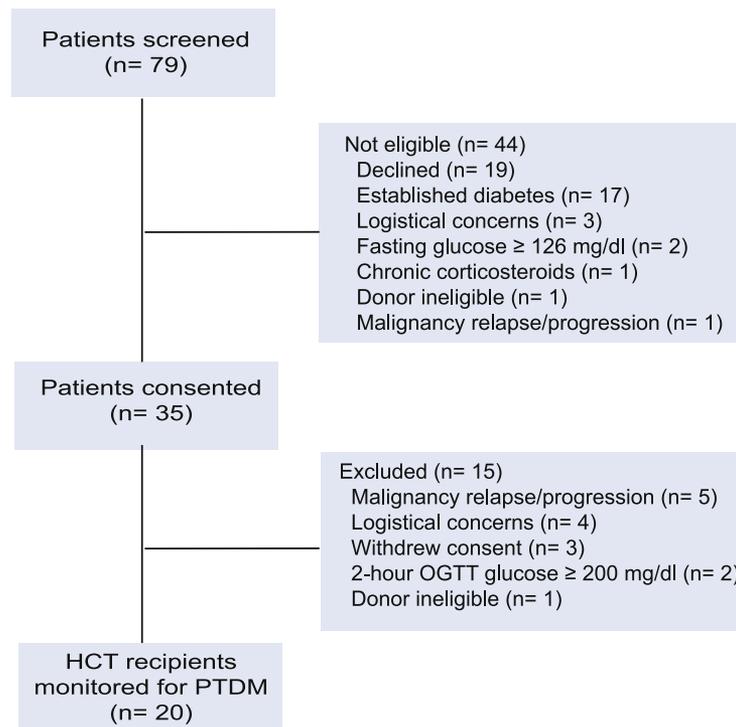


Figure 1. Screening and disposition of possible study patients who were evaluated for related, HLA-identical, peripheral blood HCT. Logistical considerations included moving patients to Nashville, Tennessee; scheduling pretransplant visits at Vanderbilt Clinical Research Center; central venous catheter placement; and coordinating care with donor apheresis team and stem cell processing lab.

Table 1
Characteristics of Patients Undergoing Related, HLA-Identical, Peripheral Blood HCT Stratified for PTDM Development

Variable	No PTDM (n = 9)	PTDM (n = 11)	P
Median age, yr (range)	56 (30-61)	55 (26-66)	.790
Male	6 (67)	9 (82)	.617
White ethnicity	7 (78)	10 (91)	.566
Diabetes family history	1 (11)	4 (36)	.319
Median pre-HCT BMI, kg/m ² (range)	27.2 (22.4-48.9)	30.3 (22.5-36.9)	.210
Median day +90 BMI, kg/m ² (range)	24.4 (19.8-46.3)	28.7 (20.1-32.9)	.201
Malignancy			
Myeloid	5 (56)	7 (64)	1.00
AML/MDS (n = 8)			
CML/MPN (n = 4)			
Lymphoid	4 (44)	4 (36)	
NHL (n = 7)			
CML lymphoid blast crisis (n = 1)			
Pre-HCT steroid treatment	3 (33)	5 (45)	.67
Chemotherapy			
Myeloablative	4 (44)	4 (36)	1.00
Reduced intensity	5 (56)	7 (64)	
GVHD prophylaxis			
FK+MTX	5 (56)	7 (64)	1.00
FK+MMF	4 (44)	4 (36)	
Grades II-IV acute GVHD	4 (44)*	5 (45)*	1.00
Steroid treatment first 100 days	5 (56) [†]	3 (27) [†]	.370
Maximum steroid dose, mg/kg (range)	.4 (.1-.5)	.5 (.1-1)	.539
NIH moderate to severe chronic GVHD	5 (56)	7 (64)	1.00

Values are n (%) unless otherwise defined. BMI indicates body mass index; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; CML, chronic myelogenous leukemia; MPN, myeloproliferative neoplasm; NHL, non-Hodgkin lymphoma; FK, tacrolimus; MTX, methotrexate; MMF, mycophenolate mofetil; NIH, National Institutes of Health.

* Grades II-IV GVHD treatment: systemic corticosteroids (prednisone or methylprednisolone, n = 5) or beclomethasone dipropionate, and budesonide (n = 4).

[†] Indications for systemic corticosteroid (prednisone or methylprednisolone) treatment: grades I-IV GVHD (n = 6), pneumonitis/pleurisy (n = 1), and gout (n = 1).

RESULTS

OGTTs and euglycemic hyperinsulinemic clamps were performed before chemotherapy conditioning and 90 days after matched related donor HCT in 20 patients without pre-existing diabetes. After transplant, HCT recipients were monitored prospectively for PTDM, defined as a weekly fasting blood glucose \geq 126 mg/dL, any random blood glucose \geq 200 mg/dL, or a 2-hour postprandial OGTT glucose \geq 200 mg/dL. Within the first 100 days of transplant, new-onset PTDM was diagnosed in 11 patients (55%) at a median of 22 days post-HCT (range, 0 to 88). Table 1 describes clinical characteristics. Neither transplant for a lymphoid malignancy nor previous treatment with corticosteroids increased PTDM risk (Table 1). All PTDM cases developed before grades II to IV acute GVHD except for 2 (18%), and no patients were receiving corticosteroids when diagnosed with diabetes. Neither the diagnosis of acute/chronic GVHD nor treatment with corticosteroids was associated with PTDM (Table 1). Parenteral nutrition was not used.

During the baseline OGTT, impaired fasting glucose (fasting plasma glucose of 100 to 125 mg/dL) and impaired glucose tolerance (2-hour plasma glucose concentration of 140 to 199 mg/dL) after a 75-g glucose load was observed in 5 (25%) and 7 (35%) of patients, respectively. When analyzed as either a continuous or dichotomous variable (normal versus impaired glucose tolerance), the pretransplant 2-hour OGTT plasma glucose values did not discriminate between patients developing PTDM and those remaining nondiabetic after HCT. However, pretransplant fasting glucose and C-peptide levels were elevated in patients diagnosed with PTDM (Table 2). Furthermore, all 5 patients with impaired fasting glucose compared with only 6 of 15 individuals with normal fasting glucose levels progressed to PTDM after HCT ($P = .038$). During the second OGTT after HCT, diabetic, impaired, and normal fasting or 2-hour postprandial glucose levels were observed in 7 versus 0, 3

versus 7, and 1 versus 2 of the PTDM and non-PTDM patients, respectively (Table 2).

To directly measure glucose use and insulin sensitivity, hyperinsulinemic clamps were performed. During insulin stimulation, HCT recipients who developed PTDM exhibited lower whole-body glucose utilization before transplant and decreased muscle glucose uptake after transplant when compared with individuals never diagnosed with PTDM (Figure 2). During the high-dose insulin phase whole-body insulin sensitivity and peripheral/skeletal muscle insulin sensitivity were calculated as the exogenous glucose infusion rate per unit of plasma insulin or as the rate of isotopically determined disappearance of glucose per unit of plasma insulin, respectively. Patients developing new-onset PTDM exhibited decreased peripheral/skeletal muscle and whole-body insulin sensitivity after transplant (Figure 3). Differences were not detected in hepatic glucose production or hepatic insulin sensitivity index before or after HCT among patients with or without PTDM (Supplemental Table 1). Because baseline measurements of insulin sensitivity could influence post-HCT comparisons, ordinary regression was performed. After adjustment for baseline/pretransplant values, regression analyses confirmed that PTDM patients had both lower whole-body ($\beta = -28.0$; 95% confidence interval [CI], -47.2 to -8.9 ; $P = .013$) and peripheral/skeletal muscle insulin sensitivity ($\beta = -58.1$; 95% CI, -97.0 to -19.3 ; $P = .012$) during the high-dose insulin infusion after HCT.

To investigate the previously noted association between PTDM and inferior HCT outcomes, an exploratory landmark survival analysis was performed [1,2]. The median follow-up for surviving patients was 21 months. Survival curves were created beginning at day +100 after both PTDM assessment and second OGTTs were complete. Estimated 2-year overall survival was decreased in patients developing PTDM compared

Table 2
OGTT Results from Recipients of Related, HLA-Identical, Peripheral Blood HCT Stratified for PTDM Development

Variable	No PTDM (n = 9)	PTDM (n = 11)	P
Fasting glucose, mg/dL			
Pre-HCT	87 ± 2.61	101 ± 3.00	.005
Post-HCT	103 ± 6.07	118 ± 6.98*	.204
2-Hour postprandial glucose, mg/dL			
Pre-HCT	124 ± 9.78	129 ± 9.23	.648
Post-HCT	151 ± 10.6	211 ± 18.8*	.008
Fasting C-peptide, ng/mL			
Pre-HCT	2.03 ± .34	2.97 ± .40	.074
Post-HCT	3.04 ± .54	4.28 ± .52*	.039
2-Hour postprandial C-peptide, ng/mL			
Pre-HCT	6.30 ± .97	7.48 ± .83	.210
Post-HCT	6.75 ± 1.15	11.3 ± 2.14*	.052

Values are mean ± SEM.

* After transplant, fasting glucose ($P = .014$), 2-hour postprandial glucose ($P = .003$), fasting C-peptide level ($P = .003$), and 2-hour postprandial C-peptide level ($P = .016$) were increased in PTDM patients when compared with their respective baseline results. Otherwise, before and after transplant values did not differ for within-group comparisons.

with non-PTDM individuals (55% [95% CI, 23% to 83%] versus 100% [95% CI, 63% to 100%], respectively; $P = .039$) and in patients with day +90 fasting hyperglycemia representing survival for individuals with either diabetic, impaired, or normal fasting glucose levels, respectively (0% [95% CI, 0% to 71%] versus 82% [95% CI, 48% to 98%] versus 100% [95% CI, 48% to 100%]; $P < .001$) (Figure 4).

DISCUSSION

The focus of the current study was to use OGTTs and euglycemic hyperinsulinemic clamps to define the onset and mechanisms causing glucose dysregulation during HCT. Although

clinical risk factors for new-onset PTDM (including older age, nonwhite ethnicity, corticosteroids, parenteral nutrition, and total body irradiation) have been previously discussed by our group and others, the actual mechanisms causing PTDM remain unknown [1,10–12]. Our OGTT and clamp results reveal that risk of progression to PTDM after HCT depends on the recipient's insulin resistance status before transplant. Specifically, PTDM pathophysiology is characterized by subtle whole-body insulin resistance before transplant followed by more robust evidence of peripheral/skeletal muscle insulin resistance after HCT. These results are remarkable for several reasons. By demonstrating pre-HCT insulin resistance as a

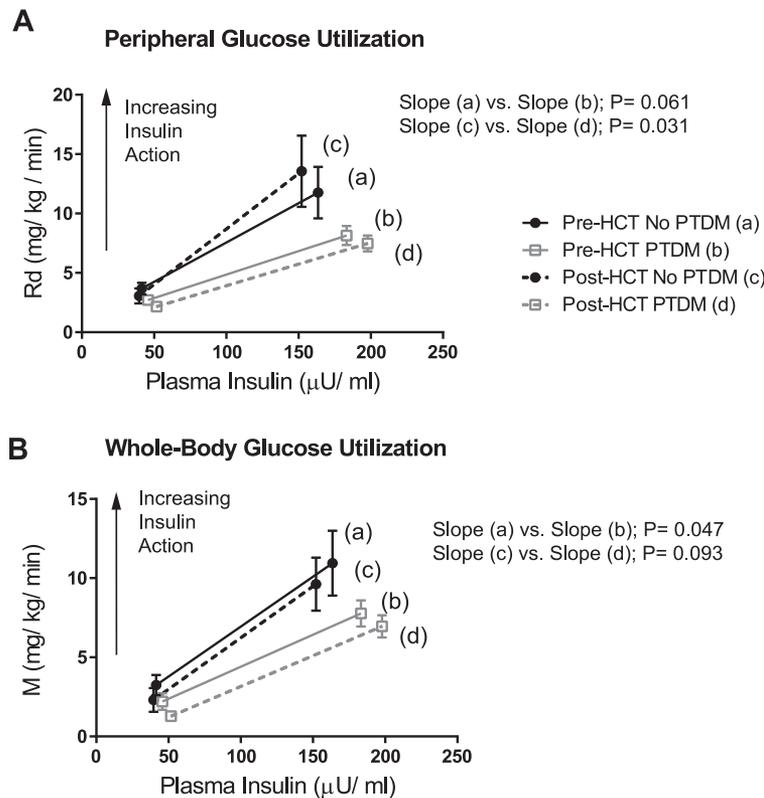


Figure 2. Insulin-stimulated glucose utilization before and 90 days after related, HLA-identical, peripheral blood HCT. Peripheral/skeletal muscle (Rd) and whole-body glucose utilization (M) were calculated during the euglycemic insulin clamp studies and plotted against the plasma insulin level (A and B, respectively). Data are expressed as mean ± SEM for 8 for pre-HCT measurements and 6 for post-HCT measurements in the "No PTDM" group and 11 for the "PTDM" cohort. Data were stratified for the development of new-onset PTDM. The slopes of the lines were compared using generalized least-squares model.

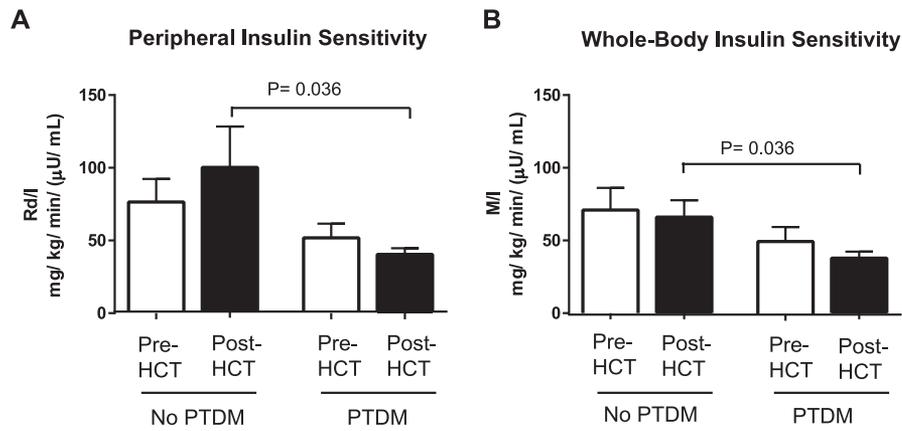


Figure 3. Insulin sensitivity before and 90 days after related, HLA-identical, peripheral blood HCT. Peripheral/skeletal muscle (Rd/I) and whole-body insulin sensitivity (M/I) were calculated during the euglycemic insulin clamp studies with high-dose insulin infusion (80 mU/m²/min) (A and B, respectively). Decreased Rd/I and M/I values reflect worsening insulin resistance and decreased glucose disposal. Data are expressed as mean ± SEM for 8 for pre-HCT measurements and 6 for post-HCT measurements in the “No PTDM” group and 11 for the “PTDM” cohort. Data were stratified for the development of new-onset PTDM. Independent and dependent groups were compared with a Mann-Whitney U test and Wilcoxon signed rank test, respectively.

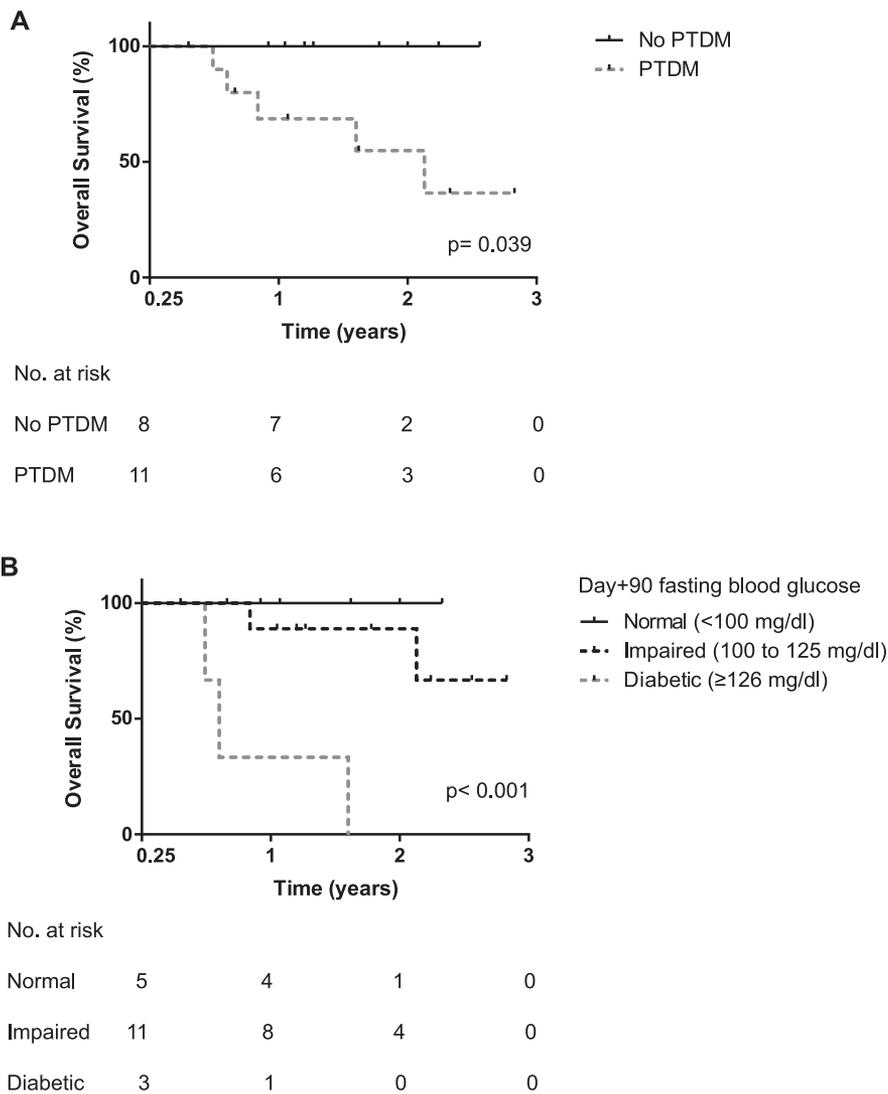


Figure 4. Kaplan-Meier estimates of overall survival beginning 100 days after related, HLA-identical, peripheral blood HCT. Survival curves were stratified for the development of new-onset PTDM during the first 100 days of transplant (A) or by fasting blood glucose level during the day +90 oral glucose tolerance test (B). Groups were compared with a log-rank test. Causes of death included GVHD (n = 2), malignancy relapse (n = 1), infection (n = 1), and myocardial infarction (n = 1).

determinant for PTDM development, we refute the misperception that PTDM is merely a side effect of immunosuppressive medications. The study identifies skeletal muscle insulin resistance as a target for therapeutic intervention to prevent glucose dysregulation and to limit transplant morbidity. Not only is a target identified, but we also show that generalized insulin resistance manifesting as fasting hyperglycemia could be used to predict PTDM.

A limitation of this research is the sample size. In general, clamp studies are smaller, but the results from this technique remain very reproducible [13]. Although the number of study participants was small, the current research is further supported by our previous prospective study in a cohort of 84 HCT patients that showed nearly identical results with PTDM incidence of 60% versus 55%, median time to PTDM diagnosis of 23 days versus 22 days, and 2-year survival of PTDM patients of 54% versus 55% for the past and present study, respectively [1]. The high incidence and early diagnosis of PTDM, especially before corticosteroid initiation, likely reflects vigilant surveillance and strict diagnostic criteria; however, multicenter trials are needed for confirmation.

Other common concerns for clinical research include treatment heterogeneity and generalizability of results. Our current study focused on a uniform group of HLA-identical sibling donor transplants receiving non-total body irradiation conditioning and tacrolimus-based immunosuppression. All patients undergoing HCT were screened for clinical trial eligibility. However, our cohort was composed predominantly of white male patients, which may reflect biases inherent to HCT or may represent the demographics of our clinical practice. The effects of this population bias are unknown; however, gender was not previously associated with PTDM [1]. Given the similarities in PTDM incidence between the current study and our past research, which included a more heterogeneous cohort, we suspect that our clamp data can be extrapolated to other types of transplants. Furthermore, the study was designed so that differences in HCT techniques (ie, conditioning intensity) or alloreactivity/immunosuppression could not affect the OGTT and clamp results obtained before transplant.

The HCT-specific comorbidity index, a commonly used clinical tool, has identified diabetes treatment before transplant as a predictor of decreased survival after HCT [14]. Similarly, our current and previous research has shown a relationship between new-onset PTDM and transplant mortality [1,2]. In general, diabetes is an accepted risk factor for cardiovascular, kidney, and infectious diseases; however, the physiology of hyperglycemia is complex. Insulin resistance is characterized by low-grade inflammation, which could have negative consequences during HCT [15,16]. Diabetes may also influence malignancy relapse or the development of secondary cancers after transplant via epigenetic pathways. A recent study showed that hyperglycemia prevents AMP-activated kinase phosphorylation and stabilizes the tumor suppressor TET2, leading to cancer susceptibility, an abnormality reversed by metformin [17]. Our preliminary survival data are consistent with past results and confirm other research demonstrating inferior survival among HCT recipients with hyperglycemia [1,2,18,19]. Larger studies are needed to elucidate the cause-specific mortality for HCT recipients developing new-onset PTDM.

Although we demonstrated evolving insulin resistance in the development of PTDM, the exact etiology for impaired insulin sensitivity during HCT remains unclear. Pretransplant treatment could contribute to impaired insulin sensitivity either directly via corticosteroid exposure or indirectly by

inducing detrimental changes in diet and exercise. Both increase in fat mass and loss of muscle mass with initial therapy or during transplant could lead to reduced glucose utilization. Accordingly, body mass index tended to be higher in the PTDM group (Table 1), and despite weight loss during transplant, there was no improvement in insulin sensitivity (Figure 2). Alternatively, preclinical studies indicate that low-grade inflammation is a driver of insulin resistance in non-transplant animal models [15,16]. Analogously, PTDM also may result from underlying immune dysregulation that worsens after transplant [2,20]. The OGTT and clamp data demonstrate changes in glucose metabolism before transplant, indicating that PTDM is distinct from alloreactivity or its treatment with corticosteroids. It remains possible that immunosuppressive medications/corticosteroids could “unmask” subtle, established metabolic changes that are otherwise discernible only with fasting labs or insulin clamps. Given the limitations of the current investigation and the complexities of PTDM, animal models and human studies pairing clamps with muscle biopsies likely will be needed to define the molecular cause and specific role of skeletal muscle insulin resistance in PTDM development.

This study enhances our understanding of PTDM, a disease that affects about half of HCT recipients and increases the mortality risk 3-fold [1,2]. The pretransplant OGTT and clamp data refute the commonly held misperception that PTDM is simply a side effect of immunosuppressive medications. Our results demonstrate that elevated fasting pretransplant glucose levels may identify PTDM risk and that pharmacologic therapies or lifestyle interventions targeting skeletal muscle insulin resistance should be studied for the prevention and treatment of new-onset PTDM after HCT. For example, medical fitness facilities specializing in patients with chronic health conditions (ie, cardiac rehabilitation) could be leveraged for peritransplant exercise training. Even short-term exercise for 7 days can improve insulin sensitivity [6]. The Diabetes Prevention Program was a randomized clinical trial comparing lifestyle intervention (7% weight reduction and moderate physical exercise, ie, brisk walk) for 150 minutes per week] or metformin 850 mg twice per day with placebo in a high-risk nondiabetic population with elevated fasting and postprandial plasma glucose concentrations. After 15 years of follow-up, diabetes incidence was reduced 18% to 27% with metformin or lifestyle interventions when compared with placebo [21]. These studies lay the ground work for a prospective trial selecting or stratifying HCT participants based on impaired fasting glucose and then investigating insulin sensitizers such as biguanides or thiazolidinediones initiated pretransplant on PTDM development and transplant mortality.

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SUPPLEMENTARY MATERIALS

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2019.02.001.

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