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Research Article
Factors Influencing Loss of Body Weight in Cord Blood Transplantation with Nutritional Support for Hematopoietic Stem Cell Transplantation

[1]Takashi Aoyama, [2]Hidekazu Arai, [3]Osamu Imataki and [4]Takashi Ikeda

[1]Division of Nutrition, Shizuoka Cancer Center, Shizuoka, Japan
[2]Division of Laboratory of Clinical Nutrition and Management, Graduate School of Integrated Pharmaceutical and Nutritional Sciences, The University of Shizuoka, Shizuoka, Japan
[3]Division of Hematology and Stem Cell Transplantation, Kagawa University Hospital, Kagawa, Japan
[4]Division of Hematology and Stem Cell Transplantation, Shizuoka Cancer Center, Shizuoka, Japan

Abstract

Background and Objective: Patients may experience nutrition-related adverse events during hematopoietic stem cell transplantation (HSCT) and long-term nutritional intervention was likely needed after cord blood transplantation (CBT) for HSCT due to the long engraftment period. Previous studies have examined nutritional therapy for HSCT but there has been no discussion of loss of body weight (LBW) for CBT patients on HSCT nutritional pathways or of the specific nutritional interventions used. The objective of this study was to identify the specific factors influencing LBW in this patient population and to evaluate the nutritional intervention implemented. **Materials and Methods:** Subjects in this retrospective exploratory pilot study were 15 patients who underwent CBT with nutritional support following the HSCT nutritional pathway at the Department of Stem Cell Transplantation, Shizuoka Cancer Center, between 2008 and 2012. Correlations were assessed using Pearson's product-moment correlation coefficients between percent loss of body weight (%LBW) and bioelectrical impedance analysis results, nutrient intake and graft-versus-host disease (GVHD) as well as between continuous oral intake percentage and nutrition-related adverse events (severity score) and orally ingested calories. Spearman rank-order correlation was used to analyze severity scores. Data was also analyzed using JMP. **Results:** Body weight and skeletal muscle mass decreased significantly during follow-up. Percent LBW was correlated with percent loss of skeletal muscle mass ($r = 0.89$, $p<0.001$), total nutrient intake (calories: $r = 0.69$, $p<0.001$ and protein: $r = 0.69$, $p = 0.02$), orally ingested intake (calories: $r = 0.53$, $p = 0.04$ and protein: $r = 0.60$, $p = 0.01$) and intestinal acute GVHD ($r = 0.63$, $p = 0.01$). Continuous oral intake percentage was correlated with nutrition-related adverse events (severity score: $r = 0.66$, $p<0.001$) and orally ingested calories ($r = -0.55$, $p<0.001$). **Conclusion:** Nutritional complications are unavoidable factors influencing LBW in CBT patients on the HSCT nutritional pathway and early nutritional intervention is required. To attenuate LBW in these patients, the intensity of nutritional intervention should be adjusted based on severity scores for nutrition-related adverse events.

Key words: Body weight, cord blood transplantation, skeletal muscle mass, intestinal acute graft-versus-host disease, nutrition-related adverse event

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Corresponding Author: Takashi Aoyama, Division of Nutrition, Shizuoka Cancer Center 1007 Shimonagakubo, Naga-izumi-cho, Sunto-gun, 411-8777 Shizuoka, Japan Tel: +81-55-989-5222 Fax: +81-55-989-5634

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT), including cord blood stem cell transplantation (CBT), has become a widespread method of transplantation in recent years. CBT enables prompt treatment in urgent cases of bone marrow transplantation, especially compared with the more time-consuming method of finding a donor for allogeneic peripheral blood stem cell transplantation. The usefulness of CBT as a transplantation method has been demonstrated[1,2]. For HSCT, the timing of CBT was easier to accommodate than the timing of bone marrow transplantation or allogeneic peripheral blood stem cell transplantation. However, CBT requires several successive engraftments of a small number of cells each time (neutrophils>500 cm^{-3}). In addition, the long engraftment period poses risks such as infection, although the high engraftment rate of 85% in Japan implies the safety of this procedure[3,4]. Studies have compensated for these small amounts of stem cells by infusing multiple cord blood units and performing early engraftment[5].

Patients can experience nutrition-related adverse events over the course of HSCT. One particularly notable adverse event was difficult with oral feeding due to gastrointestinal symptoms or mucosal injury, which often begins at the start of treatment (pretreatment) and lasts throughout the cytopenic phase. This markedly reduces quality of life (QOL)[3,6,7]. Difficulty with oral feeding can also overlap with acute graft-versus-host disease (aGVHD), leading many patients to eventually need total parenteral nutrition (TPN)[7,8]. A large proportion of patients on long-term TPN develop hyperglycemia and this may be associated with loss of body weight (LBW), infection and death[9,10]. To prevent hyperglycemia, it was desirable to quickly transition patients from TPN to oral feeding and this requires nutritional intervention tailored to their clinical condition[11-14]. Moreover, it was necessary in cancer care to prevent significant LBW by intensive oral nutritional intervention, achieved through patient counseling[15-17]. Various approaches to nutritional intervention have been proposed in Japan to date, including nutritional pathways and PES statements (Problem, Etiology, Signs and Symptoms), however, the actual effectiveness of the approaches implemented has not been investigated[18,19].

Since Shizuoka Cancer Center opened in 2002, an HSCT nutritional pathway has been used that was tailored to patient preferences and clinical symptoms. This pathway involves monitoring input (nutrient intake) and output (weight analysis) for all consenting HSCT patients[20-24]. The usefulness of nutritional therapy in autologous peripheral blood stem cell transplantation (auto-PBSCT) and nutritional risk in allogenic stem cell transplantation has been previously assessed at the center[22,23] but its usefulness has not yet been assessed in CBT, where nutritional intervention was likely to be lengthy due to the long engraftment period. Some previous studies examined nutritional therapy for HSCT but not specifically LBW after CBT in patients following an HSCT nutritional pathway and they have not discussed the nutritional interventions used[25-27].

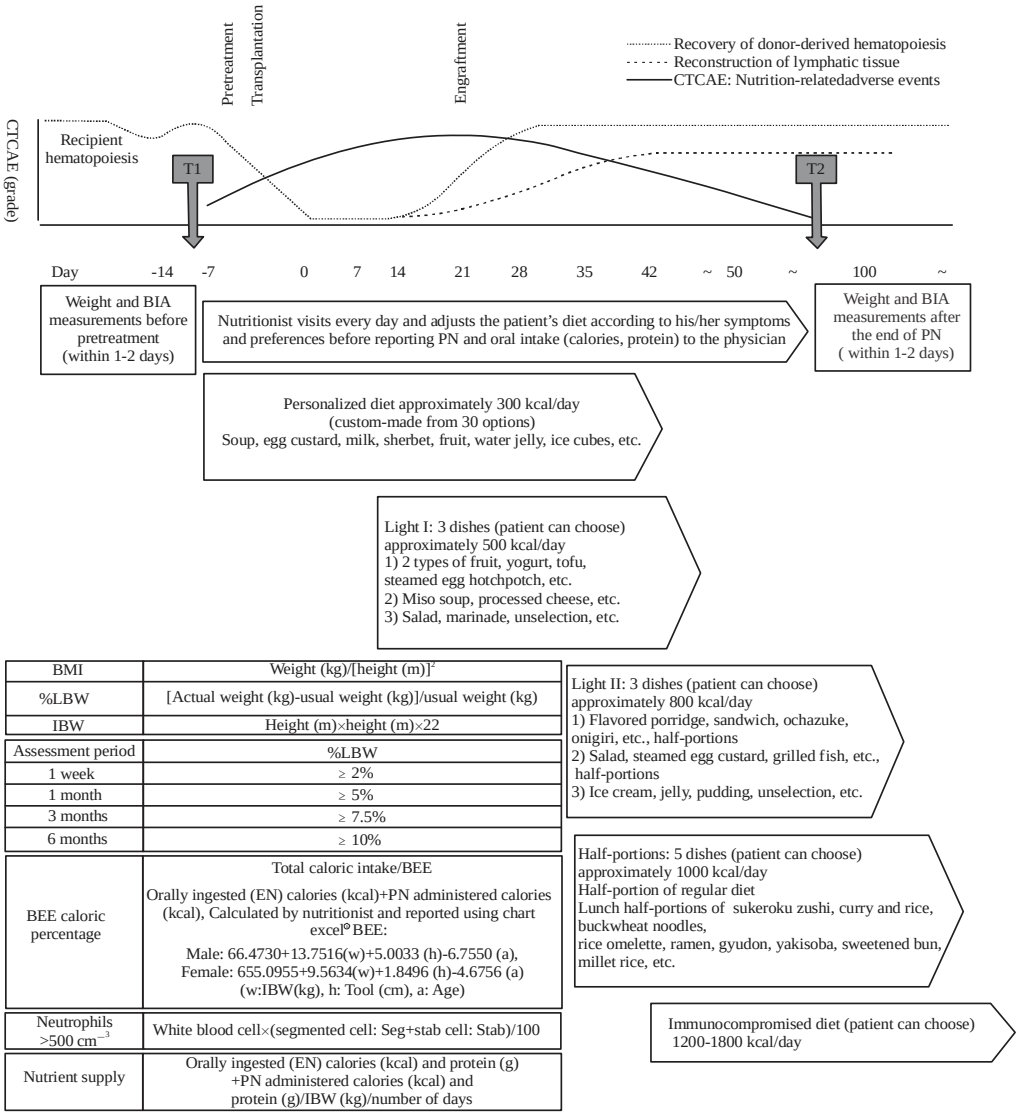
Against this background, this retrospective exploratory pilot study aimed to identify specific factors influencing LBW in CBT patients following the center's HSCT nutritional pathway, in order to evaluate implementation of the nutritional intervention provided and determine any improvements to be made.

MATERIALS AND METHODS

Subjects and study design: This pilot study was conducted between 2008 and 2012 as a precursor to a prospective study that was currently ongoing to verify the findings reported here. It involved 30 patients at the Department of Stem Cell Transplantation of Shizuoka Cancer Center who had undergone CBT (transplant date: 0 day) and discontinued PN by day 100 during the study period.

Methods: Parameters in the center's nutritional pathway were assessed from 1-2 days before the initiation of pretreatment to 1-2 days after discontinuation of PN[23]. In the nutritional pathway (Fig. 1), a nutritionist visited patients daily to adjust the diet according to their symptoms and preferences and then reported PN and oral intake (calories, protein) to the physician. Nutritional support consisted of ordinary cuisine and foods[20-24] and immuno-nutrition such as glutamine or arginine was not routinely used.

The BMI was evaluated before initiation of pretreatment, LBW was evaluated from 1-2 days before initiation of pretreatment to 1-2 days after the end of PN and the number of patients exhibiting a significant rate of change in body weight (%LBW $\geq$7.5 over 3 months) was assessed as defined by White *et al.*[28]. Bioelectrical impedance analysis (BIA) was also evaluated before and after assessments of skeletal muscle mass, body fat mass and phase angle (which were measured by weight analysis) and the respective variations were compared as previously reported (Fig. 1)[29]. The BIA measurements were performed using the In Body S20 body composition analyzer (Biospace, Korea) from



BMI	Weight (kg)/[height (m)]^2
%LBW	[Actual weight (kg)-usual weight (kg)]/usual weight (kg)
IBW	Height (m)×height (m)×22

Assessment period	%LBW
1 week	≥ 2%
1 month	≥ 5%
3 months	≥ 7.5%
6 months	≥ 10%

BEE caloric percentage	Total caloric intake/BEE Orally ingested (EN) calories (kcal)+PN administered calories (kcal), Calculated by nutritionist and reported using chart excel® BEE: Male: 66.4730+13.7516(w)+5.0033 (h)-6.7550 (a), Female: 655.0955+9.5634(w)+1.8496 (h)-4.6756 (a) (w:IBW(kg), h: Tool (cm), a: Age)
Neutrophils >500 cm^{-3}	White blood cell×(segmented cell: Seg+stab cell: Stab)/100
Nutrient supply	Orally ingested (EN) calories (kcal) and protein (g) +PN administered calories (kcal) and protein (g)/IBW (kg)/number of days

Fig. 1: Details of the nutritional path way used with patients undergoing HSCT at Shizuoka Cancer Center, Japan, HSCT: Hematopoietic stem cell transplantation, BIA: Bioelectrical impedance analysis, PN: Parenteral nutrition, BMI: Body mass index, %LBW: Percentage loss body weight, IBW: Ideal body weight, BEE: Basal energy expenditure and EN: Enteral nutrition

10:00-12:00, 2 h after the patient's breakfast. Six frequency impedance values were measured (1, 5, 50, 250, 500 and 1000 kHz) in descending order at 8 locations, both thumbs and middle fingers, both heels and side of each foot[30]. The ratio of intracellular fluid to extracellular fluid (ECF) in physical composition was 2:1 and the ratio of intracellular water to extracellular water (ECW) was 62:38 and thus the standard value for ECF/total body fluid was 0.35 and that for ECW/total body water was 0.40. Owing to the effect of other forms of hydration that are unrelated to PN in patients undergoing CBT, slight increases in ECF/total body fluid up to 0.38 and in ECW/total body water upto 0.43 were allowed for. If these values were exceeded, measurements were repeated the following day.

Correlations of %LBW with the following parameters were assessed:

- **BIA:** Percent loss of skeletal muscle mass (%LSMM) and percent loss of fat mass
- **Nutrient intake:** Total daily nutrient intake (calories and protein) was calculated by adding the orally ingested calorie intake to the PN calorie intake (including total parenteral nutrition, amino acid supplement and 5% dextrose in water) per ideal body weight (IBW)[31]

- Basal calorie expenditure (BEE) per IBW was calculated using the Harris-Benedict equation. Total calorie intake was divided by BEE to calculate the BEE caloric percentage[32] and its correlation with the grade of aGVHD over the observation period was then assessed[7]
- Correlation of aGVHD grade with orally ingested calories (IBW/day) was also assessed
- Magnitude of change to the minimum albumin (Alb) level and to the maximum C-reactive protein (CRP) level from levels before pre-treatment was determined

Because oral intake becomes increasingly difficult over the course of HSCT and peaks at engraftment day, meal offerings must be tailored according to the severity of adverse events, which gradually decrease after myelosuppression and to the patient's needs[21-23]. Therefore, to evaluate implementation of the HSCT nutritional pathway for CBT, correlations were assessed between oral intake percentage (percentage of provided calories orally ingested) and daily caloric requirements (kcal/IBW kg/day) and PN caloric percentage (percentage of the daily caloric requirements from PN calories).

To examine the total daily oral intake percentage, total volume of oral intake per day for all subjects was divided by the number of subjects and presented as a cumulative graph, then orally ingested calories were added to assess as a time-series graph.

To examine overlapping symptoms in patients undergoing CBT, grades for specific adverse events were used based on the Japan Clinical Oncology Group, Japanese version of the Common Terminology Criteria for Adverse Events (CTCAE v3.0-4.9: Revised in 2009). The CTCAE grades were noted in the medical records by each subject's primary nurse or physician. In the nutritional pathway, vomiting, nausea, anorexia, mucositis/stomatitis and taste alterations, which pose obstacles to oral intake are listed among the CTCAE as "nutrition-related adverse events", grade 1 or greater ($\geq$G1) vomiting, $\geq$G2 nausea, $\geq$G2 anorexia, $\geq$G2 mucositis/stomatitis and $\geq$G2 taste alterations are associated with an actual decrease in food intake and thus are set as cut-off values for severity scores of nutrition-related adverse events (Table 1)[33]. To assign a total severity score for each subject, the mean severity score for each nutrition-related adverse event they experienced was summed as in this example: G3 anorexia (severity score 1)+G1 taste alterations (severity score 0) = total severity score 1. To examine symptoms that resolved over time, the total daily severity score for each nutrition-related adverse event was divided by the number of subjects and presented as a cumulative graph, then oral intake percentage was added to assess as a time-series graph.

Table 1: Grading of nutrition-related adverse events in CTCAE v3.0 and v4.0

Adverse event	Grade	Symptom by CTCAE
Vomiting	Version 3.0: Grade 1	1 episode in 24 h
	Version 4.0: Grade 1	1-2 episodes (separated by 5 min) in 24 h
Nausea	Version 3.0: Grade 2	Oral intake decreased without significant weight loss, dehydration or malnutrition, IV fluids indicated <24 h
	Version 4.0: Grade 2	Oral intake decreased without significant weight loss, dehydration and or malnutrition
Anorexia	Version 3.0: Grade 2	Oral intake altered without significant weight loss or malnutrition and oral nutritional supplements indicated
	Version 4.0: Grade 2	Oral intake altered without significant weight loss or malnutrition and oral nutritional supplements indicated
Mucositis/stomatitis (functional/symptomatic) -Select: Oral cavity	Version 3.0: Grade 2	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet, respiratory symptoms interfering with function but not interfering with ADL
	Version 4.0: Grade 2	Moderate pain, not interfering with oral intake, modified diet indicated
Taste alteration (dysgeusia)	Version 3.0: Grade 2	Altered taste with change in diet (e.g., oral supplements), noxious or unpleasant taste and loss of taste
	Version 4.0: Grade 2	Altered taste with change in diet (e.g., oral supplements), noxious or unpleasant taste and loss of taste

CTCAE: Common terminology criteria for adverse events

The Ethics Committee of Shizuoka Cancer Center approved this study. Written informed consent was obtained from participants.

Statistical analysis: All assessments used median values (min-max). Pearson's product-moment correlation coefficient was used to analyze weight and body composition. Spearman rank-order correlation was used to analyze severity scores for nutrition-related adverse events and orally ingested calories. Significance was set at $p<0.05$. All statistical analysis was performed using JMP version 12.0 for windows (SAS Institute, USA).

RESULTS

A total of 30 patients underwent CBT during the study period and all consented to the HSCT nutritional pathway. Of the remaining 15 patients that were excluded, 11 died of transplantation-related complications and 4 were still on PN after 100 days because of aGVHD. Underlying diseases were myelodysplastic syndrome in 6 patients, acute lymphoid leukemia in 4, acute myelogenous leukemia in 3 and malignant lymphoma in 2. Pre-treatment regimens before allo-SCT were fludarabin-melphalan (-total body irradiation [TBI]: 4Gy) in 8 patients, busulfan-cyclophosphamide (-TBI:12Gy) in 5 and fludarabine-busulfan in 2.

Table 2 shows patient characteristics before pre-treatment and the results of nutritional assessments from before pretreatment until PN was discontinued.

The main findings were as follows:

- Percent LBW was correlated with %LSMM (Fig. 2a)
- Percent LBW was correlated with total calorie intake and orally ingested calorie intake as well as total protein intake and orally ingested protein intake (Fig. 2b,c)
- BEE caloric percentage or the percentage of BEE from the total calorie intake was correlated with %LBW
- Cutaneous aGVHD and intestinal aGVHD were observed. Grade of intestinal aGVHD was correlated with %LBW ($r = 0.64$, $p = 0.009$) and orally ingested calories (IBW/day, $r = 0.69$, $p = 0.004$, Table 3)

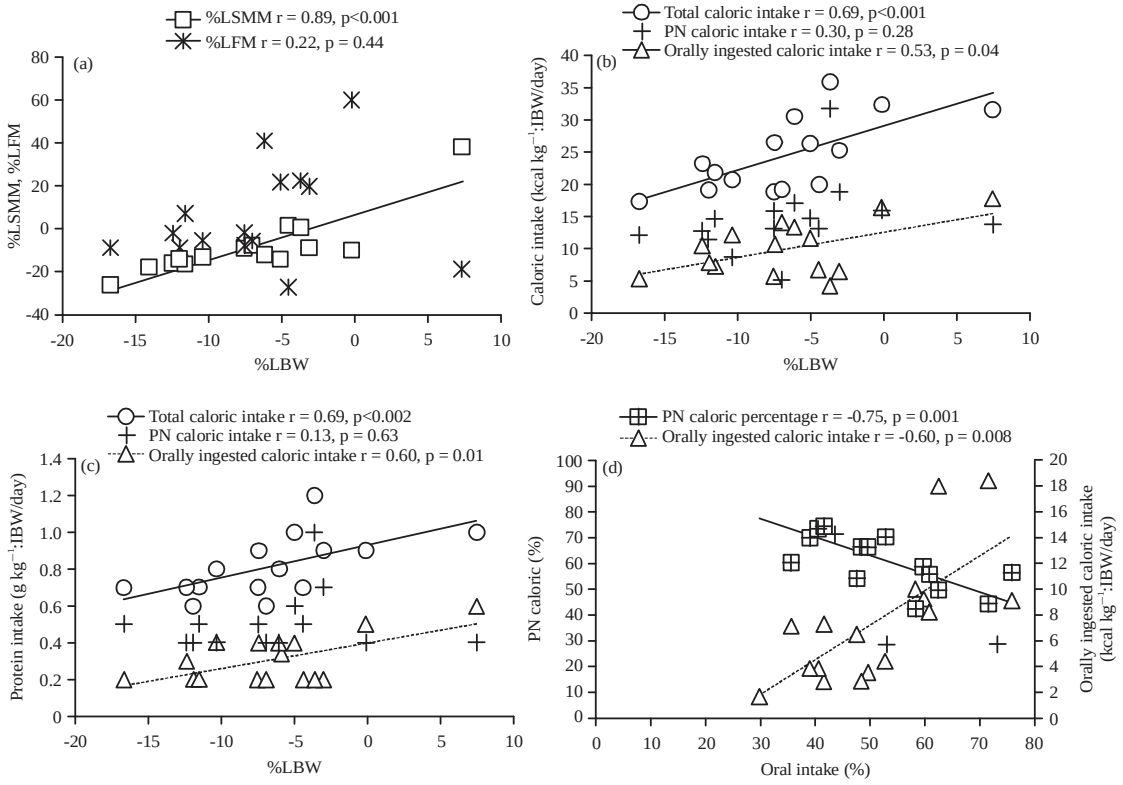


Fig. 2(a-d): Correlations of %LBW with (a) %LSMM, (b) Calorie intake (total, PN, and orally ingested), (c) Protein intake (total, PN, and orally ingested) and (d) Correlation of oral intake percentage with daily orally ingested calories (IBW/day) and PN caloric percentage. IBW: Ideal body weight, %LBW: Percent loss of body weight, %LSMM: Percent loss of skeletal muscle mass and PN: Parenteral nutrition

Table 2: Patient background and nutritional assessment parameters measured in the HSCT nutritional pathway

Assessment parameters	Results
Study period	2007/04-2012/12
Sample size, n (female/male)	15 (7/8)
Age, years (range)	55 (18-68)
Preoperative BMI, kg m^{-2} (min-max)	21.1 (17.8-23.8)
Preoperative %IBW (min-max)	97.9 (80.7-111.2)
Assessment period, days (min-max)	69 (48-104)
%LBW (min-max)	-7.0 (-16.7-7.4)
Significant %LBW cases: %LBW $\geq$7.5, n	7/15
Total caloric intake (min-max): a	23 kcal/IBW/day (17-36)
PN caloric intake (min-max): b	14 kcal/IBW/day (5-32)
Orally ingested caloric intake (min-max): c	11 kcal/IBW/day (4-18)
Total protein intake (min-max)	0.8 g/IBW/day (0.6-1.2)
PN protein intake (min-max)	0.5 g/IBW/day (0.4-1.0)
Orally ingested protein intake (min-max)	0.2 g/IBW/day (0.2-0.6)
BEE/IBW (min-max): d	22 kcal/IBW/day (21-26)
BEE caloric percentage (min-max): d/a	1.0 (0.7-1.7)
Engraftment day (min-max)	Day 23 (13-35)

	Before pretreatment	After stopping PN	Variations during assessment period	p-value*
Body weight (min-max)	56.2 kg (39.8-65.8)	53.5 kg (37.8-59)	-3.8 kg (-9.2-3.3)	0.0009
Skeletal muscle mass (min-max)	22.2 kg (10.8-28.8)	20 kg (13.8-25.1)	-2.5 kg (-5.1-4.1)	0.0082
Body fat mass (min-max)	13.1 kg (6.5-25.2)	12.7 kg (8.6-22.8)	-0.4 kg (-4.4-3.9)	0.79
BIA: ECF/TBF, ECW/TBW (min-max)	0.34 (0.33-0.37),	0.35 (0.26-0.38),	0.01 (0.07-0.02),	0.41
	0.39 (0.38-0.41)	0.40 (0.31-0.43)	0.01 (0.07-0.02)	0.48
Phase angle (min-max)	4.98°(3.28-6.61)	4.5°(2.65-6.14)	-0.62°(-2.33-2.81)	0.1165

BMI: Body mass index, LBW: Loss of body weight, IBW: Ideal body weight, BEE: Basal energy expenditure, PN: Parenteral nutrition, BIA: Bioelectrical impedance analysis, ECF, Extracellular fluid, TBF: Total body fluid, ECW: Extracellular water, TBW: Total body water. Median (min-max) *p-value before (Before pretreatment) versus after (After discontinuing PN) assessment period (Wilcoxon signed-rank test)

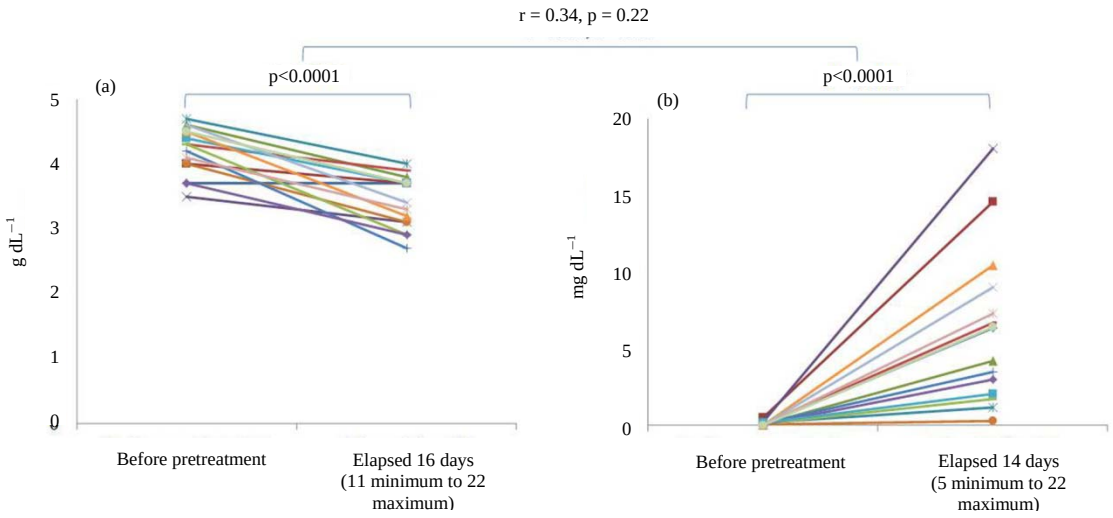


Fig. 3(a-b): Relationship between and changes in Albleveland CRP level. Alb: Albumin, CRP: C-reactive protein, (a) ALB changes (median: -0.8 g dL^{-1}, 0.0 minimum, 0-1.5maximum) and (b) CRP changes (median: -6.29 mg dL^{-1}, 0.22 minimum, 17.85 maximum: -1.5)

Table 3: GVHD grading, %LBW and orally ingested calories in the 15 CBT patients who were following the HSCT nutritional pathway in this study

aGVHD-skin	aGVHD-liver	aGVHD-intestine	aGVHD-Grade	%LBW	Orally ingested calories kcal/IBW/day
3	0	1	2	-9.2	4
3	0	1	2	-7.7	6
1	0	1	2	-7.8	7
2	0	1	2	-7.4	4
3	0	1	2	-6.8	10
1	0	1	2	-4.5	4
0	0	0	0	-4.2	9
1	0	1	2	-3.8	4
1	0	0	1	-3.7	8
2	0	0	1	-2.0	9
2	0	1	2	-2.5	3
2	0	1	2	-1.6	2
0	0	0	0	-1.4	7
1	0	0	1	-0.1	18
1	0	0	1	3.3	18

GVHD: Graft-versus-host disease, HSCT: Hematopoietic stem cell transplantation, CBT: Cord blood transplantation, LBW: Loss of body weight

- Magnitude of change from pretreatment values to minimum Alb and maximum CRP was significant, with no correlation between them (Fig. 3). Percent LBW was not correlated with change in Alb ($r = 0.28$, $p = 0.32$) or CRP ($r = 0.16$, $p = 0.57$)

Oral intake percentage during the intervention period showed a positive correlation with daily orally ingested calories ($r = 0.69$, $p = 0.008$, Table 1) and a negative correlation with PN caloric percentage (Fig. 2d). Continuous oral intake percentage was correlated with orally ingested calories and severity score (Fig. 4a,b).

DISCUSSION

The finding that nutrient intake affected %LBW is not unexpected. However, the specific aim of this exploratory pilot study was to reveal which factors influenced %LBW in CBT patients following an HSCT nutritional pathway. It was found that %LBW was influenced by %LSMM, total nutrient intake (calories and protein) and total orally ingested nutrient intake (calories and protein).

Past studies have shown the rate of aGVHD to be relatively lower in patients undergoing CBT than in patients undergoing HSCT from an unrelated donor but aGVHD

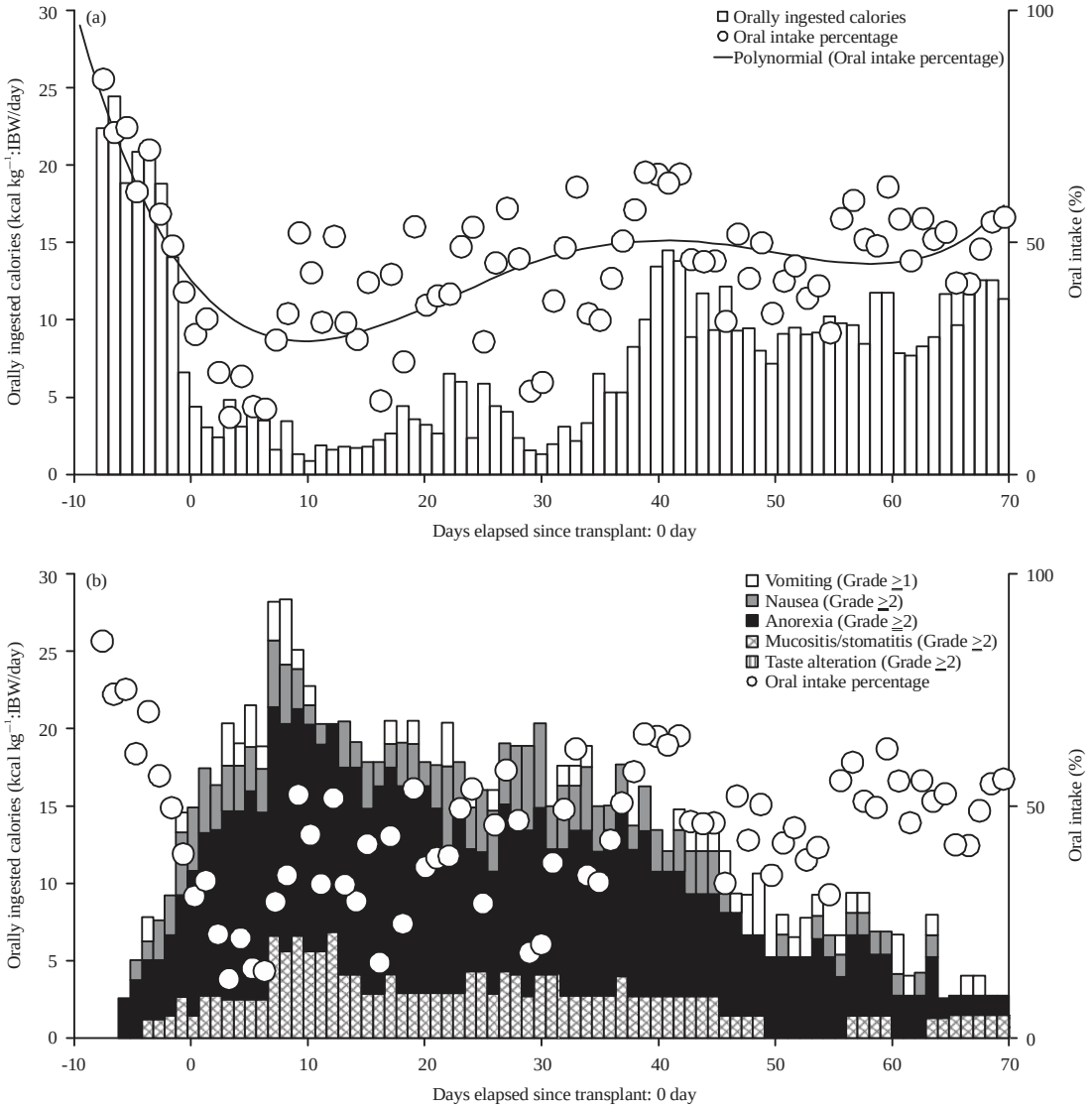


Fig. 4(a-b): Correlations of continuous oral intake percentage over the observation period with (a) Orally ingested calories (IBW/day) and (b) Severity score. IBW: Ideal body weight

Spearman rank-order correlation: r = -0.55, p<0.001

occurred in 13 of the 15 patients in the present study, including 9 with intestinal aGVHD (Table 3)[2]. It was also found that intestinal aGVHD was correlated with %LBW and orally ingested calorie intake. Diarrhea (grade 1>500 mL) is a symptom of intestinal aGVHD and the resulting dyspepsia and reduced absorption of nutrients may impede adequate intake of orally ingested calories[7,20]. However, fluid intake cannot easily be increased to compensate for the decrease in absorption and relatively low intake of orally ingested calories seen with intestinal aGVHD, because an excessive increase can exacerbate engraftment syndrome[34]. Intestinal aGVHD appears to be an unavoidable factor that influences %LBW after CBT. The utility of glutamine supplements as PN is currently under debate and future studies should also explore the association of these supplements with intestinal aGVHD when following an HSCT nutritional pathway[35,36].

Magnitude of change in CRP and Alb over the observation period was significantly higher around engraftment but decreased thereafter. These are transient changes caused by engraftment syndrome and are not believed to be associated with %LBW[34].

Studies indicate that nutritional intervention for cancer patients aids in maintaining QOL[7,37]. In the evaluation of the HSCT nutritional pathway for CBT used at Shizuoka Cancer Center, oral intake percentage was found to correlate with orally ingested calories (IBW/day) and PN caloric percentage

(Fig. 2d). Continuous oral intake percentage showed a positive correlation with orally ingested calories and severity score (Fig. 4a,b). These findings indicate that coordinating orally ingested calories (calculated from the oral intake percentage) with PN calorie control in the HSCT nutritional pathway may be associated with maintenance of QOL.

The above-mentioned points are considered in the nutritional pathway proposed by Muto (nutrition management with LBW)[18] and PES in the nutrition care process proposed by the Academy of Nutrition and Dietetics[19]. Consequently, 7 of the present 15 patients showed severe %LBW (>7.5%) over a 3 months period and nutritional input, output and intestinal aGVHD (etiology) influenced %LBW (signs and symptoms). Therefore, because of the risk of intestinal aGVHD, nutritional input (nutrient intake) and output (weight analysis) must be monitored and nutritional intervention initiated soon after the start of treatment to prevent severe %LBW (>7.5% over a 3 months period) in CBT patients following the HSCT nutritional pathway[15-19,23,28,37-39].

The present study has some limitations. One is that it was a retrospective study of a small number of patients who are currently participating in a prospective clinical study that is now under way. Another is that patients were not stratified by pre-treatment regimen or followed up for the same period of time.

CONCLUSION

Early nutritional intervention is required for CBT because patients showed nutritional-related LBW (nutritional risk) and experienced unavoidable nutrition-related adverse events. The HSCT nutritional pathway for CBT used at Shizuoka Cancer Center may attenuate LBW (nutritional risk) and this hypothesis is currently being investigated in a prospective study of intensive nutritional intervention, with the group from this study serving as the historical group.

SIGNIFICANCE STATEMENTS

This study revealed the factors affecting nutritional risk (loss of body weight, LBW) after cord blood transplantation in patients undergoing hematopoietic stem cell transplantation. It was shown that early nutritional intervention provided as part of a nutritional pathway can be beneficial to attenuate LBW.

The findings will help clinicians to understand why delayed engraftment occurs after cord blood transplantation and how nutritional intervention can be tailored to the patients' general condition to help reduce treatment burden.

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