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ORIGINAL ARTICLE

Blood Glucose and Triglyceride Changes Following the Administration of Commercial Enteral Nutrition Solutions with Differing Glucose and Fat Contents

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Abstract

Objective. To clarify whether reducing the energy ratio of carbohydrates and increasing the ratio of fats contribute to suppressing blood glucose elevation not only under normal conditions, but also under the effects of glucocorticoids.

Methodology. Three test enteral nutrition solutions, differing in energy ratios and used in actual clinical settings, were given to rats: HINEX E-Gel (ST) with 20% fat and 64% carbohydrate content; HINEX E-Gel LC (LC) with 34% fat and 50% carbohydrate content; and HINEX Renute (RN) with 50% fat and 26% carbohydrate content. The time course data of plasma glucose, triglyceride, and insulin levels after a single oral administration of the test EN solution were obtained in normal rats (Experiment 1) and hyperglycemia model rats treated with dexamethasone (Experiment 2).

Result. In both normal and dexamethasone-induced hyperglycemic rats, plasma glucose levels were lower in the groups given RN than in the groups given ST. The differences in EN solutions did not significantly affect plasma triglyceride and insulin levels in both rat models.

Conclusion. This study suggested that the EN solution that is high in fat and low in carbohydrate suppressed the post-administration increase of blood glucose levels even in a state of steroid-induced hyperglycemia with insulin resistance.

Key words: enteral nutrition, blood glucose, steroid-induced hyperglycemia, surgical stress, triglycerides, plasma insulin

INTRODUCTION

In acute medical care, the control of blood glucose levels is considered important for patients with impaired glucose tolerance caused by underlying diseases or the use of steroids.[1,2] Stress from surgical invasiveness or other causes increases plasma concentrations of corticosteroids, which then increase blood glucose levels.[3-5] Particularly in brain surgery patients, a high blood glucose level is associated with a risk of poor neurological outcomes.[6] The effect of nutrient administration on blood glucose levels is thus a matter of concern.

High-fat, low-carbohydrate enteral nutrition (EN) solutions slow the post-administration rise in the blood glucose level; therefore, they are presumed to be beneficial for patients in the acute stage of illness, particularly patients with serious internal medical diseases or stroke who require emergency medical care.[2] However, patients with such conditions often demonstrate insulin resistance caused by upregulated stress hormones.[7] Under these conditions, nutrients other than carbohydrates can serve as substrates for gluconeogenesis,[8] making it difficult to assume that the nutritional composition of EN solutions will be directly reflected in blood glucose levels. A comprehensive understanding is required to determine how the composition of enteral nutrition impacts blood glucose levels in the context of steroid-induced hyperglycemia, whereas there is a lack of basic studies comparing EN solutions with different fat and carbohydrate compositions.

The aim of this study was to clarify whether reducing the energy ratio of carbohydrates and increasing the ratio of fats contribute to suppressing blood glucose elevation not only under normal conditions, but also under the effects of glucocorticoids. To confirm the basis for the benefits of high-fat, low-carbohydrate EN solutions in steroid-induced hyperglycemia, normal rats and dexamethasone-

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Table 1. Main nutrient compositions of the test EN solutions

	ST (HINEX® E-Gel)	LC (HINEX® E-Gel LC)	RN (HINEX® Renute)
Calories (kcal/mL)	0.8	0.8	1
Protein (g/100 kcal)	4	4	6
Sugars (g/100 kcal)	15.4	11.8	5.9
Dietary fiber (g/100 kcal)	1.4	1.5	1.2
Fat (g/100 kcal)	2.2 (MCT 34%)	3.8 (MCT 34%)	5.6 (MCT 50%)
P:F:C	16:20:64	16:34:50	24:50:26
L-carnitine (mg/100 kcal)	0	25	40
Vitamin B1 (mg/100 kcal)	0.225	0.225	5

P:F:C indicates the energy ratio of protein, fat, and carbohydrates. The energy ratio of carbohydrates includes that of sugars and dietary fiber.

induced hyperglycemia model rats were used to compare the changes in blood glucose levels and other blood biochemistry indices after a single oral administration of three different EN solutions with varying proportions of carbohydrates and fats.

METHODOLOGY

This study was performed in accordance with the animal experiment guidelines of Otsuka Pharmaceutical Factory, Inc. (Tokushima, Japan) and conducted at its in-house research facilities. It was approved by the Otsuka Pharmaceutical Factory animal experiment review committee (approval numbers (Experiment 1): OPFCAE-2023219, (Experiment 2): OPFCAE-2023224).

Experiment 1

Experimental animals

Seven-week-old, male Wistar rats (The Jackson Laboratory Japan, Inc., Kanagawa, Japan) were used in the experiment. They were kept in an environment with room temperature of 23 ± 3 °C, humidity of 55±15%, and a 12-h light-dark cycle (light 07:00–19:00). An acclimation period of at least 7 days was set, and during the test period, they were given a standard chow (AIN-93G; Oriental Yeast Co., Ltd., Tokyo, Japan) and water ad libitum. Animals were fasted for 16 h before administration, and body weight and blood glucose levels were measured at 09:00 on the day of administration. Whole blood glucose levels were measured using a glucose analyzer, Glutest Mint (Sanwa Kagaku Kenkyusho Co., Ltd., Aichi, Japan), immediately after blood was collected prior to the administration of the test EN solution in each of the groups. Thirty-six rats were evenly assigned to three groups (n = 12 per group) through stratified randomization based on their pre-administration body weight and blood glucose levels. Each group of animals was then administrated HINEX E-Gel (ST) (Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan), HINEX E-Gel LC (LC) (Otsuka Pharmaceutical Factory, Inc.), and HINEX Renute (RN) (Otsuka Pharmaceutical Factory, Inc.). The main nutrient compositions of the test EN solutions are shown in Table 1. The body weight of each group of rats used in Experiment 1 prior to the administration of each EN solution was 337.9 ± 12.6 g (ST group), 338.3 ± 11.1 g (LC group), and 337.7 ± 14.7 g (RN group). The doses of ST, LC, and RN were 12.5 mL/kg, 12.5 mL/kg, and 10 mL/kg, respectively, so that the total calories of each of the test substances were the same in all three groups (10 kcal/kg). The animals in each group were given a single oral administration of the respective EN solution, and blood was collected at the prescribed times. In Experiment 1, there were no dropouts, and blood sampling was successfully conducted at all time points, resulting in no missing data. After the blood was collected, the animals were euthanized by cervical dislocation under isoflurane anesthesia.

Experiment 2

Adjustment of administered substances

Dexamethasone (Fujifilm Wako Pure Chemical Corp., Osaka, Japan) was dissolved to a concentration of 4 mg/mL using dimethyl sulfoxide (Fujifilm Wako Pure Chemical Corp.), and after sterilizing with a membrane filter (ADVANTEC DISMIC-28CP 0.20 μm; Toyo Roshi Kaisha, Ltd., Tokyo, Japan), it was stored at −20 °C. Immediately before administration, a three-fold amount of physiological saline was added to the dexamethasone that had been returned to room temperature to make a 1 mg/mL dexamethasone solution. The prescribed solutions were administered subcutaneously once daily to the animals.

Experimental animals

Seven-week-old, male Wistar rats were used in the experiment. They were kept in an environment with room temperature of 23 ± 3 °C, humidity of 55 ± 15%, and a 12-h light-dark cycle (light 07:00–19:00). An acclimation period of at least 7 days was set, and during the test period, they were given AIN-93G and water ad libitum. The dexamethasone solution was administered subcutaneously once a day from 4 days before the administration of the EN solution. After 16 h of fasting, body weight and blood glucose levels were measured at 09:00 on the day of administration of the EN solution. Whole blood glucose levels were measured using a glucose analyzer, Glutest Mint (Sanwa Kagaku Kenkyusho Co., Ltd.). Thirty-six rats were evenly assigned to three groups (n=12 per group) through stratified randomization based on their pre-administration body weight and blood glucose levels. Each group of animals was then administered HINEX E-Gel (ST) (Otsuka Pharmaceutical Factory, Inc), HINEX E-Gel LC (LC) (Otsuka Pharmaceutical Factory, Inc.), and HINEX Renute (RN) (Otsuka Pharmaceutical

Table 2. Results of nonparametric repeated measures ANOVA

Factor	df	Statistic	*p*-value
Experiment 1. Plasma glucose concentrations			
Between-subject factor: type of test EN solution	1.9346	28.3981	<0.0001
Within-subject factor: time from the administration of the EN solution	3.4528	244.7147	<0.0001
Interaction	5.9558	6.7364	<0.0001
Experiment 1. Plasma triglyceride concentrations			
Between-subject factor: type of test EN solution	1.9986	1.8981	0.1499
Within-subject factor: time from the administration of the EN solution	3.8829	89.6708	<0.0001
Interaction	7.1345	1.6804	0.1070
Experiment 1. Plasma insulin concentrations			
Between-subject factor: type of test EN solution	1.9302	1.5585	0.2112
Within-subject factor: time from the administration of the EN solution	3.1190	225.1788	<0.0001
Interaction	5.5430	0.5237	0.7769
Experiment 2. Plasma glucose concentrations			
Between-subject factor: type of test EN solution	1.8588	0.9174	0.3935
Within-subject factor: time from the administration of the EN solution	2.9440	26.3660	<0.0001
Interaction	5.2779	3.3618	0.0041
Experiment 2. Plasma triglyceride concentrations			
Between-subject factor: type of test EN solution	1.9672	0.2134	0.8042
Within-subject factor: time from the administration of the EN solution	2.2660	16.2958	<0.0001
Interaction	4.3450	1.1698	0.3218
Experiment 2. Plasma insulin concentrations			
Between-subject factor: type of test EN solution	1.9441	0.4323	0.6433
Within-subject factor: time from the administration of the EN solution	3.8731	41.9002	<0.0001
Interaction	6.9259	1.4160	0.1944

The approximate degrees of freedom (df), test statistics, and p-values were obtained from nonparametric repeated measures ANOVA.

Factory, Inc.). The main nutrient compositions of the test EN solutions are shown in Table 1. The body weight of each group of rats used in Experiment 2 prior to the administration of each EN solution was 236.8 ± 7.4 g (ST group), 243.0 ± 8.6 g (LC group), and 254.4 ± 9.9 g (RN group). A single oral administration of the respective test EN solution was given to each group, and blood was collected at the prescribed times after administration. In Experiment 2, there were no dropouts during either the dexamethasone administration period or the liquid diet administration trial. Blood sampling was successfully conducted at all time points, resulting in no missing data. After the blood was collected, the animals were euthanized by cervical dislocation under isoflurane anesthesia.

Blood analysis

Before (0 min) and 15, 30, 60, 90, and 120 min after administration of the test EN solution, 150 μL of blood each time were collected from the subclavian vein without anesthesia. After treatment with heparin, the blood was centrifuged for 10 min at 3,000 *g* at 4 °C to obtain plasma. The plasma was frozen and stored in a freezer set at −80 °C until analysis. For all plasma specimens, the concentrations of blood glucose and triglycerides were measured by enzymatic methods using a Quick Auto Neo GLU-HK (Shino-Test Corp., Tokyo, Japan) and L-type Wako Triglyceride M (Fujifilm Wako Pure Chemical Corp., Osaka, Japan). Plasma insulin levels were determined by ELISA using a Morinaga Ultra Sensitive Rat Insulin ELISA Kit (Morinaga Institute of Biological Science, Inc., Kanagawa, Japan).

Statistical analysis

The results are shown as mean ± standard deviation values. In Experiments 1 and 2, the data for plasma glucose, triglyceride, and insulin concentrations in each group and at each time point were tested for normality using the Shapiro-Wilk test. Since the hypothesis of normality was rejected for all parameters, nonparametric repeated measures analysis of variance (ANOVA) was performed with type of test EN solution as a between-subject factor and time from the administration of the EN solution as the within-subject factor for each blood test item in the ST, LC, and RN groups. The approximate degrees of freedom, test statistics, and p-values obtained from the nonparametric repeated measures ANOVA test are shown in Table 2. Pairwise comparisons between each pair of groups at each time point were performed using the Brunner-Munzel test. The multiplicity of tests within and across time points was adjusted using the Benjamini-Hochberg method. The significance level was taken to be a two-tailed 5%. Statistical analysis and tests were performed using R software version 4.3.2. The nonparametric repeated measures ANOVA tests were performed using the nparLD package version 2.2 in R.

RESULT

Experiment 1

First, healthy normal rats were weighed, and an isocaloric dose of three different test EN solutions was administered orally based on their body weight ratios. Following the administration of each test EN solution, plasma glucose,

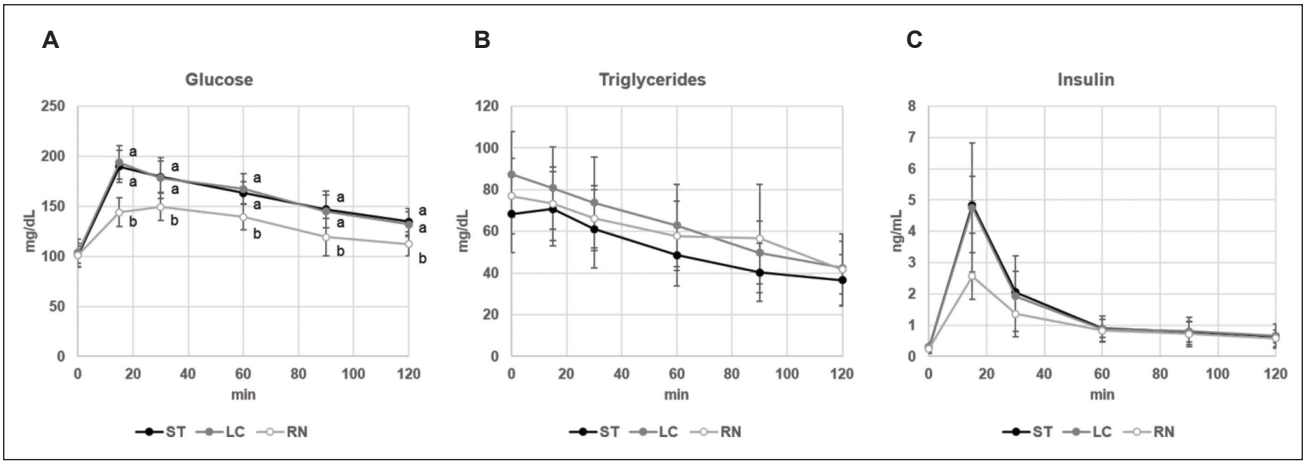

Figure 1. Changes in plasma glucose, triglyceride, and insulin levels in the normal rats.

Data are presented as mean ± standard deviation values. Different letters indicate a significant difference between groups (Brunner-Munzel test, α=0.05).

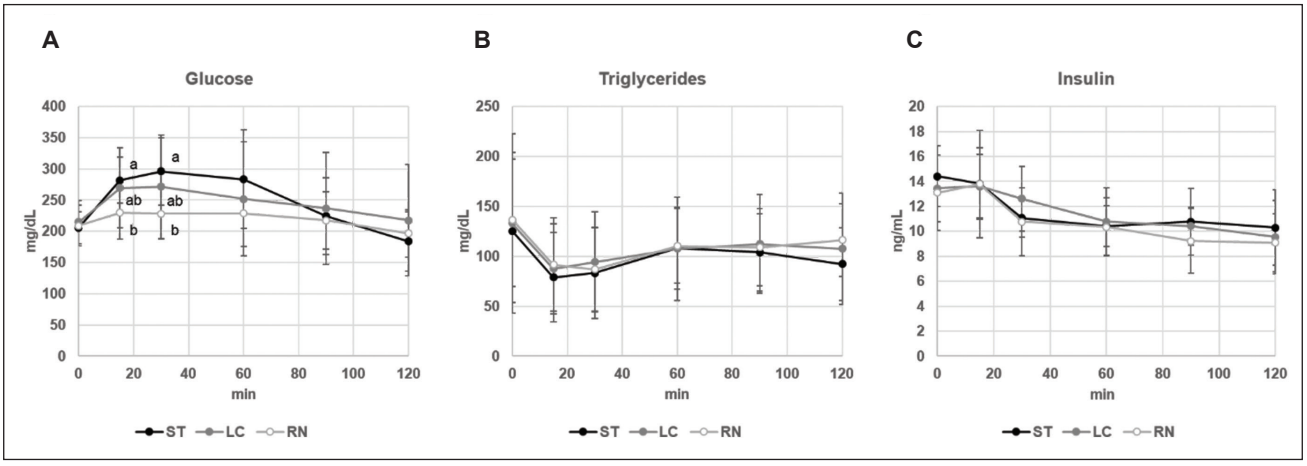

Figure 2. Changes in plasma glucose, triglyceride, and insulin levels in the dexamethasone-induced hyperglycemia model rats.

Data are presented as mean ± standard deviation values. Different letters indicate a significant difference between groups (Brunner-Munzel test, α=0.05).

triglyceride, and insulin concentrations were measured through repeated blood sampling from the same individuals. The time courses of blood glucose levels in each group are shown in Figure 1A. The mean plasma glucose levels peaked at 15 min post-administration in the ST and LC groups, and at 30 min post-administration in the RN group, followed by a gradual decrease. The results of nonparametric repeated measures ANOVA showed main effects of both the type of test EN solution and time from administration of the EN solution, and interactions were significant. When compared at each time point, the blood glucose level was significantly lower in the RN group than in the two other groups at all time points more than 15 min after administration.

The plasma triglyceride levels in each group are shown in Figure 1B. The results of nonparametric repeated measures ANOVA showed that only the main effect of time from administration of the EN solution was significant; interactions were not significant.

The changes in plasma insulin levels in each group are shown in Figure 1C. The mean plasma insulin concentrations in all groups showed a transient increase. At the 15-min peak, the mean plasma insulin concentrations were lower in the RN group than in the ST and LC groups. The results of nonparametric repeated measures ANOVA showed that only the main effect of time from administration of the EN solution was significant; interactions were not significant.

Experiment 2

To elucidate whether reducing the energy ratio of carbohydrates contributes to the suppression of blood glucose elevation not only under normal conditions, but also under the influence of steroids, an investigation using hyperglycemic model rats induced by dexamethasone administration was conducted. The rats given dexamethasone at a dose of 1 mg/kg for 4 days showed lower body weights than the age-matched rats used in Experiment 1. In this experiment, there were no dropouts

during either the dexamethasone administration period or the liquid diet administration trial. Blood sampling was successfully conducted at all time points, resulting in no missing data. Following the administration of each test EN solution, plasma glucose, triglyceride, and insulin concentrations were measured in the same manner as in Experiment 1. The time course of blood glucose levels in each group at the time of administration of the test EN solution is shown in Figure 2A. Basal blood glucose levels were increased in rats administered dexamethasone. The results of nonparametric repeated measures ANOVA showed that the main effect of time from administration of the EN solution and interactions were significant. When compared at each time point, the blood glucose level after administration of the EN solution was significantly lower in the RN group than in the ST group at 15 and 30 min.

The plasma triglyceride level was increased in the animals that were given dexamethasone (Figure 2B). The results of nonparametric repeated measures ANOVA showed that only the main effect of time from administration of the EN solution was significant; interactions were not significant.

In the rats given dexamethasone, elevated plasma insulin levels were seen even before the administration of the EN solution. In contrast to normal rats, transient increases in plasma insulin concentrations following EN solution administration were not observed in dexamethasone-induced hyperglycemic model rats (Figure 2C). The results of nonparametric repeated measures ANOVA showed that only the main effect of time from the administration of the EN solution was significant; interactions were not significant.

DISCUSSION

It has been assumed that the energy ratio of enteral nutrition has an impact on post-administration blood glucose levels, but sufficient data have not been available on the fluctuations in blood glucose levels following administration of EN solutions with varying energy ratios of carbohydrates and fats in basic studies. In the experiment on normal rats, it was presumed that blood glucose levels after the administration of EN solution would be the lowest in the RN group, which received the EN solution with the lowest proportion of carbohydrate calories, but it was necessary to confirm whether the suppression of the rise in blood glucose levels was also exerted in the condition of steroid-induced hyperglycemia, with insulin resistance and elevated gluconeogenesis.

The results of blood tests in Experiment 1, as expected, showed that, in normal rats, the blood glucose levels were lower in the RN group than in the two other groups at all time points after administration of the EN solution. Although not significant, the mean plasma insulin levels were lower in the RN group than in the two other groups at 15 and 30 min after administration of the EN solution. This was considered to reflect the more gradual increase in blood glucose levels observed in the RN group. In addition to having a low proportion of carbohydrates, the EN solution administered to the RN group also contains a high amount of vitamin B1 (Table 1), which is known to be involved in glucose metabolism and is reported to lower intracellular glucose levels under a glucose load.[9] This suggests the possibility that the absorbed glucose was rapidly metabolized in cells.

For plasma triglyceride levels, despite the difference in fat contents of each EN solution, the main effect of type of test EN solution was not significant. The reasons for this may be that, although the EN solution administered to the RN group contains a large amount of fat, medium-chain triglycerides (MCTs) account for about 50% of its triglycerides. Both long-chain triglycerides (LCTs) and MCT are absorbed into intestinal epithelial cells and converted into fatty acids. However, unlike long-chain fatty acids (LCFAs), which are re-esterified to triglycerides, incorporated into chylomicrons, and secreted into the lymphatic system, medium-chain fatty acids (MCFAs) are directly secreted into the bloodstream as free fatty acids.[10,11] MCFAs are also known to be more rapidly metabolized than LCFAs; whereas LCFAs require a membrane transporter to pass through the plasma membrane and a carnitine shuttle to traverse the mitochondrial membrane,[12,13] MCFAs are directly transported to the mitochondrial intermembrane space without these systems.[14,15] In addition, the amount of L-carnitine, which is known to promote the oxidative metabolism of long-chain fatty acids,[16] was also highest in the EN solution administered to the RN group. These compositional differences were considered to contribute to the lack of significant differences in plasma triglyceride concentrations observed after administration.

In a previous study, we reproduced a condition of steroid-induced hyperglycemia with insulin resistance by administering dexamethasone subcutaneously at a dose of 1 mg/kg/day for 4 days to normal rats (data not shown). Dexamethasone is a synthetic glucocorticoid widely used in clinical settings as an anti-inflammatory drug,[17] but dexamethasone and such glucocorticoids activate glucocorticoid receptors and enhance gluconeogenesis,[18,19] and they are also known to induce whole-body insulin resistance.[20]

In the blood test results in Experiment 2, the blood glucose levels 15 and 30 min after the administration of the EN solution were significantly lower in the RN group than in the ST groups, even in the dexamethasone-induced hyperglycemia model rats. Although no significant difference was observed, from 30 to 60 min after administration of the EN solution, the blood glucose levels in the LC group showed intermediate characteristics between those of the ST and RN groups, which were considered to reflect the carbohydrate content of the EN solution. For the plasma insulin levels, the main effect of the type of test EN solution was not significant, and there

was confirmed to be no transient, conspicuous rise in the insulin level, as was seen when the EN solutions were administered to normal rats. A possible reason was that these model rats were in a state of insulin resistance that showed higher blood glucose and higher insulin levels than normal rats even when fasting, resulting in saturation or malfunction of insulin secretion by pancreatic islet β-cells. Therefore, the lower blood glucose level in the RN group than in the ST groups was not due to insulin, but rather was thought to be due to the specific nutrient composition of the EN solution, including the low proportion of carbohydrate calories. The plasma triglyceride levels, as in Experiment 1, showed no significant difference by type of test EN solution, and the nutrient composition rich in MCTs and L-carnitine was thought to be able to promote the rapid absorption and metabolism of lipids even in a state of steroid-induced hyperglycemia.

In order to simulate clinical conditions, the test EN solutions used in this study were commercially available products. Therefore, not only the carbohydrates and fat, but also the composition of other nutrients in the test enteral nutrition did not match exactly. There was a possibility that in a state of enhanced gluconeogenesis, the different proportions of protein in the test EN solution affected the blood glucose levels. However, in Experiment 2, the blood glucose levels in the RN group, which received the EN solution with a high proportion of protein calories, were lower. From this, it was judged that the effects of the protein composition on blood glucose levels were negligible compared with those of the carbohydrate composition.

CONCLUSION

The results of this study showed that administration of an EN solution containing 50% fat and 26% carbohydrates decreased the post-administration increase in blood glucose levels compared with the product with 20% fat and 64% carbohydrate content, even in dexamethasone-induced hyperglycemic rats. This suggested that in states of steroid-induced hyperglycemia with insulin resistance, reducing the percentage of carbohydrates and increasing that of fats in EN solutions may be beneficial for proper blood glucose management.

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Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
HK: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing – original draft preparation; **SM**: Formal analysis, Writing – original draft preparation, Writing – review and editing, Supervision; **IY**: Formal analysis, Writing – original draft preparation, Supervision, Project administration

Data Availability Statement
Datasets generated and analyzed are included in the published article.

Author Disclosure
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