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Prognostic Factors in the Resumption of Oral Dietary Intake After Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) in Children

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Abstract

Background—Parenteral nutrition (PN) is a common supportive care therapy in patients undergoing hematopoietic stem cell transplantation (HSCT). Inadequate oral dietary intake may necessitate prolonged courses of PN, which have been associated with metabolic, infectious, and hepatobiliary complications. The objective of this study was to identify demographic, clinical, and nutrition factors associated with the resumption of oral dietary intake following HSCT.

Methods—This was an observational cohort study of 37 children undergoing allogeneic HSCT. Repeated-measures regression analysis was performed to identify factors associated with the resumption and macronutrient composition of oral nutrient intake after HSCT.

Results—Mean oral dietary intake during the first 2 weeks after HSCT was <280 kcal/d. At all times, oral carbohydrate intake was high, ranging from 58% to 74% of oral energy. Age, time since transplant, degree of oral mucositis, and severity of graft-*vs*-host disease (GVHD) were all significantly correlated with the resumption of oral energy intake, as well as oral intake of carbohydrates. Oral protein and fat intake were also associated with elapsed time since HSCT, severity of mucositis, and GVHD. Factors not associated with oral dietary intake included gender, pre-HSCT nutrition status, diagnosis, type of donor, and infections.

Conclusions—Children undergoing HSCT exhibit a marked reduction in oral dietary intake and a preference for a diet high in carbohydrates. Careful attention should be directed to the oral dietary intake and nutrient requirements of children during HSCT, especially in younger patients and those who experience severe mucositis or GVHD.

Myeloablative conditioning regimens used in preparation for hematopoietic stem cell transplantation (HSCT) typically lead to prolonged anorexia, mucositis, and other gastrointestinal toxicities. Parenteral nutrition (PN) is an integral part of supportive care for these patients and has been shown to improve nutrition status and to improve engraftment and survival rates.^{1,2} Prolonged use of PN, however, has also been associated with multiple

complications including infections, fluid and electrolyte imbalances, hyperglycemia, hypertriglyceridemia, and hepatic dysfunction.^{3–6} Most HSCT patients receive PN when their oral dietary intake falls substantially below their nutrient requirements. Courses of PN commonly last until engraftment occurs and upper and lower gastrointestinal toxicities improve.

Successful weaning of PN after HSCT requires aggressive transitioning to oral or enteral intake. Continuation of PN, compared with IV hydration alone, may delay the return of normal oral energy intake.⁷ Other potential contributors to delayed oral intake may include mucositis, regimen-related toxicity, graft-vs-host disease (GVHD), as well as demographic and psychosocial considerations. Clinical experience suggests that there is wide variability in the rates at which individual patients resume adequate oral intake after courses of PN, but published data are limited. We performed an open-label trial of a multifaceted supportive care regimen in pediatric HSCT patients^{8,9} that included careful measurements of parenteral and oral dietary intake. Using the dietary intake data from these subjects, we examined which medical, demographic, and nutrition factors were associated with the transition from parenteral to oral dietary intake.

MATERIALS AND METHODS

The study was part of a prospective intervention designed to reduce regimen-related toxicity among allogeneic HSCT patients. The regimen included (1) prescribed use of leucovorin (folinic acid) rescue after the methotrexate portion of GVHD prophylaxis; (2) routine oral supplementation with vitamin E during the week before and month after HSCT; (3) oral ursodeoxycholic acid for the month after HSCT; and (4) titration of parenteral energy intake to meet 100% of estimated or measured resting energy expenditure (REE), rather than the conventional practice of providing 130%–150% estimated basal energy needs.¹⁰ The results of the main study have already been reported.^{8,9}

Study Population

Patients undergoing allogeneic HSCT at Dana Farber Cancer Institute/Children's Hospital Boston were eligible for enrollment, provided that "short course" methotrexate (given on days +1, 3, 6, and 11) and cyclosporine were used for GVHD prophylaxis. Patients undergoing unrelated donor HSCT (n = 24) also received 1 mg/kg/d IV methylprednisolone from day +7 to day +21 after HSCT, tapered as appropriate for grade of GVHD. Patients who were receiving experimental protocols that conflicted with this study and patients receiving alternative approaches to GVHD prophylaxis were ineligible. Patients with known allergy or hypersensitivity to any of the study reagents were also ineligible. Study enrollment occurred between July 1998 and June 2000.

Medical Management and Assessment

Oncologic management—All patients received myeloablative conditioning using 2 or more of the following agents: total body irradiation (n = 33), cyclophosphamide (n = 32), antithymocyte globulin (n = 6), busulfan (n = 2), etoposide (n = 1). Transplants were carried out in laminar flow rooms. All patients received oral, nonabsorbable antibiotics for gut

decontamination and prophylactic antipneumocystis, antiviral, and antifungal treatment per institutional guidelines. IV immunoglobulin was administered at 400–500 mg/kg/dose to maintain IgG levels >500 mg/dL. Hematopoietic growth factors were not administered. Pain and nausea were assessed by nurses and attending oncologists throughout the peritransplantation period. Pain was treated with opiates, and antiemetic agents were prescribed prophylactically to all patients. Cultures were obtained as indicated by symptoms for any fever or evidence of infection. Once initiated, broad-spectrum antibiotics were administered until hematopoietic recovery. Antifungal therapy was administered for persistent fever. Patients who developed GVHD >grade I were treated at the discretion of the attending physician. Initial treatment generally consisted of initiation of or increased dose of IV corticosteroids.

Assessment of toxicity—Severity of oral mucositis was assessed daily by the attending HSCT physician and graded according to adapted common toxicity criteria (CTC) for stomatitis in bone marrow transplant patients.¹¹ According to the CTC, the use of PN automatically implies mucositis of at least grade 3 severity. In our patients, PN was provided for a number of reasons, including refusal to eat due to nausea or pain and to supplement oral intake to reach energy goals. Because the institution of PN could never reliably be attributed to mucositis alone, we omitted use of PN from the mucositis grading system. The adapted CTC are as follows: grade 0 = no pain and normal-appearing mucosa; grade 1 = painless ulcers, erythema, or mild soreness with no lesions; grade 2 = mucositis with painful erythema, edema, or ulcers but able to swallow secretions; grade 3 = mucositis preventing swallowing of secretions; and grade 4 = mucositis requiring tracheal intubation.

The presence and severity of acute GVHD were assessed daily by the attending HSCT physician and graded according to Glucksberg criteria^{12–14} modified to score organs as unevaluable if another etiology for the findings was established. Infections were defined by the presence of positive cultures or specific molecular, histologic, or other diagnostic tests or if there were pathognomonic radiologic findings (eg, pneumonia). The presence of fever and neutropenia was insufficient to diagnose infection. Engraftment was defined as the first of 3 sequential days in which the absolute neutrophil count was $\geq 500/\mu\text{L}$. Assessment of regimen-related toxicities (hepatic, pulmonary, and renal) was made daily during hospitalization by the HSCT attending according to the National Cancer Institute CTC.

Nutrition Assessment and Management

Nutrition management—Throughout the study, a low-bacteria, low-lactose diet, including lactase-treated milk and lactase tablets, was offered to all subjects. Education concerning appropriate food choices within the diet was provided to each participant throughout their hospitalization; no other dietary limitations were applied. Oral intake was allowed *ad libitum*, and patients selected items from a varied menu. None of the subjects received enteral (eg, gastrostomy) feedings. PN was initiated when oral energy intake fell to <75% of measured or estimated REE for 5–7 days, usually on or near the day of HSCT (day 0). Parenteral energy intake was titrated daily so that total energy intake (oral + parenteral) provided approximately 100% measured REE or, when measured REE was unavailable,

estimated REE. PN was discontinued when oral energy intake met estimated or measured REE.

Anthropometric assessment—Body weight was measured daily from admission through hospital discharge on an electronic digital scale accurate to 0.1 kg. Standing height was measured at admission by stadiometer accurate to the nearest 0.1 cm. Triceps skinfold thickness (TSF) was measured at admission and discharge to the nearest 0.2 mm using Lange skin calipers. Midarm circumference was measured at admission and discharge to the nearest 0.1 cm using a flexible nonstretchable plastic tape. Midarm muscle area (MAMA) was calculated as follows: $MAMA = (\text{middle upper arm circumference} - 3.14159 \times \text{TSF})^2 / 4 \times 3.14159$. Arm measurements were made by a single observer (L.B.). Arm anthropometric data were compared with published norms.¹⁵ Weight, height, weight for height, and body mass index Z scores were calculated with Epi Info 2002 (Centers for Disease Control and Prevention, Atlanta, GA).

Dietary intake assessment—Nutrient intake was measured by concurrent notation of all oral and IV intake at the bedside by trained nurses. Complete dietary collection was aided by the fact that patients remained in laminar flow rooms from admission until engraftment. Daily records were reviewed by the clinical dietitian. In order to accurately reflect weekly changes in oral intake, a representative day of each week's oral and parenteral intake was selected and analyzed by the clinical dietitian for each patient. The daily total oral intake of calories, protein, carbohydrate, and fat was calculated by nutrient analysis software Nutritionist IV (First Data Bank, San Bruno, CA). Energy and macronutrient intake from PN and dextrose-containing IV fluid intake was calculated according to standard methods.¹⁶

REE—In subjects able to cooperate ($n = 25$; mean age, 12.3 years; range, 1.3–19.1 years), REE was measured weekly by indirect calorimetry using the Vmax 29N metabolic monitor (Sensormedics, Yorba Linda, CA).⁹ Estimated REE was calculated for all patients using published predictive equations.¹⁷

Data Analysis

Data were analyzed with SPSS (release 10.1; SPSS Inc, Chicago, IL) and SAS (version 9.1, SAS Institute Inc, Cary, NC).

To identify possible predictors of oral dietary intake, we created 4 separate repeated-measures regression models, with the 4 dependent variables being (1) oral dietary intake of total energy, and g/d of oral dietary intake as (2) carbohydrates, (3) protein, and (4) fat. Variation of each intake over the 8 weeks of observation was allowed to follow an arbitrary pattern (7 degrees of freedom), with first-order autoregressive correlation among successive times within subject. In order to control for the possible effects of gender and nutrition status, these variables (gender, weight and height for age Z scores) were maintained in all models as obligatory covariates. Candidate explanatory variables included diagnosis (malignant *vs* nonmalignant), MAMA, TSF, week after HSCT, days to engraftment, type of donor (matched unrelated *vs* matched sibling), presence of identified bacterial or viral

infection, peak grade of each regimen-related toxicity (pulmonary, hepatic, and renal), peak severity of mucositis, and peak grade of GVHD.

Ethics

Written informed consent was obtained from the parents or guardians of all subjects. Assent was obtained from subjects in an age appropriate manner. The protocol was approved by the Dana Farber Cancer Institute scientific review committee and institutional review board.

RESULTS

Baseline characteristics of the study cohort are shown in Table I. The 37 subjects enrolled had a variety of hematologic diagnoses and had generally normal anthropometric measures. Subjects had elevated peripheral fat stores, as demonstrated by a mean (SD) triceps skinfold of 16.5 (7.4) mm, which was 143% of age- and sex-matched standards. In the 25 subjects (68%) for whom baseline REE was measured, REE was normal at $97.5\% \pm 19.1\%$ predicted levels. The mean (SD) duration of PN use was 23.1 (15.8) days (range = 0–66). Median length of stay was 38 days, and median time to engraftment was 20 days. Median peak mucositis grade was 2 (range = grade 0–3; mean = 1.8). Median peak GVHD grade was 0 (range = 0–4; mean = 1.2).

Total oral energy intake changed significantly over time ($p < .0001$; Figure 1). Oral energy intake declined progressively after HSCT, with a mean nadir intake of 23% of estimated REE during week 2 after HSCT. By week 4 after HSCT, mean oral intake exceeded 70% of estimated REE and by week 6 had increased to 85% estimated REE.

Mean oral dietary intake during weeks 1 and 2 was <280 kcal/d (Table II). Of the 37 subjects, 14 (38%) and 17 (46%) received 100% of their energy intake from PN and IV fluids during weeks 1 and 2, respectively. Oral energy intake gradually increased through weeks 3 and 4 to baseline levels, as parenteral energy intake declined. By week 5 after HSCT, 28 of 37 (76%) subjects were fully weaned from PN.

When evaluated as a percent of oral intake (Figure 2), significant time-related changes in macronutrient intake were noted. At all weeks, the mean percentage of energy from oral carbohydrates was high, ranging from 61% of energy during the week before HSCT to 76% in the first week after HSCT. By 4 weeks after HSCT, carbohydrate intake was 65% of oral energy intake on average. Likewise, oral energy intake from fat was low at all time points, ranging from 27% in the week before HSCT to 16% in the first week after HSCT. By 4 weeks after HSCT, mean fat intake was 23% of oral energy intake.

Results of repeated-measures regression analysis are shown in Table III. Significant predictors of oral dietary energy intake, in addition to time ($p < .0001$) and the obligatory covariates (gender; height and weight for age), included age ($p < .01$), mucositis score ($p < .01$), and grade of GVHD ($p < .05$). For every 1-year increment of age in our subjects, our model showed an average incremental intake of 25 kcal/d over the course of HSCT. For every 1-unit increment in the peak mucositis score, our model showed a reduction of 297 kcal/d over the course of HSCT. For every 1-unit increment in highest GVHD grade, our

model showed a reduction of 118 kcal/d over the course of HSCT. Time to engraftment; donor type; diagnosis; grade of pulmonary, hepatic, and renal toxicities; peripheral fat mass (TSF); peripheral lean mass (MAMA); and the occurrence of infections were not associated with changes in oral energy intake.

Oral carbohydrate, protein, and fat intake also changed over time ($p < .0001$; Figure 2). As with energy, increasing oral carbohydrate consumption was significantly correlated with increasing age ($p < .005$), lower peak mucositis score ($p < .01$), and less severe GVHD ($p < .05$). Similarly, oral fat intake was inversely correlated with peak mucositis score ($p < .001$) and severity of GVHD ($p < .05$); however, its relationship with age was only of marginal significance ($p = .08$). Increasing protein intake was associated with less severe mucositis ($p < .005$) and GVHD ($p < .01$) but was not significantly related to age. Nutrition status (weight for height Z score, BMI Z score, TSF, and MAMA), gender, and diagnosis were not associated with the resumption of individual oral macronutrients.

DISCUSSION

We evaluated the dietary intake patterns of 37 children undergoing HSCT and identified significant correlates of the resumption of oral dietary intake, as well as with the macronutrient composition of that intake. Carbohydrates made up a high percentage of oral energy consumption at baseline and throughout the post-transplant period. The most significant factor associated with changes in oral dietary intake was elapsed time from HSCT. In addition, we found significant relationships between severity of oral mucositis, severity of GVHD, and subject age with the resumption of oral intake. Patients with less severe mucositis, less severe GVHD and greater time since HSCT exhibited higher amounts of oral energy intake than those earlier in the post-transplant course and those with more severe mucositis or GVHD. Older patients also ingested more energy and carbohydrate by mouth than did younger ones. Underlying diagnosis, donor type, preexisting nutrition status, gender, infections, and time until engraftment were not associated with the resumption of oral dietary intake.

Our finding of a significant relationship between the resumption of oral dietary intake and the severity of mucositis was not surprising, given the known gastrointestinal toxicities associated with high-dose chemotherapy or radiation therapy but has not been previously documented in children undergoing HSCT. In a multicenter study of adults undergoing HSCT, severity of mucositis was correlated with an increased risk of infection, time receiving PN, narcotic use, length of stay, hospital charges, and mortality. Dietary intake was not reported.¹⁸ The duration of mucositis caused by conditioning for HSCT is typically longer than that caused by chemotherapy alone. A number of agents are under investigation for treating or preventing mucositis,¹⁹ and these may significantly affect the natural history of mucositis and thus its impact on oral intake.

The severity of GVHD in our cohort was also associated with oral dietary intake. Symptoms of GVHD frequently include diarrhea, vomiting, or abdominal pain, so it seems logical that patients with more severe GVHD might exhibit a delay in the resumption of oral dietary intake. The relationship between GVHD and oral dietary intake, however, is likely

complicated. Patients who were at higher risk for GVHD received corticosteroids in addition to cyclosporine and methotrexate for prophylaxis, and patients who developed GVHD received corticosteroid treatment. Steroids have been shown to enhance oral intake,²⁰ although this relationship has not been well examined in the setting of HSCT. The timing of the diagnosis of GVHD may also have influenced oral intake. In this study, we only examined GVHD diagnoses that occurred during the first 7 weeks after HSCT, whereas patients remain at risk for GVHD for weeks to months after transplantation. It is possible that cases diagnosed after the study time period, or cases with shorter or longer duration, had a different impact on oral dietary intake. The impact of GVHD specifically on oral intake has not been well studied but is known to cause significant nutrition-related problems in children and adults.^{10,21} In a cohort of 18 children with multiorgan GVHD, a mean decrease in BMI of 20.9% was noted from HSCT date to the lowest BMI recorded.²²

We were unable to document a relationship between donor type and oral dietary intake. A small study of adults found that more patients who were able to achieve nutrition goals with oral feeding alone had matched related donors.²³ Most patients in this study who had grade 3 or 4 mucositis or grade 3 or 4 GVHD did require PN support, suggesting that these complications affected oral intake more significantly than type of donor. Similarly, our sample showed a reduction in oral intake in those patients with more severe mucositis or GVHD.

Few studies have investigated the oral nutrient intake of HSCT patients, especially in children. In a prospective randomized trial in 55 well nourished adults with breast cancer, Roberts et al²⁴ compared the outcomes of PN to that of oral-diet recipients who were treated with autologous HSCT. There were no significant differences between the 2 groups with respect to length of stay, engraftment time, infection rate, survival, or days to achieve >66% nutrient needs orally. These results imply that PN did not influence appetite or resumption of oral intake post-transplant. In comparison with complete oral diet, however, PN better preserved nutrition status and lean body mass (as measured by midarm muscle circumference).

A recent comparison of PN vs IV hydration fluid alone as supportive care for children with chemotherapy-induced oral mucositis found that PN did not improve clinical outcomes such as white blood cell recovery, incidence of infections, hospitalization time, and delay of next chemotherapy cycle.²⁵ Children in the PN group did gain significantly more body weight than the group that received only IV fluids. Estimates of body composition made with bioelectrical impedance analysis showed a decline over time in total body water and fat-free mass in the PN group, whereas these parameters increased over time in the group receiving IV fluids. Oral dietary intake was not reported in this study, so its relationship to mode of nutrition (PN vs hydration) is unclear. In addition, the validity of BIA measurements in the setting of children receiving chemotherapy has not been widely demonstrated.

Other studies have found that PN may play a role in delaying resumption to oral intake by increasing satiety.²⁶ Charuhas et al⁷ conducted a double-blind randomized trial of standard, lipid-free PN (25% dextrose, 4.25%–5% amino acids) vs hydration alone (5% dextrose) given to 258 HSCT recipients for the first 28 days of outpatient treatment. The group that

received hydration alone resumed oral intake that met 85% estimated energy requirements 6 days sooner than the group that received PN. Among 10 stable patients with limited gastrointestinal disease, a reduction in parenteral energy intake was associated with a significant increase in oral dietary intake,²⁷ suggesting that PN may interfere with appetite. It is not yet understood how PN induces satiety. In a small crossover study, MacGregor et al²⁸ found that patients receiving PN had a slower rate of gastric emptying, which was correlated with an increase in blood glucose while receiving PN. A retrospective survey of pediatric patients receiving home PN found that 66% of those responding experienced nausea, vomiting, or both. The authors hypothesized that because the majority of patients experienced their symptoms during the weaning period of their PN infusion, the symptoms may have been related to blood glucose fluctuations.²⁹

Our data are limited by a relatively small sample size and the fact that oral intake may have been influenced by the prescription of PN in lower amounts of energy than is customarily prescribed during HSCT.¹⁰ In addition, we are unable to evaluate whether these findings apply to patients undergoing autologous HSCT, where the preparative regimen and clinical and nutrition outcomes are likely different.

The nutrition management of pediatric patients undergoing HSCT is largely based on empirical estimates of energy and nutrient needs. As survival rates improve for these patients, long-term nutrition issues including obesity,³⁰ short stature,³¹ and insulin resistance are becoming more common.³² The subjects in our study showed a high percentage of oral carbohydrate intake, and this was especially evident when PN provided the greatest portion of energy intake (weeks 1–3 after HSCT). Although there are many confounding variables in this patient population, including pharmacologic agents, clinical complications, and genetic background, the extent to which insulin resistance and later obesity may be related to a dietary preference for carbohydrates bears follow-up. Our data also show that common complications of HSCT (mucositis, GVHD) are associated with a delay in oral dietary intake. Identification and prevention of these factors would help the nutrition management of patients at risk for prolonged dependency on PN after allogeneic HSCT.

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Figure 1. Changes in oral energy intake over time in children undergoing allogeneic HSCT (n = 37). CHO, carbohydrate; HSCT, hematopoietic stem cell transplantation; REE, resting energy expenditure; SE, standard error of the mean.

Figure 2.

Changes in oral carbohydrate (CHO), fat and protein intake over time in children undergoing allogeneic HSCT (n = 37). HSCT, hematopoietic stem cell transplantation; SE, standard error of the mean.

Table I

Admission demographic and nutrition characteristics of 37 children undergoing allogeneic hematopoietic stem cell transplantation (HSCT) (mean [SD] except where noted)

Variable	Value
n	37
Age, y	9.1 (6.4)
Male sex, no. (%)	17 (46)
Diagnosis	
Malignant	
Acute lymphoblastic leukemia	10
Chronic myelogenous leukemia	5
Acute myelogenous leukemia	3
Myelodysplastic syndrome	3
Juvenile myelomonocytic leukemia	1
Burkitt's lymphoma	1
Nonmalignant	
Aplastic anemia	7
Wiskott-Aldrich syndrome	3
Hurler's syndrome	1
Familial erythrophagocytic leukohistiocytosis	1
Congenital bone marrow failure	1
Griscelli's syndrome	1
Type of stem cell transplantation	
Matched, unrelated	24
Sibling-matched	13
Weight, kg	35.9 (22.4)
Weight age Z score (n = 34)	+0.13 (1.22)
Height, cm	126.9 (38.9)
Height age Z score (n = 34)	-0.18 (1.38)
Body mass index (n = 28), kg/m ²	20.0 (3.3)
Weight for height or BMI Z score (n = 37)	+0.52 (1.00)
Triceps skinfold (% std)	143 (63)
Midarm circumference (% std)	105 (14)
Midarm muscle area (% std)	103 (20)
Prealbumin (mg/dL)	19.6 (6.5)
Resting energy expenditure (n = 25)	
kcal/d	1295 (357)
% predicted	97.5 (19.1)

Table II
Oral dietary intake during hematopoietic stem cell transplantation (HSCT) in children (n = 37)

Time after HSCT	CHO, kcal/d	Protein, kcal/d	Fat, kcal/d	Energy <i>via</i> oral intake, kcal/d	Total energy intake, * kcal/d	Total energy <i>via</i> oral intake, %
Baseline (days -7 to 0)	360 (305)	87 (91)	177 (183)	616 (514)	938 (502)	59 (32)
Week 1 (days +1 to +7)	188 (314)	22 (46)	48 (92)	254 (416)	1050 (487)	27 (36)
Week 2 (days +8 to +14)	185 (311)	32 (55)	60 (132)	275 (472)	1053 (450)	23 (33)
Week 3 (days +15 to +21)	376 (451)	69 (89)	134 (178)	574 (674)	1120 (567)	47 (41)
Week 4 (days +22 to +28) [†]	482 (519)	91 (104)	160 (160)	725 (669)	1135 (566)	60 (40)

All data expressed as mean (SD).

* Includes all oral, PN, and dextrose-containing IV fluid intake.

[†]
n = 31

CHO, carbohydrate.

Table III

Multivariate model of oral energy and macronutrient intake in children after hematopoietic stem cell transplantation (HSCT)

Coefficient (SE) *	Intake/d			
	CHO, g	Fat, g	Protein, g	Total energy, kcal
Per year of age	4.8 (1.6) [‡]	0.4 (0.2)	0.4 (0.3)	25.2 (9.0) [‡]
Per point of mucositis score	-41 (15) [‡]	-9 (2) [‡]	-10 (3) [‡]	-297 (85) [‡]
Per grade of GVHD	-16 (8) [‡]	-3 (1) [‡]	-5 (2) [‡]	-118 (43) [‡]

* From repeated-measures regression adjusted for gender, WAZ, HAZ, and nonlinear variation across weeks 1–8.

[‡] $p < .05$.

[‡] $p < .005$.

CHO, carbohydrate.