平成２７年度がんサバイバーシップ研究助成金

# 研　究　報　告　書

平成２８年　５月２５日

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（研究課題）
（４）がん患者の栄養・食事環境の設備に関する研究
造血幹細胞移植サバイバーにおける生活習慣病の実態調査

平成２７年　７月２２日付助成金交付のあった標記研究課題について英文誌に掲載されましたのでご報告いたします。

研究代表者の藤および共同研究者の大橋に加え欧米の著名な研究者と造血幹細胞移植後糖尿病に関しての文献をreviewし総説としてBone Marrow Transplantation誌に掲載されました。これまで世界的にも造血幹細胞移植後に限ると移植後糖尿病に限定しての総説というのはなく、当院での取り組みを含め近年の造血幹細胞移植および他の領域での血糖管理に関する情報をまとめたことが評価されたものと考えております。

Bone Marrow Transplantation (2016), 1–9

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REVIEW

# How do I manage hyperglycemia/post-transplant diabetes mellitus after allogeneic HSCT

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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients frequently develop glucose intolerance and post-transplant diabetes mellitus (PTDM). The clinical importance of PTDM and its detrimental impact on HSCT outcomes are under-recognized. After allo-HSCT, various mechanisms can contribute to the development of PTDM. Here we review information about hyperglycemia and PTDM after allo-HSCT as well as PTDM after solid organ transplantation and describe ways to manage hyperglycemia/PTDM after allogeneic HSCT. Taking into consideration a lack of well-established evidence in the field of allo-HSCT, more studies should be conducted in the future, which will require closer multidisciplinary collaboration between hematologists, endocrinologists and nutritionists.

*Bone Marrow Transplantation* advance online publication, 4 April 2016; doi:10.1038/bmt.2016.81

## INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a standard treatment modality for patients with hematological diseases. Novel strategies using lower intensity conditioning regimens enable this therapy for older patients or patients with preexisting comorbidities. However, one major obstacle is the high incidence of morbidity and mortality related to infectious diseases, acute/chronic GVHD and organ failure. Late complications such as metabolic syndrome and cardiovascular diseases emerge as a concern in long-term survivors.[1] Strategies to reduce the risk of such complications include prevention and treatment of hyperglycemia/post-transplantation diabetes mellitus (PTDM), as its unfavorable impact on clinical outcomes has been demonstrated in various retrospective studies not only in allo-HSCT but also in solid organ transplantation.[2] Considering the increased prevalence of diabetes mellitus (DM) in the general population, more allo-HSCT recipients will have DM as comorbidity in the future.[3,4] In addition, HSCT survivors have a higher risk of developing hyperglycemia/PTDM owing to pretransplant and post-transplant exposures. Prospective interventions to prevent and treat PTDM are widely tested in the field of kidney transplantation.[5,6] There is a paucity of data available for allo-HSCT recipients. Here we aim to review the information about hyperglycemia/PTDM after allo-HSCT and describe its management.

## PATHOGENESIS OF PTDM

There are various causes of PTDM after allo-HSCT. During the early phase, hyperglycemia and PTDM are mainly the consequence of immunosuppressive drugs and inflammation. In long-term survivors, even off immunosuppressive drugs, this risk is still increased, mainly owing to transplant-related factors.

### Immunosuppressive drugs

Early after HSCT, PTDM may occur owing to the adverse effects of immunosuppressive drugs, which are associated with dysfunction of pancreatic β cells and decrease in insulin sensitivity.[5] In patients with pretransplant type 2 DM, glucose control can be expected to worsen in conjunction with the effects of immunosuppressive drugs (Figure 1).

Calcineurin inhibitors (CNIs) such as tacrolimus and cyclosporin A substantially impair insulin secretion. PTDM was more frequently reported with tacrolimus than with cyclosporin.[7] However, the risk of developing PTDM with tacrolimus was not increased as compared with cyclosporin when lower levels of tacrolimus were used, although the reduced dose of tacrolimus might increase the risk of GVHD.[8]

The use of glucocorticoids impairs peripheral glucose uptake and increases hepatic gluconeogenesis and glycogenolysis.[9] The plasma concentrations of various corticosteroids peak at approximately 1 h and their average half-life is about 2.5 h.[9] Prednisone and methylprednisone demonstrate their peak effect on blood glucose levels at 4–8 h with duration of action up to 12–16 h but not typically for 24 h.[10,11] Dexamethasone has a more extended effect up to ⩾20 h.[9] Patients who receive glucocorticoids usually have normal fasting glucose levels and high postprandial levels. There is little information available on the efficacy of oral agents in glucocorticoid-induced DM.

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Received 10 December 2015; accepted 17 February 2016

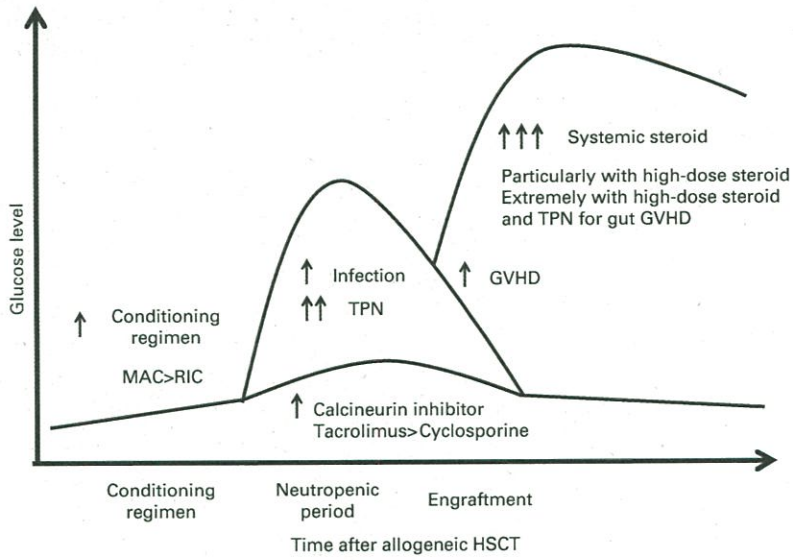


**Figure 1.** Causes of hyperglycemia during the early period after allo-HSCT. MAC = myeloablative conditioning; RIC = reduced-intensity conditioning; TPN = total parenteral nutrition.

Sirolimus, a mammalian target of rapamycin inhibitor, can also cause PTDM, although the pathophysiology of mammalian target of rapamycin inhibitor-induced PTDM is less clear.

### Transplant-related factors

Rates of impaired glucose tolerance, DM and hyperinsulinemia are all increased in allo-HSCT survivors independent of exposure to immunosuppressive medications or corticosteroids. In a study of 180 allo-HSCT recipients, Majhail *et al.*[12] reported 30% prevalence of DM within the first 2 years post transplantation and was similar in children and adults; DM had not resolved in 32% of these patients by 2 years. Exposure to high-dose corticosteroids (cumulative dose of $>0.25$ mg/kg/day) increased the likelihood of developing PTDM and its persistence at 2 years. In the general population, metabolic syndrome (MS) increases the risk for type 2 DM sixfold. The reported prevalence of MS in children and adolescence is about 30% after allo-HSCT, which is 3.5 times higher than that reported in healthy children.[13] In a cross-sectional study of adult HSCT recipients, the prevalence of MS was 42%, which was 2.2 times higher than the general population.[14] However, the prevalence of hyperglycemia was 41% and was comparable to general population controls. Among 23 young patients transplanted between the age of 3 and 18 years, 12 (52%) showed insulin resistance: 2 with normal glucose tolerance, 6 with impaired glucose tolerance, and 4 with DM. The factors related with hyperinsulinemia and abnormal glucose tolerance are time elapsed from HSCT, history of GVHD, hypogonadism[15] and TBI.[16]

### Body composition

In the general population, obesity is associated with reduced glucose tolerance, type 2 DM and MS. Despite higher risk for PTDM and other cardiovascular risk factors, obesity is not a major concern in long-term allo-HSCT survivors. In 22 patients who received allo-HSCT during childhood, the cumulative incidence of DM/impaired glucose tolerance was 11.6% at 5 and 69.3% at 10 years. However, none of the patients were obese/overweight.[17] In another cohort of childhood-transplanted patients, 15% of 45 patients showed abnormal glucose tolerance but only 1 was obese. However, a waist/height ratio of $>0.5$ was associated with abnormal glucose tolerance in 85%, compared with 42% of patients with normal glucose tolerance, and 23% of controls.[16] HSCT survivors may present normal body mass index (BMI) but develop significant changes in their body composition, resulting in increased visceral and IM fat and a reduction of muscle mass. This finding termed 'sarcopenic obesity' leads to loss of myocyte insulin receptors and increase in adipocyte insulin receptors, which are less efficient in binding insulin and clearing glucose.[18,19] Therefore, waist circumference may be a better marker of preclinical metabolic abnormalities than BMI in transplant survivors.[20] Majhail *et al.*[14] reported the prevalence of elevated waist circumference in adult allo-HSCT survivors as 44%, which was comparable to that of general population controls.

### Vitamin D concentration

Vitamin D deficiency has been shown to increase the risk of MS and DM. A study including 6682 volunteers of a preventive health program revealed that high serum 25-hydroxy vitamin D concentrations at baseline and increasing levels during follow-up independently contribute to a risk reduction of MS.[21] Promotion of adequate vitamin D condition might therefore reduce type 2 DM, MS and cardiovascular disease. Patients undergoing allo-HSCT are at increased risk for vitamin D deficiency through prolonged hospitalizations, avoidance of sunlight, decreased nutritional status and malabsorption syndrome. Blood levels of 25-hydroxy vitamin D are decreased in 70% of patients at transplantation and in 58% of patients at day 100.[22] Around a third of long-term survivors have low 25-hydroxy vitamin D levels, which is inversely related to prednisone use.[23] Recently, the potential role of vitamin D in the pathogenesis of GVHD has been discussed.[24] So far, despite a low level of evidence in allo-HSCT patients, it seems reasonable to screen, prevent and correct deficiency of vitamin D in long-term survivors.

### Inflammation

After allo-HSCT, various inflammatory cytokine levels are significantly increased[25,26] and seem to be associated with complications, such as sinusoidal obstructive syndrome and GVHD. In addition to lymphocyte-secreted cytokines, adipocyte-derived cytokines may have a role in the development of insulin resistance and subsequent type 2 DM. Patients with post-HSCT MS have significantly higher levels of leptin, C-reactive protein and TNF-α compared with non-transplanted patients with MS.[27,28]

There are some controversies about the correlation between serum leptin and the risk of hyperglycemia/PTDM. Serum leptin was increased in post-HSCT patients with MS, independently of BMI.[27] Factors contributing to leptin overproduction were hypogonadism and increased serum insulin concentrations. These findings were not confirmed by other studies, in which only age >6 years at the time of HSCT in a pediatric cohort was associated with increased risk of PTDM/impaired glucose tolerance.[17]

## DIAGNOSIS OF HYPERGLYCEMIA/PTDM

Early intervention during the asymptomatic stage of hyperglycemia improves the long-term outcome in the general population.[29] Therefore, screening for hyperglycemia and PTDM is indicated in high-risk patients at the early-stage post HSCT and during the long-term surveillance. However, given the high incidence of new-onset PTDM during the first 100 days, an argument could be made that all allo-HSCT recipients should be routinely screened early after transplant. Screening tests to detect hyperglycemia are fasting glucose, oral glucose tolerance test (OGTT) and measurement of glycated hemoglobin A1c (HbA1c). Routine monitoring of glucose level is recommended in all patients who undergo allo-HSCT. Even in patients without a history of DM, hyperglycemia develops often after allo-HSCT. Diagnosis of PTDM is basically the same as that of type 2 DM: fasting plasma glucose ⩾126 mg/dL (7.0 mmol/L), random plasma glucose ⩾200 mg/dL (11.1 mmol/L), 2-h plasma glucose after OGTT ⩾200 mg/dL (11.1 mmol/L), or HbA1c ⩾6.5%.[30] Urine glucose measurement is not recommended for screening owing to its low sensitivity to detect early stage of diabetes. Furthermore, caution must be exercised when interpreting HbA1c results. Patients with hematological disorders often receive transfusion support before and after allo-HSCT that could confound the interpretation of the HbA1c results. The determination of fasting glucose level alone in HSCT patients receiving glucocorticoids has a low sensitivity for an accurate detection of abnormal glucose status. When glucocorticoids are administered in the morning, the pattern is characterized by rising glucose concentrations throughout the day, peaking between lunch and dinner time. After solid organ transplantation, predinner glucose measurements can often detect patients with hyperglycemia (>200 mg/dL; 11.1 mmol/L), even in individuals who have relatively normal fasting glucose levels in the morning.[31,32] In addition, the accuracy of HbA1c level after allo-HSCT can be decreased owing to the hemoglobin variations observed in such patients.[33] Furthermore, as ethnicity might affect the cutoff values of HbA1c level to diagnose DM, physicians at each country/region should follow their local guidelines.[33] Another option to monitor glycemic control is measurement of glycoalbumin or fructosamine levels.[34] Because of rapid turnover of serum albumins compared with hemoglobin, the fructosamine and glycoalbumin levels reflect glucose control over a short period of 2–3 weeks.

In addition, allo-HSCT recipients should be regularly screened for other cardiovascular risk factors that are commonly associated with diabetes. These factors include: life style characteristics (smoking; physical activity; dietary habits; body measurements), dyslipidemia, and arterial hypertension. Because of the risk of sarcopenic obesity after allo-HSCT, in addition to height/weight measurements, waist circumference should be assessed too.

## HYPERGLYCEMIA AND COMPLICATIONS

### Risk of infectious diseases

Infection is a common cause of morbidity and mortality after allo-HSCT because of the milieu of immunosuppressive drugs and both insufficient and delayed immune reconstitution. The risk of infectious diseases can be exaggerated in patients with DM owing to well-documented defects in neutrophil function, such as chemotaxis, phagocytosis and killing, attributable to hyperglycemia.[35]

Non-transplant diabetic patients have a significantly increased risk of infectious diseases, including infections of the respiratory and urinary tracts, skin and mucosa.[35–37] Infection-related mortality,[38] as well as pneumonia-related hospitalization, are also increased in patients with DM. A Danish population-based study showed that patients with DM had an increased relative risk of infectious diseases with each 1-mmol/L increase in plasma glucose at baseline. In patients with autoimmune diseases such as rheumatoid arthritis[39,40] and inflammatory bowel disease[41] who receive immunosuppressive drugs, the presence of DM increases the risk of infectious diseases. In hospitalized patients with autoimmune disease, presence of hyperglycemia was reported to be associated with an increased risk of mortality. In patients with hematological malignancies, hyperglycemia was also associated with an increased risk of infectious diseases. Patients with DM were reported to be at higher risk for invasive fungal diseases during chemotherapy.[42] In summary, the association between DM and infection is widely acknowledged.

### PTDM and clinical outcomes

In the field of kidney transplantation, the unfavorable impact of hyperglycemia on the clinical outcome is well established. The efficacy of various glucocorticoid-sparing regimens has been examined in organ transplantation.[43]

PTDM increases the risk of mortality after solid organ transplantation.[44] Using large databases, Hayer *et al.*[45] reported that pretransplant DM was associated with an increased risk of overall and specifically infection-related mortality after kidney transplantation. In multivariate analysis, pretransplant DM was a highly significant risk factor for infection-related death (hazard ratio 1.71, 95% confidence interval 1.36–2.15, $P < 0.001$). Wyzgal *et al.*[46] reported that early hyperglycemia after kidney transplantation was predictive for DM development and allograft dysfunction. In long-term follow-up using United States Renal Data System, the cumulative incidence of PTDM at 3 years was 24% and was a strong predictor of mortality after kidney transplantation (relative ratio 1.87, 95% confidence interval 1.60–21.8).[47] The development of PTDM had a similar impact on the clinical outcome as acute rejection after kidney transplantation.[48] During an OGTT, each mmol/L increase in 2-h plasma glucose was associated with an increased risk of overall graft failure and cardiovascular mortality.[49] Early post-transplantation hyperglycemia is an independent risk factor for rehospitalization of non-diabetic kidney allograft recipients mainly owing to infectious diseases.[50] These results strongly suggest that the development of PTDM increases the risk of mortality after kidney transplantation, primarily owing to infectious diseases. Similarly, preliminary data indicates that new-onset PTDM following allo-HSCT is also associated with decreased survival and increased treatment-related mortality.[51,52]

Considering the significant impact of glucose dysregulation on clinical outcomes, various strategies can be applied to prevent PTDM. First, patients at high risk for PTDM should be identified.[31] For such individuals, transplant physicians could consider using corticosteroid-free and/or CNI-free immunosuppression regimens if possible. Second, intensive early glucose control may reduce the incidence of PTDM. Early insulin treatment of peritransplant hyperglycemia is commonly applied in solid organ transplantation. Continuous insulin infusion might improve the impaired neutrophil function observed in DM.[53,54] During the peritransplant period, enormous stress/inflammation or corticosteroids can induce insulin resistance, which leads to hyperglycemia owing to an insufficient insulin secretion to overcome such insulin resistance. CNI also decreases the secretion of insulin by

pancreatic β cells. In such cases, oral drugs inducing insulin secretion can temporarily work but may subsequently lead to an exhaustion of β-cell function. Therefore, early application of exogenous insulin may not only control hyperglycemia during the early post-transplant period but also prevent PTDM in long-term survivors. In a prospective randomized control trial assessing the efficacy of basal insulin coverage to prevent PTDM after kidney transplantation,[54] the incidence of diabetes was significantly lower in the basal insulin group than in the control group, which supports the idea that early basal insulin coverage could contribute to β-cell protection after kidney transplantation. Kiddis *et al.*[55] showed that outcomes following renal transplantation could be improved with intensive blood sugar management in patients with established DM. Currently, there are several ongoing trials assessing the efficacy and safety of PTDM prevention using the DPP-4 inhibitor sitagliptin after kidney transplant (NCT00936663).

In allo-HSCT, the evidence of the clinical effects of hyperglycemia/PTDM is still limited. However, emerging data from several retrospective studies are now available. Pretransplant DM has an adverse impact on post-transplant outcomes.[56,57] Pretransplant DM was associated with an increased risk of non-relapse mortality (NRM) and is now included in HSCT-comorbidity index.[56] Results based on Japanese registry data confirmed these findings.[57] It is also important to assess the glycemic status before allo-HSCT. The risk of infection-related mortality was high in patients with pretransplant DM, especially the risk of invasive fungal diseases.[57,58] Furthermore, elevated pretransplant fasting C-peptide levels predicts both early PTDM and mortality after allo-HSCT.[51]

Hyperglycemia during the early phase after allo-HSCT is common even in patients without history of DM, likely caused by immunosuppressive drugs, parenteral nutrition (PN) and inflammatory cytokines associated with the conditioning regimen, and GVHD (Figure 1).[2] Hyperglycemia itself increases the risk of infectious complications that may induce elevation of cytokines, which can further exacerbate hyperglycemia (Figure 2).[2,59] PTDM may affect cellular immune responses after allo-HSCT, including regulatory T-cell subset frequencies and immune regulation.[52] C-peptide level may be elevated transiently during the early period after allo-HSCT; however, the increased insulin levels are insufficient to compensate for the worsening insulin resistance.[60]

Several retrospective studies consistently showed that post-transplant hyperglycemia was associated with an increased risk of subsequent morbidity and mortality after HSCT.[61–65] Patients with hyperglycemia during the neutropenic period after allo-HSCT had an increased risk of subsequent GVHD and NRM.[62] Similarly, an increased risk of GVHD was observed in patients with severe hyperglycemia (⩾180 mg/dL) during the early period after allo-HSCT.[64] Substantial elevation of glucose levels during the early period after allo-HSCT may reflect inflammation-induced insulin resistance, which could possibly be associated with subsequent acute GVHD development.[60,62,64] Hammer *et al.*[61] reported the adverse impact of hyperglycemia between days 0 and 100, which was associated with an increased risk of infectious diseases and NRM. Patients receiving systemic glucocorticoids as GVHD treatment are at higher risk to develop hyperglycemia, which is associated with inferior clinical outcome.[66] In terms of late complications, some studies have demonstrated PTDM to be an independent risk factor for cardiovascular post-transplant complications. However, diabetes was often associated with other cardiovascular risk factors, such as arterial hypertension, dyslipidemia and unhealthy heart lifestyle.[67–69] In summary, hyperglycemia after allo-HSCT is common and is associated with an increase in morbidity and NRM.

## TREATMENT/MANAGEMENT OF PTDM

### Early period after allo-HSCT

The Leuven I study showed that intensive glucose control (target blood glucose concentrations 4.4–6.1 mmol/L) compared with a conventional glucose control (target concentrations 10–12 mmol/L) significantly reduced morbidity and mortality in patients admitted to a surgical Intensive Care Unit.[70] The Leuven II study demonstrated similar results for patients who were admitted to the medical Intensive Care Unit for >5 days.[71] However, the NICE-SUGAR trial failed to reproduce the beneficial effects of intensive glucose control. There might be various reasons for such differences.[72] One important limitation in the NICE-SUGAR trial was inconsistent glucose control. In both Leuven studies, 70% of the patients in the intensive glucose control group were on average in target, whereas this was <50% in the NICE-SUGAR study.[72,73] Standardization of blood glucose measurement and adequate training of nursing staff could be relevant not only in a large

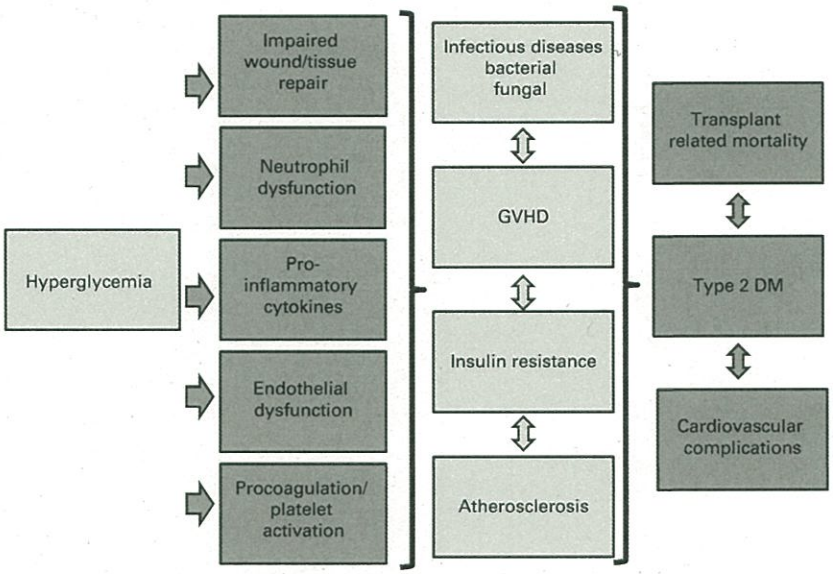


**Figure 2.** Possible adverse effects caused by hyperglycemia in allo-HSCT.

multicenter trial but also in daily care of the patients. Theoretically, intensive insulin therapy can break the vicious cycle (Figure 1 and 2) and mitigate the adverse impact of hyperglycemia,[74] leading to reduced risk of post-transplant complications. Glucose control is feasible in patients after HSCT because patients frequently receive PN. However, the timing, the duration and the dose of PN may differ.[70,75] In a small prospective study designed to assess the feasibility and effectiveness of intensive glycemic control (IGC) after allo-HSCT, there were no serious hypoglycemic complications and significantly fewer documented infections in patients undergoing IGC, compared with the matched-control group.[76] A multicenter clinical trial incorporating IGC for patients treated with allo-HSCT using myeloablative conditioning regimen is ongoing in Japan (UMIN000001189).

A common misconception concerning inpatient glucose control is that sliding scale insulin (SSI) protocol alone is sufficient for appropriate glucose control. SSI simply reacts to hyperglycemia instead of preventing the occurrence of hyperglycemia and could lead to a higher glucose level variability, which might be associated with an inferior outcome.[77,78] Therefore, SSI alone is not recommended as inpatient glucose control.[79–81] Basal-bolus insulin (BBI) is more reliable for inpatient glucose control. In the RABBIT2 Surgery study, BBI led to a better glucose control compared with SSI and to a decreased risk of postsurgical complications.[82] Using continuous insulin infusion, a significant lower rate of complications was observed in non-diabetic patients treated with intensive (target glucose level, 100–140 mg/dL) versus conservative treatment regimen (141–180 mg/dL).[83] Therefore, based on the clinical scenario, continuous insulin infusion for basal insulin coverage or BBI may be used to achieve glucose control.

In general, hyperglycemia is common in patients who receive PN.[84] After allo-HSCT, PN-associated hyperglycemia is also common and was reported to be associated with infectious

**Table 1.** Oral glucose-lowering drugs and PTDM management

| *Drug* | *Mechanism/indication* | *Side effects* | *Precaution in PTDM* |
|---|---|---|---|
| Metformin[4,100] | Most commonly used drug for type 2 DM<br>Effective irrespective of BMI, can be used in both lean and obese patients with insulin resistance | GI symptoms, nausea and diarrhea<br>Lactic acidosis (mainly in renal insufficiency)<br>Malabsorption of vitamin B12 | Reduced glomerular filtration rate ( < 60 ml/min/1.73 $m^2$); no consensus on acceptable threshold of renal insufficiency<br>In case of GI symptoms, differential diagnosis of infection or GVHD<br>Because of risk of lactic acidosis, metformin should be held 48 h before and after iodinated contrast media<br>Evaluation for B12 deficiency; substitution if indicated |
| Thiazolidine-diones (TZD) | Act as ligands for PPAR-γ receptors enhancing insulin action in skeletal muscle and adipose tissue<br>Little effect on insulin secretion | Edema, heart failure, hepatotoxicity[101]<br>Possible risk of bone fracture[102] | Caution in long-term survivors with cardiac heart failure, hepatotoxicity or decreased bone mass<br>Increased risk of bone fractures, particularly in patients who receive systemic corticosteroids, or those with reduced bone density |
| α-Glucosidase inhibitors | Effective to improve postprandial hyperglycemia | GI side effects | In case of GI symptoms, differential diagnosis of infection or GVHD |
| Sulfonylureas (SU)[103] | One of the most often prescribed drugs in type 2 DM | Hypoglycemia, weight gain treatment failure<br>Together with CNI, which is often associated with β-cell dysfunction, SU may cause β-cell exhaustion | Risk of hypoglycemia<br>in patients with single morning doses of prednisolone, the hyperglycemia effect of prednisolone does not persist up to 24 h, while long-acting SU (glimepiride or glibenclimide) still are effective.<br>in patients with renal dysfunction, it is better to prescribe short-acting SU (gliclazide or glipizide)<br>in patients not eating reliably |
| Glinides | Enhance early-phase insulin secretion and improve postprandial hyperglycemia | Hypoglycemia (but lower risk than SU) | Repaglinide is more potent than nateglinide, but the incidence of symptomatic hypoglycemia can be higher<br>Repaglinide is contraindicated in patients taking gemfibrozil |
| Incretin drugs, including[104]<br>DPP-4 inhibitors<br>GLP-1RA | Enhance insulin secretion in a glucose-dependent manner<br>Combination of incretin drugs and insulin is a good option[105]<br>DPP-4 inhibitors might enhance hematopoiesis[106]<br>Ongoing study on sitagliptin in umbilical cord blood transplantation (NCT00862719) | Nausea and vomiting are common<br>Low risk of hypoglycemia and weight gain | No particular cautions in PTDM<br>Incretin drugs do not interact with IS drugs<br>Incretin drugs are effective for corticosteroid-induced DM[107,108] |
| SGLT2 inhibitors | New drugs with an insulin-independent mechanism of action<br>Increase urinary glucose excretion, promoting body weight reduction<br>Modest reductions in blood pressure | Higher glucose concentration in urine, leading to bacterial and fungal urogenital infections<br>Polyuria with risk of dehydration and prerenal insufficiency | Considering the risk of genital and urinary tract bacterial and mycotic infections, SGLT2 inhibitors should be cautiously used in immunosuppressed patients such as those after allo-SCT[109] |

Abbreviations: allo-SCT = allogeneic stem cell transplantation; BMI = body mass index; CNI = calcineurin inhibitor; GI = gastrointestinal; IS = immunosuppressant; PPAR = peroxisome proliferator-activated receptor; PTDM = post-transplant diabetes mellitus.

complications.[65,85,86] In the allo-HSCT setting, regular insulin can be added in the PN bag. A common initial regimen is 0.1 units of insulin per gram of glucose in the PN infusion. If the patient is already hyperglycemic (>150 mg/dL), higher dose of insulin (0.15 units of insulin per gram of glucose in PN) should be used.[87] In order to control glucose level tightly (80–110 mg/dL), the mean dose of insulin was around 0.2 units of regular insulin per gram of glucose in PN.[76] Significantly elevated insulin resistance and insufficient insulin secretion after allo-HSCT contribute to the higher insulin requirement during the early period after allo-HSCT.[2,60] A sufficient amount of fat emulsion to cover the caloric needs and thereby reduce the dose of glucose in PN is also recommended.[88–90]

## Outpatient management of PTDM

There is a paucity of data related to treatments for PTDM after allo-HSCT. Various treatments are available for type 2 DM, but for PTDM there are caveats mainly owing to organ dysfunction, in particular kidney function, and concurrent medications, including immunosuppressive drugs. There is no consensus on the glycemic target in PTDM. It is reasonable to follow the guidelines for DM in the general population.[91] Summary of glycemic control recommendation by American Diabetes Association is as follows: preprandial capillary plasma glucose 80–130 mg/dL (4.4–7.2 mmol/L), postprandial capillary plasma glucose <180 mg/dL (<10.0 mmol/L), and HbA1c <7.0%.[91] Better glucose control (preprandial glucose <110 mg/dL, postprandial glucose <140 mg/dL and HbA1c <6.5%) can be the target if these goals can be achieved safely without hypoglycemia.[91,92] Although HbA1c is usually followed every 3 months, it should be checked monthly early after the introduction of drugs to monitor response and adjust treatment. In patients using insulin, self-monitoring of blood glucose is most helpful in guiding titration of insulin.

Lifestyle and nutrition counseling are essential for PTDM as for type 2 DM in the general population.[93] In a large retrospective study on cardiovascular risk factors and complications including >2300 long-term HSCT survivors, diabetes development was associated with tobacco abuse, lower fruit/vegetable intake, physical inactivity and obesity.[94] These results suggest that improved adherence by patients to lifestyle recommendations and attention to effective control of diabetes by clinicians may reduce the risk for cardiovascular morbidity after HSCT.

Similar to the management of individuals with non-transplant-associated type 2 DM, various classes of approved oral glucose-lowering drugs can be considered as treatment for PTDM patients with mild-to-moderate hyperglycemia.[92,95] In principal, management with oral hypoglycemics does not differ in PTDM, with the exception of drug interactions and conditions specific for allo-HSCT. The different oral glucose-lowering drugs with their indications, side effects and precautions in HSCT patients are shown in Table 1.

Insulin is considered the treatment of choice for patients with persistent hyperglycemia despite oral antidiabetic medications, individuals with symptomatic or markedly elevated blood glucose levels or those undergoing treatment with high-dose steroids. Introduction of insulin in the general population can vary based on the guidelines.[96,97] Here we describe a possible method in allo-HSCT recipients, focusing on steroid-induced hyperglycemia. There is no clear consensus about the dose of steroid and the decision to introduce insulin. Patients who take ⩾0.5 mg/kg/day of prednisolone often require exogenous insulin to achieve glucose control. This is influenced by each individual's insulin sensitivity and β-cell function, as well as by comorbidities, such as renal or hepatic dysfunction that may prevent the use of oral drugs for PTDM. The initial dose of insulin is usually 0.4 U/kg/day.[98] It can be lower in patients with low insulin resistance (for instance, ⩽0.3 U/kg/day) and higher in patients with high insulin resistance (for instance, ⩾0.5 U/kg/day). The total dose of insulin can be divided into prandial and basal insulin. As prandial insulin, rapid-acting insulin such as lispro, aspart or gluisine is used, and as basal insulin, long-acting insulin such as glargine, determir or degludec can be applied. If patients receive a single daily steroid dose in the morning, intermediate-acting insulin in the morning may be appropriate, considering the risk of fasting hypoglycemia with long-acting insulin. In the general population, often half of total daily dose is given as basal insulin and the another half is administered as prandial insulin. Alternatively, basal insulin alone can be added to oral drugs.[97,99] In patients with steroid-induced hyperglycemia, a higher proportion of insulin is needed for prandial insulin. At the beginning, use of prandial insulin alone can be an option. If patients have persistent fasting hyperglycemia, basal insulin coverage can be added. If sufficient glucose control is achieved with a low-dose of insulin (that is, 10–20 units/day), it would be reasonable to convert the insulin to an oral diabetes regimen as the steroids are tapered.

**Table 2.** Summary of how to prevent/manage PTDM

| |
|---|
| *1. Pretransplant* |
| Assessment of glycemic status and other CV risk factors when the physician considers the possibility of allogeneic HSCT |
| Assessment of familial risk factors for DM and cardiovascular diseases |
| Control of glucose level in patients with pretransplant DM |
| Weight loss in patients with obesity to decrease insulin resistance |
| *2. Early period after allogeneic HSCT* |
| Close monitoring of glucose level (including postprandial glucose in patients receiving systemic steroid or high fasting glucose level/high insulin dose) |
| Routine use of insulin in patients with TPN to reduce the burden on β-cell/preserve β-cell function |
| Basal/bolus/correction insulin order instead of sliding scale insulin order (usually have to be adjusted daily or once in 2–3 days at the beginning) |
| Appropriate GVHD prophylaxis to reduce the need of systemic steroid |
| Consult endocrinologist when patients develop/are at high risk for PTDM (for example, before the start of systemic steroid) |
| *3. Long-term follow-up after allogeneic HSCT* |
| Routine follow-up of glucose level itself and glucose control marker such as HbA1c or glycoalbumin or fructosamine |
| Regular screening and early management for other cardiovascular risk factors (arterial hypertension; dyslipidemia; obesity) |
| Regular healthy heart lifestyle counseling and surveillance on adhesion to preventive measures |
| Consult endocrinologist when patients develop/are at high risk for PTDM (for example, before the start of systemic steroid) |

Abbreviations: CV = cardiovascular; HbA1c = glycated hemoglobin A1c; HSCT = hematopoietic stem cell transplantation; PTDM = post-transplant diabetes mellitus; TPN = total parenteral nutrition.

## CONCLUSION

PTDM is a common complication after allo-HSCT. Further research is necessary in order to develop appropriate treatment algorithms for the optimal management of PTDM. It is reasonable to follow general guidelines for DM or guidelines for PTDM after solid organ transplantation. Patients with PTDM often have co-existing arterial hypertension and dyslipidemia, which should also be part of the routine management of allo-HSCT survivors. Management includes regular screening, counseling and early treatment, starting pretransplant but continuing lifelong after allo-HSCT (Table 2). PTDM is an under-recognized complication of allo-HSCT. Prospective studies to mitigate the adverse impacts of PTDM are warranted. In the future, meaningful clinical trials will require close collaboration between hematologists, oncologists, endocrinologists and other metabolism experts.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ACKNOWLEDGEMENTS

This work was supported in part by Foundation for Promotion of Cancer Research in Japan. This work was also supported by the National Institutes of Health/National Heart, Lung, and Blood Institute Grant 1K23HL122143-01A (to BGE).

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