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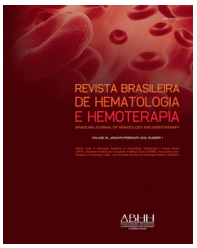

Review article

Nutritional status and hyperglycemia in the peritransplant period: a review of associations with parenteral nutrition and clinical outcomes

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ABSTRACT

Hematopoietic stem cell transplantation is an established treatment option for various hematological diseases. This therapy involves complex procedures and is associated with several systemic complications. Due to the toxic effects of the conditioning regimen used in allogeneic transplantations, patients frequently suffer from severe gastrointestinal complications and are unable to feed themselves properly. This complex clinical scenario often requires specialized nutritional support, and despite the increasing number of studies available, many questions remain regarding the best way to feed these patients. Parenteral nutrition has been traditionally indicated when the effects on gastrointestinal mucosa are significant; however, the true benefits of this type of nutrition in reducing clinical complications have been questioned. Hyperglycemia is a common consequence of parenteral nutrition that seems to be correlated to poor transplantation outcomes and a higher risk of infections. Additionally, nutrition-related pre-transplantation risk factors are being studied, such as impaired nutritional status, poorly controlled diabetes mellitus and obesity. This review aims to discuss some of these recent issues. A real case of allogeneic transplant was used to illustrate the scenario and to highlight the most important topics that motivated this literature review.

Introduction

HSCT is widely used to treat hematological and non-hematological malignancies. Compared to autologous HSCT, allogeneic HSCT (allo-HSCT) causes more severe nutritional consequences and side effects due to its more intense ablative and immunosuppressive conditioning regimen. Mucositis, nausea and vomiting, diarrhea, poor oral intake, malabsorption and prolonged malnutrition are some of the complications often observed.[1–3]

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Therefore, adequate nutritional support is paramount during all the phases of the transplant procedure,[4,5] and is an important measure for better outcomes in the short and long term.[6] Most patients need artificial nutrition at some point and for different lengths of time. Allo-HSCT patients suffering from severe gastrointestinal symptoms usually require prolonged support, frequently via parenteral nutrition (PN) because of very poor oral intake and intolerance to enteral nutrition (EN).[4–7] In cases of severe graft-versus-host disease (GVHD) with gastrointestinal complications, the use of PN usually becomes necessary again.[8] Nevertheless, as PN is an invasive procedure and not free of risks, its use in the quite complex scenario of allo-HSCT has been questioned.[9–11] Recent studies demonstrate that PN can actually be harmful under some circumstances, due to higher risk of hyperglycemia and blood stream infections.[12–14] In addition, despite the increasing number of studies, there is still no clear consensus regarding the benefits of EN versus PN in HSCT patients.[15]

There are several studies demonstrating the importance of a complete nutritional status assessment before the transplant.[16–18] Associations between abnormal body mass index (BMI) and non-relapse mortality (NRM) have been documented.[7,19–21] Correlations between pre-transplantation comorbidities and poor outcomes, especially diabetes mellitus, have also been discussed.[22]

The brief case scenario described below is used to illustrate some difficult situations that can be found in the context of HSCT. The importance of adequate nutritional support, the controversial findings in terms of the best approach and type of nutrition, and some of the deleterious consequences of PN in HSCT patients are emphasized here. Recent findings related to nutritional assessment, pre-transplantation diabetes mellitus and obesity are also reviewed.

Clinical vignette

WSA, a 27-year-old male with diagnosis of acute myeloid leukemia subtype M5 refractory to multiple chemotherapy regimens, was admitted to the Hospital de Clínicas de Porto Alegre for related mismatched allogeneic stem cell transplantation. He was obese (BMI: 30.5 kg/m^2), an active smoker, and on anti-hypertensive treatment. His performance status was ECOG 0. He received Busulfan and Cyclophosphamide plus thymoglobulin as the conditioning regimen, as well as cyclosporine and methotrexate for GVHD prophylaxis. Engraftment occurred around the third week after transplantation; it was followed by acute gastrointestinal (grade III) and hepatic (grade II) GVHD with diagnosis based on the National Institute of Health (NIH) consensus criteria.[23] This complication was refractory to first-line corticosteroid therapy (methylprednisolone 2 mg/kg) and partially responsive to basiliximab (anti-CD25 monoclonal antibody) and infliximab (anti-TNF monoclonal antibody).

An individually compounded PN was initiated on Day 5 after transplantation due to neutropenic enterocolitis with paralytic ileus and oral mucositis grade IV. The PN was calculated based on the patient's body weight of 90 kg at that time, to provide 30–35 kcal/kg/day, at least 1.5 g of protein/kg/day and a maximum of 1.0 g of lipids/kg/day. This composition corresponded to 20–25% of total calories coming from protein (10% amino acid solution), 50–60% from dextrose (50% glucose monohydrate solution) and up to 30% of total calories from lipids (20% lipid emulsion).[1] This diet was maintained for approximately three weeks because of very poor oral tolerance and no safe access for tube feeding due to thrombocytopenia. However, the PN had to be discontinued for short times during this period because of severe hyperglycemia. The patient had a medium glycemic level of around 80–120 mg/dL before starting PN. This complication, related to the use of corticosteroids and immunosuppressants, became clearly worse after the introduction of PN as his serum glucose peaked at 300–400 mg/dL. Even with a reduction of the glucose infusion rate, reduction of total caloric amount of PN to 20–25 kcal/kg/day and high doses of continuous IV insulin administration, the glycemia remained poorly controlled. The PN was interrupted. The patient refused tube feeding, so oral nutrition was initiated according to his tolerance. He had several infectious complications, such as bacterial sinusitis and pneumonia, and died from gram-negative sepsis three months after hematopoietic stem cell transplantation (HSCT).

Pre-transplantation nutritional assessment

HSCT involves an increase in nutritional and metabolic demands that is partially explained by the deleterious effects of the conditioning regimen on the gastrointestinal tract.[1] Furthermore, the occurrence of fever, infections, and the prolonged time of immunosuppression create a hypermetabolic state that can further exacerbate nutritional deficits.[5,24] It is known that an impaired nutritional status before transplantation can affect complications and clinical outcomes of HSCT, in particular allo-HSCT.[16,19,20] In malnourished patients, there is evidence of increased mortality rates, prolonged length of hospitalization and delayed time to engraftment. Moreover, the NRM is higher for the extremely underweight, overweight and obese.[21,25]

There are innumerous available nutritional assessment methods, although none are specific for the HSCT population. Screening questionnaires can be used when combined with a physical examination, biochemical markers, and anthropometry, i.e., the measurement of weight, height, skin folds and circumferences. Single methods have limitations and are inefficient.[18] Liu et al. evaluated and compared different questionnaires in patients with leukemia, and showed a better clinical applicability of the Nutritional Risk Screening 2002 questionnaire (NRS 2002) to detect malnutrition before transplantation.[26,27] The main components of the NRS 2002 are: (1) severity of primary disease and its impact on nutritional status, (2) recent changes of body weight, (3) changes in dietary intake and (4) body mass index. A NRS score $\geq$3 defines nutritional risk, information that can contribute to the planning of peritransplant nutritional support.[28]

In terms of body weight before the procedure, studies show a tendency of high BMI being correlated to higher risk of GVHD and NRM; similar risks are seen in patients with BMI below normal.[19] In addition to BMI and anthropometric measurements of body composition, Urbain et al. evaluated the benefit of using bioelectrical impedance analysis in HSCT patients.[29]

The phase angle, one datum obtained from this procedure, has been correlated with worse clinical prognosis in various diseases as a reduced phase angle can reflect body cell mass loss, especially muscle loss.[30] The study showed that patients with extremely low pre-transplantation phase angles had an increased risk of death in the first two years after transplantation.[29]

Therefore, a complete assessment is a very important step prior to HSCT, and should combine all available tools in order to detect nutritional issues that can be improved prior to the procedure. Also, this approach allows the team to plan adequate nutritional support in advance and to take appropriate measures to maintain this support during and after the procedure.[11,16]

Pre-transplantation comorbidities – the role of obesity and diabetes mellitus

Apart from malnutrition and low body weight, traditionally associated with poor outcomes in cancer patients, other prognostic factors associated to nutritional status have been described recently. Among these, obesity and diabetes mellitus seem to play an important role in HSCT patients.[22,31–33] Sorror et al. established the hematopoietic cell transplantation-comorbidity index (HCT-CI), which is a scoring system to predict the risk of NRM after transplantation. This index, which includes dysfunction of different organs, such as pulmonary, hepatic, cardiac, and renal dysfunction, also includes diabetes and obesity as deleterious comorbidities (based on a BMI > 35 kg/m^2 in adults).[34] It has been validated in several countries as a predictor of HSCT complications.[35]

There is a growing number of studies, albeit retrospective studies, that show an association of high BMI before transplantation with a greater risk of GVHD and NRM.[7,20,31,33] Gleimer et al. observed a significant increase in NRM among obese patients submitted to allo-HSCT.[7] To confirm these findings, Nakao et al. conducted a meta-analysis to assess whether overweight patients submitted to HSCT actually experience worse outcomes. A statistically significant association was found between excess of body weight and poor outcomes after allo-HSCT, but no significant impact was found on survival in autologous HSCT. That correlation was especially true for the occurrence of acute GVHD among overweight patients.[31] The possible reasons involved could be inappropriate doses of conditioning regimen due to different medication pharmacokinetics in the obese, the dose of infused stem cells and of GVHD prophylaxis. In this case, the ideal body weight could be a better predictor of dose adequacy.[36] Other possible factors involve cytokine-related mechanisms, such as the effect of T-cell proliferation and function driven by adipocytokines.[31]

Pre-transplantation diabetes mellitus has also been reported as an important risk factor for worse transplantation outcomes and NRM. A significantly greater number of invasive fungal diseases and impaired neutrophil function have been described in diabetic patients submitted to HSCT.[22,32] Although Takano et al. showed that pre-engraftment hyperglycemia could be a risk factor for infectious diseases, acute GVHD and NRM, hyperglycemia after the procedure can also increase the risk of subsequent NRM.[12,37,38] Fuji et al., however, stated that it is still unclear whether a better control of diabetes mellitus prior to HSCT would actually reduce these complications, and further research is still necessary.[12]

Specialized nutritional support after HSCT – enteral versus parenteral nutrition

The prolonged gastrointestinal symptoms that occur in the first days after the transplantation give rise to the need of specialized nutritional support. The first 10–15 days are critical especially due to neutropenic mucositis, nausea and poor oral intake.[4,24] It is suggested that maintaining the functions of the digestive tract, even with small volumes of nutrition, could bring beneficial effects in terms of maintenance of the immunological gut barrier and glucose level control.[39–41] However, the use of tube feeding in this population is still being studied and is not standard practice, mainly because of the challenges of establishing a safe enteral access in patients with severe mucositis, gastrointestinal tract damage and thrombocytopenia.[24] When the caloric target is not achieved or the patient presents significant gastrointestinal intolerance, the use of PN may be justified to minimize nutrient deficiencies and maintain body weight. However, its advantages and disadvantages are still under discussion considering the potentially higher risk of bacteremia, catheter-site infections, hyperglycemia and fluid overload observed in PN recipients.[10]

The use of PN in HSCT has been described in the literature since the 1980s and these pioneering studies are still used as reference.[42,43] In 1987, Weisdorf et al. compared PN versus intravenous dextrose solution to adult and pediatric patients undergoing allogeneic and autologous HSCT from seven days before cytoreductive chemotherapy until 28 days after the transplant. Patients in the allogeneic group on PN had a better 2-year overall survival, although presented a higher rate of bacteremia compared to the control group. No difference in time to engraftment, length of hospitalization and incidence of GVHD were observed.[43] Over the last decades, similar studies have been published.[9,39,44–46] Nevertheless, most of them had heterogeneous populations of children and adults undergoing autologous and allogeneic HSCT, making an analysis of the results a difficult task. Lough et al. for example, compared total PN (TPN) and intravenous 5% dextrose solution in adults submitted to both types of HSCT; there was a trend towards more fluid overload, longer time of fever and a higher number of positive blood cultures in the TPN arm.[45] Muscaritoli et al., in 1998, compared glucose-based and lipid-based PN in both types of transplant, demonstrating a trend towards more acute GVHD and hyperglycemia in the glucose group.[46] More recently, Cetin et al. evaluated the effects of TPN versus partial PN in autologous patients; the TPN group had higher rates of hyperglycemia, more infections and delayed platelet engraftment.[44] Therefore, as Arfons et al. demonstrated, to construct clear recommendations about the use of PN in this scenario is still challenging considering the heterogeneity of the available studies.[10]

In terms of timing to initiate PN in HSCT patients, there are two described approaches in recent literature: soon after

the transplantation (Day 0 or 1) independently of oral tolerance, or according to the nutritional needs of the patient. The former approach is less used, although some centers still prefer this form of nutritional intervention: starting on the first day after allo-HSCT and continuing for 15–21 days.[1] Therefore, when to start PN is another matter of controversy. The European Society for Clinical Nutrition and Metabolism (ESPEN) proposes to initiate PN once oral feeding falls below 60–70% of requirements for three consecutive days,[47] and this recommendation is followed by the Sociedade Brasileira de Nutrição Parenteral e Enteral (SBNPE).[48] The American Society for Parenteral and Enteral Nutrition considers 7–14 days an appropriate definition of "prolonged period of time" of unsatisfactory oral/enteral nutrition before establishing PN.[24] Table 1 shows the current recommendations of nutritional support and use of PN in HSCT from different societies and study groups.

When PN is compared to EN, most studies showed several benefits of maintaining the use of the digestive tract during the transplant phases.[39–41] In the same year as Weisdorf et al. published their study on PN, Szeluga et al. conducted a study to compare EN and PN in pediatric and adult HSCT patients. There were no differences between groups in terms of survival, immunological recovery, length of hospitalization, and GVHD; however, a non-statistically significant difference was observed in the incidence of bacteremia, catheter-site infections, hyperglycemia and fluid overload in the PN patients.[11] Since then, a growing number of trials have been conducted to demonstrate the safety and feasibility of EN in this context, but up-to-date guidelines with clear recommendations are still lacking. According to Guiese et al., there are few studies comparing EN to PN among allo-HSCT patients, although the available evidence shows a clear trend of reduction in the incidence of acute GVHD and low infection-related mortality within the first 100 days after transplant in patients receiving EN.[39,40] The only meta-analysis available until today, published in 2008, concluded that there is still insufficient data to determine clear benefits of EN versus PN in patients undergoing allo-HSCT.[15] Even with these limitations, the authors propose that EN should be adopted as the first choice for nutritional support while the gut remains functional, with supplementary PN being added only when energy requirements are not achieved or there is a clear intolerance to tube feeding.[15] The ESPEN also shares these recommendations: PN should be reserved for use in patients with severe mucositis (grade 3–4), prolonged ileus, and intractable vomiting.[47] A prospective randomized controlled trial comparing PN and EN after myeloablative HSCT is ongoing in France (NEPHA study), and hopefully will elucidate this important issue in the near future.[49]

Post-transplantation hyperglycemia: the role of parenteral nutrition

Hyperglycemia frequently occurs after HSCT, mainly because of the effects of glucocorticosteroids, immunosuppressive drugs and the use of PN.[12,37,38] The hyperglycemic environment may cause a delay in neutrophil recovery, impair neutrophil function, promote greater risk of infections and prolong engraftment times.[50] Additionally, the metabolic alterations that occur in the early phase after transplantation result in more endogenous glucose production, increased insulin resistance and an impaired capacity to oxidize plasma glucose.[51] Factors that were independently associated with hyperglycemia during the first ten days after allo-HSCT were greater BMI and insulin resistance, use of tacrolimus and glucocorticoids, myeloablative conditioning with total body irradiation and the use of total PN.[37] It has been demonstrated that the odds of developing hyperglycemia after PN is nearly four-fold (odds ratio: 3.9; 95% confidence interval: 2.7–5.5) that of patients not submitted to PN after controlling for donor type, race, age, and conditioning chemotherapy.[50]

It has been hypothesized that the negative consequences of impaired glucose control in the inflammatory cascade can also increase the risk of acute GVHD, which itself raises hyperglycemia even further, creating a vicious cycle.[52,53] Gebremedhin et al. showed a higher incidence of acute GVHD after allo-HSCT when severe hyperglycemia was present. However, this association varied by category of BMI: among normal-to-overweight subjects, severe hyperglycemia was markedly associated with acute GVHD, and lean BMI seemed to be a protective factor against this complication.[37] Fuji et al. also demonstrated a greater cumulative incidence of grade II–IV GVHD in patients presenting hyperglycemia (glucose levels > 150 mg/dL) during the neutropenic phase after transplant. According to these authors, it is reasonable to speculate that the increased production of inflammatory cytokines by hyperglycemia can act as a risk factor in the pathogenesis of acute GVHD and organ dysfunction.[12] According to Sheean et al., PN has inherently greater risks of infections when compared with EN or standard oral diets, and because of its adverse consequences, several authors have challenged the intuitive conclusion that PN is beneficial and necessary during HSCT.[14] A higher risk of catheter-related bloodstream infections in PN recipients is well described in the literature[54] as the micro- and macronutrient composition of PN can facilitate the growth of microorganisms.[55] Furthermore, it has been suggested that these infectious complications could also be related to bacterial translocation due to atrophy of the gut mucosa and gut-associated lymphoid tissue, as a consequence of PN or absence of EN.[56] However, according to Jeejeebhoy et al., human studies did not demonstrate intestinal atrophy related to PN and there is little evidence that EN can prevent bacterial translocation.[57]

A multicenter study conducted with non-critically ill inpatients that received PN demonstrated increased in-hospital mortality, mainly because of hyperglycemia and infections.[52] The goal of glycemic control in non-critically ill patients that receive PN should be up to 180 mg/dL according to the authors.[52] Contrarily, Sheean et al. proposes that until more experimental evidence is available, blood glucose levels during TPN administration should not exceed 150 mg/dL.[58] In the critically-ill, Van den Berghe et al. showed that rigid control of hyperglycemia with intensive insulin therapy (blood glucose level from 80 to 110 mg/dL) reduced morbidity and mortality.[59] Nonetheless, the NICE SUGAR study demonstrated worse clinical outcomes with such tight glucose control in the intensive care unit.[60] Currently, glucose levels between 140-180 mg/dL in critically ill patients are acceptable, and recent data suggest

Table 1 – Nutritional support recommendations and use of PN in HSCT by different societies and study groups.

	Indications for NST	Energy requirements	Protein requirements	PN discontinuation criteria	Areas of uncertainty	PN adverse effects
ASPEN[9]	Malnourished patients unable to absorb/ingest adequate nutrients for 7–14 days Criteria to initiate PN not specified	Not mentioned	Not mentioned	After stem cell engraftment when adequate EN or oral intake is feasible	Benefits of a lipid based PN vs. glucose based PN to decrease risk of GVHD Use of glutamine	Increased morbidity, more diarrhea, more hyperglycemia, delayed time to engraftment
ESPEN[47]	Start NST if: - Undernourished - Inability to eat >60% of nutritional needs for >7 days PN preferred if increased risk of hemorrhage and infection related to tube placement	Ambulant patient: 30–35 kcal/kg/day Bedridden patient: 20–25 kcal/kg/day (recommendations for general oncology patients)	1.2–2.0 g/kg/day (recommendations for general oncology patients)	Not mentioned	Benefits of glutamine and omega 3	Not mentioned
Italian group University La Sapienza, Rome[2]	PN routinely initiated on Day-1 of allo-HSCT and continued for 15–21 days. Oral intake not allowed during this period	130–150% of basal energy requirements or 30–35 kcal/kg/day	1.5 g/kg/day	Not mentioned	Benefits of a lipid based PN in decreasing risk of acute GVHD use of glutamine	Not mentioned
FNCLCC[18]	NST indicated to malnourished patients (>10% loss of body weight) irrespective of the type of transplant or conditioning PN if oral/EN intolerance, GI obstruction or severe mucositis	Non-protein calorie intake of 25–35 kcal/kg/day	Daily nitrogen intake between 200 and 250 mg/kg	Oral and/or EN able to provide > 60% of nutritional requirements	Benefits of a lipid based PN in decreasing risk of acute GVHD use of glutamine	Not mentioned
Spanish group Univesity La Paz, Madrid[6]	Start PN if: - Loss of >10% of initial weight - BMI <18.5 kg/m^2 - Oral intake < 60–70% of required over 3 days	130–150% of the estimated basal energy requirements, or 30–50 kcal/kg/day	1.5–2.0 g/kg/day of standard amino acid solution	Oral diet covers > 50% of daily energy needs	Benefits of glutamine, antioxidants (selenium, vitamins C and E) and omega 3	Catheter-related infections Atrophy of villi and increase in bacterial translocation
SBNPE[48]	Start PN if: - Severe malnutrition at hospital admission - 7–10 days of inadequate oral intake - Weight loss > 10% during treatment	130–150% of basal energy requirements or 30–35 kcal/kg/day	1.5 g/kg/day	Oral intake and/or EN able to provide > 50% of nutritional requirements	Timing to initiate PN: - 24–36 h after transplantation OR - When oral intake <60–70% of nutritional requirements	More hyperglycemia, higher risk of infections and positive blood cultures, prolonged hospitalization and need of transfusions

NST: nutritional support therapy; ASPEN: American Society for Parenteral and Enteral Nutrition; ESPEN: European Society for Clinical Nutrition and Metabolism; FNLCCC: Fédération Nationale des Centres de Lutte Contre le Cancer; SBNPE: Sociedade Brasileira de Nutrição Parenteral e Enteral; EN: enteral nutrition; PN: parenteral nutrition; GI: gastrointestinal tract; GVHD: graft versus host disease; BMI: body mass index.

that the glycemic goal in non-critically ill patients receiving TPN should be at a mean level of 180 mg/dL.[52]

Conclusions

This review aimed to discuss some relevant topics related to nutritional status of patients submitted to HSCT and complications caused by PN in this population, in particular hyperglycemia and its adverse effects. The amount of scientific evidence regarding the best nutritional approach for HSCT patients is still insufficient and inconclusive, as there is no consensus or clear recommendations regarding the timing and criteria to initiate EN and PN. A complete nutritional assessment prior to HSCT is recommended by all societies, as it gives information essential to build a nutritional support plan for the peritransplant period.

Despite the inherent risks of PN, and the insufficient amount of studies demonstrating clear benefits of this type of nutrition in the HSCT population, it continues to be recommended as part of transplant care. Therefore, assessment of risk factors for hyperglycemia prior to HSCT, a careful choice of the conditioning regimen and all efforts to avoid prolonged PN in patients at higher risk for this complication contribute to successful post-transplant recovery.

Conflicts of interest

The authors declare no conflicts of interest.

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