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Comparison of metabolic parameters between oral and total parenteral nutrition in children with severe eating disorders

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Abstract

Background : This study investigated changes of lipid parameters in children with severe eating disorders during refeeding in order to explore the optimal timing for lipid preparation administration.

Methods : We prospectively assessed the physical conditions of patients with eating disorders after the start of nutrition therapy. The assessments were performed at admission and at 2 and 4 weeks. Lipid metabolism was assessed based on triglyceride (TG), total cholesterol (TC), and free carnitine (FC) levels, as well as acylcarnitine/free carnitine (AC/FC) ratio.

Results : A total of 18 patients were included. Of these, 12 and 6 received an oral diet (OD group) and total parenteral nutrition (TPN group), respectively. The mean body mass indexes at hospital admission were 12.8 kg/m^2 in the OD group and 12.7 kg/m^2 in the TPN group. At 2 weeks after the start of refeeding, TC, TG, and AC/FC levels were significantly lower in the TPN group than in the OD group. Other blood test results did not show any significant differences between the two groups.

Conclusions : Fat-free glucose-based nutrition promoted lipid metabolism over a 2-week period after the start of refeeding, suggesting that balanced energy and lipid intake are essential, even in TPN.

Key words : severe eating disorders, refeeding, nutrition therapy, total parenteral nutrition, lipid metabolism

Introduction

Eating disorder treatment requires a multifaceted approach, encompassing bio-psycho-social support. However, no single approach has been shown to be clearly superior ; thus, a combination of refeeding with anorexia nervosa-specific psychotherapy may be most effective[1)]. As chronic undernutrition results in reduced basal metabolism and heightened catabolism for energy production, one important goal of this care is recovery from malnutrition, primarily achieved through various refeeding methods, such as enteral nutrition via oral intake, tube feeding, and intravenous therapy. However, a rapid glucose influx during refeeding increases the intracellular demand for key minerals, leading to metabolic fluctuations[2)]. This response elevates the risk of refeeding syndrome due to energy supply-demand imbalances that may manifest after one or two weeks from the start of refeeding. In addition, another concern has been suggested in some case reports regarding severe repercussions in gravely malnourished patients (BMI of 9-12 kg/m^2), such as intractable hypoglycemia and fatal cardiac complications, after starting refeeding[3,4)]. Notably, complications like refeeding syndrome can arise irrespective of refeeding approach[5-7)]. Refeeding syndrome can result in organ dysfunction due to ab-

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normal electrolyte levels and water imbalances[8]. Established guidelines, such as those of the UK's National Institute for Health and Care Excellence (NICE), have identified extreme leanness and prolonged undernutrition as key risk factors for refeeding syndrome[2]. Recommended preventive measures include an initial energy dose reduction to 5–20 kcal/kg/day for those with an extremely low BMI (< 14 kg/m^2)[9], as well as supplements of thiamine, potassium, phosphate, calcium, and magnesium before and during the first 10 days of refeeding, unless their blood levels are high the reference range[10,11].

However, the most effective and safe treatment for weight restoration in children and adolescents with eating disorders remains controversial[12]. Although there are few previous studies that compared short-term outcomes of oral intake and intravenous therapy for eating disorder patients[13], a standardized and safe refeeding protocol for eating disorders has not yet been achieved due to insufficient evidence in support of changing the current standard refeeding approach[14]. A further challenge is to decide when to administer lipid preparations for patients receiving intravenous therapy such as fat-free total parenteral nutrition (TPN) due to inability of oral intake. A lipid preparation supplies high energy, but for severely lean patients, it is recommended to initiate refeeding with low energy loads because high energy loads are thought to increase the risk of refeeding syndrome in these patients. In short, not much is known with respect to the right amount and composition of energy doses and the right timing to initiate refeeding therapy, especially for severely lean patients. Consequently, clarity is lacking with regard to the right energy dose as well as the composition and timing of refeeding[15]. When it comes to lipid-based energy, the high energy load in intravenous therapy makes initiating treatment with fat preparations challenging in severely lean patients. Currently, there are no defined metrics to guide the timing and dosage of fat preparations during the refeeding process.

We hypothesized that the metabolism of eating disorder patients is primarily dependent on glucose immediately after the start of refeeding therapy, resulting in persistently elevated lipid levels. Given that, in a state of chronic undernutrition, the body predominantly relies on lipids for energy, a rapid shift to glucose dependence during refeeding can lead to potential energy imbalances such as lipid metabolism abnormalities[16]. The data found in a previous systematic review and meta-analysis clearly showed elevated lipid and lipoprotein concentrations in individuals with anorexia nervosa (AN) compared with healthy controls, and persistence of elevated lipid concentrations in AN after partial weight restoration[17], thus supporting our hypothesis.

The aims of the present study were to elucidate the variations in lipid metabolism as per refeeding strategies, determine the fluctuations in lipid demand during metabolic transition from pre- to post-refeeding states, and discern the optimal timing for lipid preparation administration.

Materials and Methods

Selection Criteria

The present study included a total of 18 patients with eating disorders who were admitted to the pediatric ward or the neuropsychiatry ward of our hospital. These patients were diagnosed with eating disorders based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria[18].

The patients were categorized into the following DSM-5 classifications : anorexia nervosa restricting type, anorexia nervosa binge-eating/purging type, and avoidance/restricted food intake disorder.

Anorexia nervosa is characterized by : weight loss or lack of weight gain in growing children ; difficulties maintaining an appropriate body weight for height, age, and stature ; and, in many individuals, a distorted body image. Anorexia nervosa restricting type (AN-R) is defined by weight loss primarily through dieting, fasting, and/or excessive exercise without recurrent episodes of binge eating or purging in the previous three months, resulting in significantly low body weight. Anorexia nervosa binge-eating/purging type (AN-BP) includes individuals with recurrent episodes of binge eating or purging behaviors (self-induced vomiting or misuse of laxatives, diuretics, or enemas) at least once a week for the last three months, in addition to significantly low body weight. Avoidant/restrictive food intake disorder (ARFID) is characterized by : an apparent lack of interest in eating or food ; avoidance of foods based on their sensory characteristics ; or concern about aversive consequences of eating.

Study Duration

The study was carried out over a five-year period, from April 2014 to March 2019. We observed physical conditions in patients with eating disorders

who received nutrition therapy for the first month after admission to hospital.

Medication Management

Patients who had taken medications that can affect carnitine metabolism, specifically sodium valproate or pivoxil, within one month prior to admission were excluded from the study.

Lifestyle Guidance

The physical conditions of the patients were assessed via daily physical examinations and weekly body weight measurements before breakfast. Blood cell and blood chemistry panels were conducted at the time of admission and again at 2 and 4 weeks, also prior to breakfast. The tests included complete blood count, liver and kidney functions, creatine kinase, electrolytes (potassium, magnesium, phosphate), blood glucose, albumin, and lipids (triglycerides, total cholesterol).

Types of Nutritional Therapy and Allocation of Patients

The refeeding method for each patient was chosen from either oral diet (OD) or total parenteral nutrition (TPN) by the physicians based on the risks and preferences of the patient and their family after comprehensive consideration of various factors, including whether the patient was capable of oral intake and whether they were hospitalized in the pediatric ward or the neuropsychiatry ward. For OD, either hospital diets or oral nutritional supplements such as ENEVO® or ENSURE LIQUID® were used. TPN was administered via infusion, which could include glucose-added acetate maintenance solution, amino acid solution, or high-calorie infusion. The energy dose at initiation of treatment, as well as its rate of increase, were determined by the attending physician. This study included a retrospective observation of previously conducted treatments, rather than interventions.

Each blood sample was centrifuged immediately after collection and stored at −80°C for further serum carnitine analysis. A general blood test was conducted three times, as described above. However, additional tests were performed at the physician's discretion. If refeeding syndrome developed, a blood sample was collected at the time of onset, and-after subsequent analyses were completed, the necessary treatment was provided to the patient accordingly.

The carnitine level was measured by performing the differential blood carnitine test using the enzyme cycling method[19]. The total carnitine level was measured using T-Carnitine reagent Kainos (KAINOS Laboratories, Inc., Tokyo, Japan), and the free carnitine (FC) level using F-Carnitine reagent Kainos (KAINOS Laboratories, Inc., Tokyo, Japan). The value obtained by subtracting the FC level from the total carnitine level was referred to as acylcarnitine (AC).

The Statistical Package for the Social Sciences software version 26 (IBM Inc., New York, USA) was used for all analyses. Normality was assessed using the Shapiro-Wilk test. If normality was observed, the independent *t*-test for single measures was performed between the two treatment groups. If there was no normality, the Wilcoxon signed-rank test was conducted. A two-way analysis of variance was performed to determine the presence or absence of time-lapse interaction between the two groups. A p value of < 0.05 was considered statistically significant.

Results

Background characteristics and biochemical parameters of patients

As shown in Table 1, refeeding methods were divided between oral nutrition (12 patients) and total enteral nutrition (6 patients). Patients who experienced a recurrence all selected OD, while younger children tended to select TPN, typically due to a refusal of oral intake or a fear of swallowing. The disease classifications, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), included AN-R (12 patients), AN-BP (3 patients), and ARFID (3 patients). The mean ages of the participants were 17.3 (range : 12-24) years in the OD group and 12.6 (range : 11-13) years in the TPN group. The OD group included patients with recurrence. The mean ages and heights at admission were significantly higher in the OD group than in the TPN group ($p < 0.01$ and $p = 0.03$, respectively). However, there was no significant difference in SD score ($p = 0.35$). The mean BMIs at admission were 12.8 (range : 11.1-15.6) kg/m^2 in the OD group and 12.7 (range : 11.2-15.2) kg/m^2 in the TPN group. When compared by SD score, the mean BMI-SDS was −5.20 (range : −8.70-−2.66) in the OD group, and that in the TPN group was −3.54 (range : −5.66-−2.34). However, there was no significant difference in body weight between the two groups. Moreover, there was no significant difference regarding duration from anorexia nervosa

Table 1. Characteristics of the OD and TPN groups at admission

Nutrition method	OD group (n = 12)	TPN group (n = 6)	p value
DSM-5 criteria (n)	AN-R (8) AN-BP (3) ARFID (1)	AN-R (4) AN-BP (0) ARFID (2)	
Initial onset/recurrence (n)	Initial onset (8)/recurrence (4)	Initial onset (6)	
Age at admission [year]	17.3 ± 4.2	12.6 ± 1.2	< 0.01
Sex (M : F)	M = 0, F = 12	M = 0, F = 6	1.00
Height [cm]	154.4 ± 5.7	146.1 ± 9.1	0.03
Height-SDS	−0.42 ± 0.93	−0.91 ± 0.99	0.35
Weight [kg]	30.5 ± 3.4	27.2 ± 4.8	0.11
BMI [kg/m^2]	12.8 ± 1.2	12.7 ± 1.5	0.87
BMI-SDS	−5.20 ± 1.82	−3.54 ± 1.25	0.09
Fasting period before admission [month]	4.9 ± 3.0	3.8 ± 2.4	0.45
Weight loss at admission [%]	−29.2 ± 11.2	−19.0 ± 6.0	0.08
White blood cell count [/μL]	4,667 ± 2,820	4,833 ± 750	0.89
Hemoglobin level [g/dL]	13.1 ± 1.8	13.5 ± 0.8	0.61
Platelet count [×10^4/μL]	19.5 ± 7.4	21.8 ± 5.5	0.52
AST level [U/L]	31.3 ± 11.3	29.2 ± 12.5	0.73
ALT level [U/L]	37.3 ± 23.8	23.3 ± 16.9	0.22
BUN level [mg/dL]	17.4 ± 9.0	22.2 ± 4.3	0.24
Cr level [mg/dL]	0.73 ± 0.13	0.73 ± 0.15	0.98
CK level [U/L]	117.7 ± 79.6	105.7 ± 139.6	0.82
K level [mmol/L]	4.0 ± 0.6	4.3 ± 0.2	0.22
P level [mg/dL]	3.8 ± 0.6	4.5 ± 0.5	0.02
Mg level [mg/dL]	1.8 ± 0.2	1.7 ± 0.3	0.57
FBG level [mg/dL]	81.5 ± 9.0	79.2 ± 20.7	0.74
ALB level [g/dL]	4.5 ± 0.5	4.8 ± 0.2	0.23
TG level [mg/dL]	112.2 ± 46.0	91.3 ± 52.1	0.40
TC level [mg/dL]	228.3 ± 65.9	256.0 ± 67.7	0.42
FC level [μmol/L]	68.7 ± 27.9	69.0 ± 19.5	0.62
AC level [μmol/L]	53.2 ± 19.0	48.5 ± 18.3	0.43
AC/FC ratio	0.28 ± 0.19	0.52 ± 0.57	0.34
free T3 level [pg/mL]	1.29 ± 0.55	1.46 ± 0.76	0.58

OD : oral diet, TPN : total parenteral nutrition, AN-R : anorexia nervosa restricting type, AN-BP : anorexia nervosa binge-eating/purging type, ARFID : avoidant/restrictive food intake disorder, BMI : body mass index, M ± SD : mean ± standard deviation, FBG : fasting blood glucose, TG : triglyceride, TC : total cholesterol, FC : free carnitine, AC : acylcarnitine, free T3 : free triiodothyronine,
Data were expressed as M ± SD, with $p < 0.05$ indicative of a significant difference between the OD and TPN groups.

onset to admission and the rate of weight loss.

All the patients' blood test results for blood count, electrolytes, and liver transaminase were within reference intervals at admission. The OD group had significantly lower serum p levels than the TPN group. However, none of the patients presented with serum p levels below the reference range. In both groups, total cholesterol (TC) and triglyceride (TG) levels at admission were within or above their respective reference ranges. FC level at admission did not significantly differ between the groups. In all patients, the free triiodothyronine (T3) value, which indicates malnutrition, was below the reference range. However, there were no significant differences between the two groups.

Metabolic parameters before and after the start of refeeding

Figure 1 shows the number of patients in the OD group and the TPN group one month after refeeding. Patients who developed refeeding syndrome were excluded. As shown in Table 2, the to-

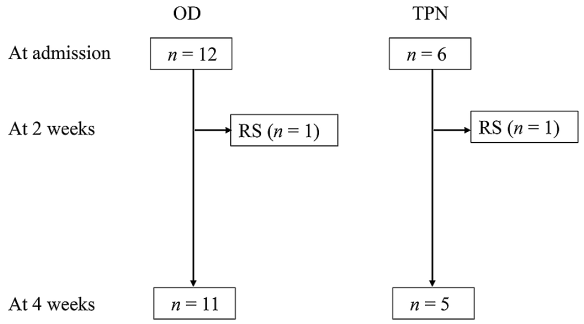

Fig. 1. Flowchart of patient enrollment and division into two nutrition methods
One patient in each group developed refeeding syndrome at day 11 of hospitalization ; they were excluded from the evaluation. Neither presented with laboratory findings indicative of lipid metabolism. Nevertheless, the condition of these patients improved with intensive care.

tal energy dose per body weight was significantly higher in the OD group (n = 11) than in the TPN group (n = 5) at the start of refeeding (32.1 kcal/kg vs 8.8 kcal/kg) and 1 week after admission (36.3 kcal/kg vs 19.8 kcal/kg), but no significant difference was shown at 2 weeks (45.6 kcal/kg vs 35.5 kcal/kg) or at 4 weeks (51.0 kcal/kg vs 46.6 kcal/kg). Figure 2 shows changes in the total energy dose and the individual doses of each of the three nutrients (Fig. 2a), as well as and variations in heart rate and BMI (Fig. 2b), over a 1-month period after starting refeeding. The TPN group had significantly lower values for total energy dose, glucose, and protein than the OD group, both at admission and at 1 week after the start of refeeding. The values for total energy dose, glucose, and protein at 2 weeks did not show a significant difference (45.6 vs 35.5 kcal/kg, p = 0.08, 5.8 vs 6.3 kcal/kg, p = 0.60, and 2.2 vs 2.6 kcal/kg, p = 0.19). However, the glucose dose at 4 weeks was significantly higher in the TPN group than in the OD group (7.2 vs 9.9 kcal/kg, p = 0.03). The lipid dose at 4 weeks was significantly higher in the OD group than in the TPN group (1.4 vs 0.7 kcal/kg, $p < 0.001$), although the latter started receiving lipid preparations after 2 weeks of hospitalization. BMI-SDS did not significantly differ between the two groups during the entire refeeding process, although HR was significantly higher in the TPN group than the OD group at 4 weeks (61.2 vs 73.4, p = 0.02) (Fig. 2b).

Blood biochemical factors at 2 weeks after the start of refeeding

Table 3 shows the general blood analysis results of the OD and TPN groups. The OD group had a significantly lower serum P level than the TPN group. However, none of the OD group patients presented with serum P levels below the reference range (2.5-4.5 mg/dL). The fasting blood glucose (FBG) and serum albumin (ALB) levels did not significantly differ between the OD and TPN groups. Nevertheless, the TPN group had significantly lower TG (92.3 vs 32.6 mg/dL, $p < 0.01$), TC level (214.9 vs 133 mg/dL, $p < 0.01$), and AC/FC ratio (0.18 vs 0.10, p = 0.04) than the OD group. Moreover, the FC and AC levels did not differ between the two groups. However, the values decreased in both groups from the pre-refeeding levels

Changes in lipid levels during the refeeding period

Figure 3 shows the changes in lipid levels over the refeeding process. At 2 weeks from the refeeding onset, the TPN group had significantly lower TC and TG levels than the OD group, although no significant differences were observed at 4 weeks. As for the FC level, two patients in the OD group and one in the TPN group had higher levels than reference range (36-74 μg/mL) at admission, which decreased to the reference range after refeeding started. On the other hand, three OD patients and one TPN group patient had lower FC levels than the reference range at admission, but after the start of

Table 2. Differences in total energy and lipid doses between the OD and TPN groups

Days after starting refeeding	Total energy dose (kcal/kg/day)			Lipid dose (kcal/kg/day)		
	OD group (n = 11)*	TPN group (n = 5)*	p value	OD group (n = 11)*	TPN group (n = 5)*	p value
At admission	32.1 ± 11.0	8.8 ± 3.9	< 0.01	0.88 ± 0.32	0.00	< 0.01
At 1 week	36.3 ± 9.2	19.8 ± 3.1	< 0.01	1.01 ± 0.27	0.00	< 0.01
At 2 weeks	45.6 ± 10.2	35.5 ± 8.6	0.08	1.25 ± 0.28	0.00	< 0.01
At 4 weeks	51.0 ± 8.3	46.6 ± 16.8	0.49	1.38 ± 0.21	0.68 ± 0.13	< 0.01

OD : oral diet, TPN : total parenteral nutrition *Patients with refeeding syndrome were excluded.

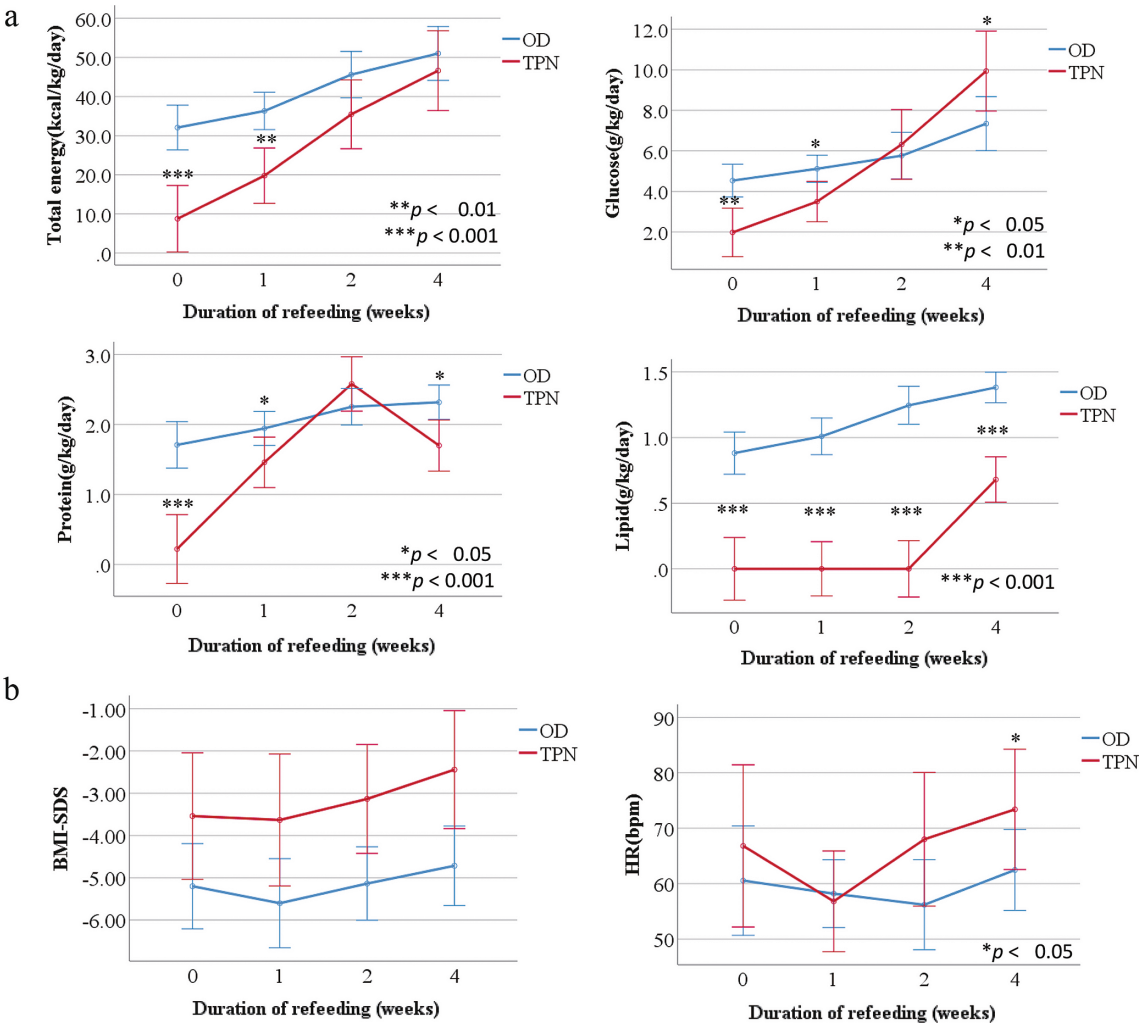

Fig. 2. Changes in the total energy dose, doses of three major nutrients, BMI, and HR

a. Changes in the total energy dose and doses of glucose, protein, and lipid. Patients in the TPN group initially had lower energy and glucose/protein doses than those in the OD group, but their glucose level sharply increased from week 2 to week 4 while that of the OD group patients showed a gradual and constant increase. This is likely associated with the initiation of lipid administration to the TPN group at 2 weeks from admission.

b. Changes in body mass index and heart rate over 4 weeks. Except for the HR at 1 week, there was no significant difference between the two groups.

BMI, body mass index ; HR, heart rate ; bpm, beats per minute.

Values are presented as mean ± SD for oral diet (n = 11) and total parenteral nutrition (n = 5). Significance values : *p < 0.05, **p < 0.01, ***p < 0.001. OD, oral diet ; TPN, total parenteral nutrition.

refeeding, their values exceeded the reference range except one OD patient. The AC/FC ratio at admission was higher than the reference value (< 0.25) in five patients each in the OD group and TPN group. The AC/FC ratio of > 0.4, indicating carnitine deficiency, was observed in two patients in the OD group and one in the TPN group. At 2 and 4 weeks after the start of refeeding, the AC/FC ratio of both groups decreased from pre-treatment levels, and all patients had an AC/FC of < 0.4. In addition, the AC/FC ratio of the TPN group was significantly lower than that of the OD group (0.18 vs 0.10, p = 0.04 at 2 weeks ; 0.15 vs 0.11, p < 0.01 at 4 weeks) (Fig. 3).

Discussion

During the one-month refeeding period with either OD or TPN, there were clear differences in metabolic parameters between the two groups. The OD group had a higher total energy dose both at the start of refeeding and one week after, but there was no difference after two weeks. The glucose dose was higher in the TPN group after four weeks. Regarding blood biochemical factors at 2 weeks, the TPN group had significantly lower levels of TG and

Table 3. Blood laboratory results of the OD and TPN groups at 2 weeks after the start of refeeding

Laboratory data at 2 weeks	OD group $n = 11$*	TPN group $n = 5$*	p value
White blood cell count [/μL]	4,227 ± 2,388	3,900 ± 1,017	0.78
Hemoglobin level [g/dL]	12.2 ± 1.0	12.6 ± 1.0	0.47
Platelet count [$\times 10^4$/μL]	19.2 ± 4.5	18.1 ± 3.5	0.66
AST level [U/L]	27.2 ± 9.7	24.0 ± 5.2	0.51
ALT level [U/L]	40.1 ± 24.3	24.2 ± 12.6	0.11
BUN level [mg/dL]	12.2 ± 1.8	13.4 ± 3.6	0.37
Cr level [mg/dL]	0.62 ± 0.07	0.62 ± 0.12	0.95
CK level [U/L]	53.5 ± 20.7	38.6 ± 10.2	0.16
K level [mmol/L]	4.1 ± 0.2	4.2 ± 0.2	0.81
P level [mg/dL]	4.0 ± 0.4	4.7 ± 0.3	< 0.01
Mg level [mg/dL]	1.7 ± 0.1	1.7 ± 0.1	1
FBG level [mg/dL]	82.1 ± 11.8	95.4 ± 13.8	0.07
ALB level [g/dL]	4.4 ± 0.6	4.0 ± 0.7	0.32
TG level [mg/dL]	92.3 ± 36.0	32.6 ± 9.2	< 0.01
TC level [mg/dL]	214.9 ± 47.2	133.0 ± 34.0	< 0.01
FC level [μmol/L]	39.1 ± 12.8	40.2 ± 5.9	0.85
AC level [μmol/L]	7.5 ± 5.3	3.9 ± 0.8	0.17
AC/FC ratio	0.18 ± 0.08	0.10 ± 0.01	0.04

OD : oral diet, TPN : total parenteral nutrition, M ± SD : mean ± standard deviation, FBG : fasting blood glucose, TG : triglyceride, TC : total cholesterol, FC : free carnitine, AC : acylcarnitine, free T3 : free triiodothyronine
Data were expressed as M ± SD, with $p < 0.05$ indicative of a significant difference between the OD and TPN groups, excluding patients with refeeding syndrome. *Patients with refeeding syndrome were excluded.

TC compared to the OD group. However, there were no significant differences in other factors, such as fasting blood glucose and serum albumin levels. The AC/FC ratio decreased in both groups after the start of refeeding, and it was significantly lower in the TPN group compared to the OD group.

It should be noted that the two groups differed in total energy and lipid doses at the beginning of refeeding because the TPN solutions did not contain lipid. This is the reason for the higher glucose and lower lipid energy load in the TPN group. In the neuropsychiatry ward, high-energy meals were provided for oral intake. In contrast, in the pediatric ward, provision of energy content was initiated with a small amount because the TPN solution contained the required energy load. Therefore, the TPN group patients, who were incapable of enteral nutrition, were disadvantaged in terms of high-energy lipid emulsion loading.

Recent studies have reported a risk of low-energy syndrome, a state of undernutrition/underfeeding due to starting a nutrition therapy with a low energy dose and later increasing it, which may lead to a loss of body weight despite increased energy intake[15]. Other studies have reported that the treatment is safe, and it does not increase the risk of complications even if a high energy dose is administered at an early stage[21-23]. According to previous studies on physical management during refeeding[2,9,24,25], the recommended total energy dose varies from 5 to 40 kcal/kg. The NICE guidelines recommend that the risk criteria for refeeding syndrome include one or more of the following : a BMI of < 16 kg/m^2 ; weight loss of 15% or more within the previous 3-6 months ; limited nutrition for 10 days or more ; and low levels of potassium, phosphate, and magnesium before the start of nutrition therapy[2]. The participants of the present study were at high risk for refeeding syndrome. There is accumulating evidence showing that high-energy diet at the early stage of refeeding is safe for patients who are not severely lean[15,21]. However, there are only a few studies that have assessed the safety of a high-energy diet in individuals with severe eating disorders, or have investigated appropriate proportions of major nutrients for such individuals. That

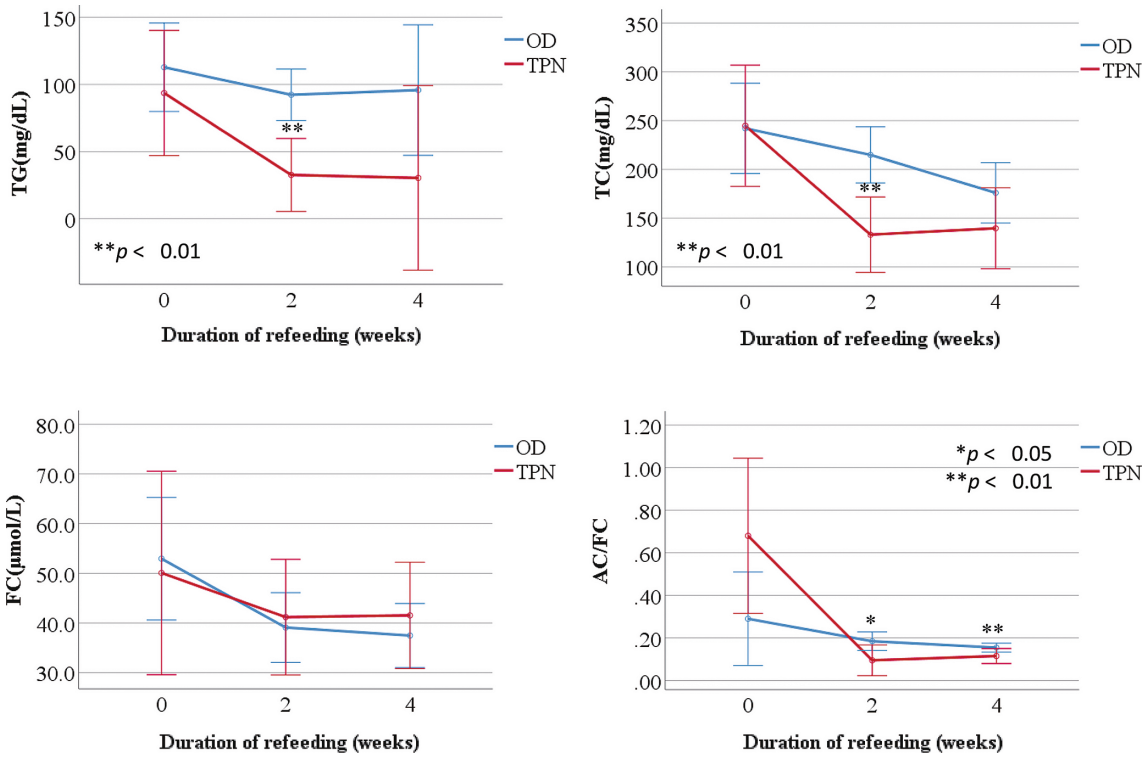

Fig. 3. Changes in lipid metabolism during refeeding
After two weeks of refeeding, the TPN group showed notably lower TC and TG levels compared to the OD group, although these differences were not significant at 4 weeks, as they had been at admission. The AC/FC ratio, an indicator of the carnitine level, was above the reference range in several patients on admission. However, after refeeding, all patients had an AC/FC of < 0.4.
The reference ranges in our hospital are TG 50–149 mg/dL, TC 150–199 mg/dL, FC 36–74 μg/mL, and AC/FC 0.25–0.4. TG, triglyceride ; TC, total cholesterol ; FC, free carnitine ; AC, acyl carnitine ; AC/FC, FC-to-AC ratio.

is to say, uncertainty still remains regarding the optimal refeeding approach for severe eating disorders. Some studies have addressed the importance of carbohydrates in diet to prevent refeeding syndrome, and have suggested 58.4% as the cutoff value for the proportion of carbohydrates[26]. Another study reported that no significance difference was observed between patients on diets with carbohydrate contents of < 40% and 50–60%[27], suggesting, again, the importance of carbohydrates in the management of refeeding syndrome risks.

Several studies have reported a relationship between refeeding and lipid metabolism. In humans, short-term fasting/refeeding increases lipid metabolism 50-fold and 6–10-fold from the fasting levels through the transcription of pyruvate dehydrogenase kinase 4 and lipoprotein lipase, respectively. Furthermore, short-term fasting/refeeding has been reported to affect the transcription of some genes in the skeletal muscle correlated with lipid metabolism[28]. These changes likely suppress glucose metabolism and lead to the shift to lipid metabolism. A previous study reported that infants showed low carnitine levels after 7–10 days of parenteral nutrition without carnitine supplementation[29]. In mouse experiments, no differences in TG levels in the liver were observed among non-fasting, fasting, and fasting/refeeding groups[30]. However, repeated fasting/refeeding significantly reduced serum TG, carnitine, and acylcarnitine concentrations in the fasting/refeeding group. This means that re-supplementation with glucose and proteins after fasting increased the energy storage capacity of the liver, which promoted fatty acid metabolism and decreased serum TG levels[21,23]. These studies' findings on humans and mice suggest that fasting reduces the liver's ability to synthesize TG. However, refeeding activates the carnitine transport system in the liver and promotes fatty acid metabolism. The results of the present study showed that supplementation with low-energy dose without lipids decreased serum TG concentrations in the TPN group (Fig. 3). These results can be explained by the same mechanism as that shown in the abovementioned studies, suggesting the TPN group had a higher lipid storage capacity in the liver after 1–2 weeks of

refeeding.

The TPN group began their lipid intake 2 weeks after starting refeeding, and the average days from admission to the start of lipid administration was 21.8 days. The lipid metabolism of this group was enhanced, and the TG and TC levels were decreased significantly by the second week of refeeding. This suggests that the refeeding regimen starting with a low energy load and not using high-energy lipids from the beginning was not physiologically relevant for the patients on TPN therapy. A report has recommended that the proportion of energy from major nutrients for refeeding of eating disorder patients be fat 25-35%, protein 15-20%, and glucose 50-60%[26]. Some other reports have suggested different compositions, but there is no established consensus. However, the findings of the present study underscore the importance of considering not only the total energy dose but also the energy composition of major nutrients, especially lipids, in refeeding therapy for eating disorders even when patients are on total parenteral nutrition.

Study limitations

There are several limitations to the present study. The subjects of this study were recruited from a small number of institutions and were not randomized, which may have led to selection bias. The sample size was relatively small, which limits the generalizability of the results. Although the OD group and the TPN group did not have significant weight differences at admission, the inclusion of relapse cases in the OD group led to a significantly higher average age compared to the TPN group, raising the possibility of inherent differences between the two groups. Although it was suggested that even patients on TPN, which contains no lipids, require lipids as an energy source, it remains unclear whether the intravenous administration of lipids can prevent refeeding syndrome. Furthermore, the present study was prospective in design, and the outcomes obtained were not based on predetermined items, which might have affected the consistency of data collection. Therefore, the results of the present study may not be applicable to larger or more diverse populations, or to different treatment settings.

Conclusion

This study investigated changes of lipid parameters in children with severe eating disorders during refeeding in order to explore the optimal timing for lipid preparation administration. At 2 weeks after the start of refeeding, TC, TG, and AC/FC levels were significantly lower in the TPN group than in the OD group. Fat-free glucose-based nutrition promoted lipid metabolism, suggesting that balanced energy and lipid intake are essential, even in TPN.

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Conflict of Interest Disclosure

All authors declare no personal conflicts of interest. The Department of Pediatrics, Fukushima Medical University, has received research funding from Otsuka Pharmaceutical Co., which was used for carnitine measurement.

Authorship Contribution

As the lead author, Yuichi Suzuki contributed to conception and design of this work, data collection, data analysis and interpretation, and preparation of this manuscript.

Shuntaro Itagaki, Maki Nodera, and Kazuhide Suyama were involved in data collection, data analysis and interpretation, as well as critical proofreading of important intellectual content, and provided the final approval of the manuscript. Hirooki Yabe and Mitsuaki Hosoya were responsible for the overall management of this study and contributed to its conception and design, as well as data analysis and interpretation, and critical review of important intellectual content. All authors have agreed on the final version of the submitted manuscript.

Declarations

Ethical approval and consent to participate : This study was approved by the Research Ethics Committee of Fukushima Medical University School of Medicine (No. 2018).

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References

1. Zipfel S, Giel KE, Bulik CM, Hay P, Schmidt U. Anorexia nervosa : aetiology, assessment, and treatment. Lancet Psychiatry, **2**(12) : 1099–1111, 2015. doi : 10.1016/S2215–0366(15)00356–9.
2. National Institute for Health and Care Excellence. Great Britain. Eating disorders : recognition and treatment. National Institute for Health and Care Excellence (NICE) ; 2017.
3. Brown K, Everwine M, Nieves J. A Case of Wernicke Encephalopathy Secondary to Anorexia Nervosa Complicated by Refeeding Syndrome and Takotsubo Cardiomyopathy. Am J Case Rep, **15** : 22 : e929891, 2021.
4. Shimizu K, Ogura H, Wasa M, Hirose T, *et al.* Refractory hypoglycemia and subsequent cardiogenic shock in starvation and refeeding : report of three cases. Nutrition, **30** : 1090–1092, 2014.
5. Garber AK, Sawyer SM, Golden NH, *et al.* A systematic review of approaches to refeeding in patients with anorexia nervosa. Int J Eat Disord, **49** : 293–310, 2016.
6. Bendall C, Taylor NF. The effect of oral refeeding compared with nasogastric refeeding on the quality of care for patients hospitalised with an eating disorder : A systematic review. Nutr Diet, **80** : 44–54, 2023.
7. Hart S, Franklin RC, Russell J, *et al.* A review of feeding methods used in the treatment of anorexia nervosa. J Eat Disord, **1** : 36, 2013. doi : 10.1186/2050–2974–1–36.
8. Mehler PS, Winkelman AB, Andersen DM, Gaudiani JL. Nutritional rehabilitation : practical guidelines for refeeding the anorectic patient. J Nutr Metab, **2010** : 625782, 2010.
9. Cuerda C, Vasiloglou MF, Arhip L. Nutritional management and outcomes in malnourished medical inpatients : anorexia nervosa. J Clin Med, **8** : 1042, 2019.
10. Oudman E, Wijnia JW, Oey MJ, van Dam MJ, Postma A. Preventing Wernicke's encephalopathy in anorexia nervosa : A systematic review. Psychiatry Clin Neurosci, **72**(10) : 774–779, 2018.
11. Mehanna HM, Moledina J, Travis J. Refeeding syndrome : What it is,and how to prevent and treat it. BMJ, **336** : 1495–1498, 2008.
12. Rocks T, Pelly F, Wilkinson P. Nutrition therapy during initiation of refeeding in underweight children and adolescent inpatients with anorexia nervosa : a systematic review of the evidence. J Acad Nutr Diet, **114** : 897–907, 2014.
13. Michihata N, Matsui H, Fushimi K, Yasunaga H. Comparison between enteral nutrition and intravenous hyperalimentation in patients with eating disorders : results from the Japanese diagnosis procedure combination database. Eat Weight Disord, **19** : 473–478, 2014.
14. Garber AK, Sawyer SM, Golden NH, *et al.* A systematic review of approaches to refeeding in patients with anorexia nervosa. Int J Eat Disord, **49** : 293–310, 2016.
15. Bargiacchi A, Clarke J, Paulsen A, Leger J. Refeeding in anorexia nervosa. Eur J Pediatr, **178** : 413–422, 2019.
16. Shimizu M, Kawai K, Yamashita M, *et al.* Very long chain fatty acids are an important marker of nutritional status in patients with anorexia nervosa : a case control study. Biopsychosoc Med, **17** : 14 : 14, 2020. doi : 10.1186/s13030–020–00186–8.
17. Hussain AA, Hübel C, Hindborg M, *et al.* Increased lipid and lipoprotein concentrations in anorexia nervosa : a systematic review and meta-analysis. International Journal of Eating Disorders, **52**(6) : 611–629, 2019.
18. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition : DSM–5. American Psychiatric Press, Washington D.C., 2013.
19. Takahashi M, Ueda S, Misaki H, *et al.* Carnitine determination by an enzymatic cycling method with carnitine dehydrogenase. Clinical Chemistry, **40**(5) : 817–821, 1994.
20. Jeejeebhoy KN. Total parenteral nutrition : potion or poison? Am J Clin Nutr, **74**(2) : 160–163, 2001.
21. Smith K, Lesser J, Brandenburg B, Lesser A, *et al.* Outcomes of an inpatient refeeding protocol in youth with anorexia nervosa and atypical anorexia nervosa at Children's Hospitals and Clinics of Minnesota. J Eat Disord, **19** : 4 : 35, 2016.
22. O'Connor G, Nicholls D, Hudson L, Atul Singhal. Refeeding low weight hospitalized adolescents with anorexia nervosa : a multicenter randomized controlled trial. Nutr Clin Pract, **31**(5) : 681–689, 2016.
23. Golden NH, Cheng J, Kapphahn CJ, *et al.* Higher-calorie refeeding in anorexia nervosa : 1–year outcomes from a randomized controlled trial. Pediatrics, **147**(4) : e2020037135, 2021.
24. Marikar D, Reynolds S, Moghraby OS. Junior MARSIPAN (Management of Really Sick Patients with Anorexia Nervosa) : Table Arch Dis Child

Educ Pract Ed, **101**(3) : 140–143, 2016.
25. American Dietetic Association. Position of the American Dietetic Association : nutrition intervention in the treatment of anorexia nervosa, bulimia nervosa, and other eating disorders. J Am Diet Assoc, **106** : 2073–2082, 2006.
26. Yamazaki T, Inada S, Sawada M, *et al.* Diets with high carbohydrate contents were associated with refeeding hypophosphatemia : A retrospective study in Japanese inpatients with anorexia nervosa. Int J Eat Disord, **54** : 88–94, 2021.
27. Draffin K, Hamilton J, Godsil S, Rudolph S, Crowe T, Newton R. Comparison of a low carbohydrate intake and standard carbohydrate intake on refeeding hypophosphatemia in children and adolescents with anorexia nervosa : a pilot randomised controlled trial. J Eat Disord, **10**(1) : 50, 2022.
28. Pilegaard H, Saltin B, Neufer PD. Effect of short-term fasting and refeeding on transcriptional regulation of metabolic genes in human skeletal muscle. Diabetes, **52**(3) : 657–662, 2003.
29. Winther B, Jackson D, Mulroy C, MacKay M. Evaluation of serum carnitine levels for pediatric patients receiving carnitine-free and carnitine-supplemented parenteral nutrition. Hosp Pharm, **49**(6) : 549–553, 2014.
30. Kang SW, Ahn EM, Cha YS. Changes in lipid and carnitine concentrations following repeated fasting-refeeding in mice. Nutr Res Pract, **4**(6) : 477–485, 2010.