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Estimation of glycemic index in a dietary formulation targeted to support enteral and oral nutritional needs

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Abstract
Background Enteral nutrition (EN) is the preferred method to extend nutritional support and mitigate the chances of malnutrition in patients who are critically ill. In these patients, the risk of hyperglycemia is high and can result in poor clinical outcomes and delayed recovery. Hence, estimation of the glycemic index (GI) of supplements used in EN becomes important to reduce all such risks.
Objective To estimate the GI of a nutritional supplement formulated for critically ill patients during hospitalization and after recovery.
Methods Ten healthy participants (mean age: 25 years; mean body mass index: 21 kg/m^2) were included in the study. The test food was a high protein energy dense supplement, that derived 25 g of available carbohydrates which was fed to all the participants. The reference food used was 27.5 g of glucose monohydrate drink. Capillary blood glucose was measured at fasting (0 min) and at an interval of 15 min till 120 min, after consuming the reference and test food, for estimating the GI. Glycemic index values were computed by using the method suggested by the Food and Agriculture Organization of the United Nations (FAO) and the the World Health Organization (WHO).
Results The mean GI of the test food was 39 ± 3 when calculated using the internationally recognized GI protocol.
Conclusion The GI of the test food was found to be in the category of low GI.

Keywords Glycemic index · Enteral nutrition · Critically ill patients

1 Introduction

Critically ill patients have 40% chance of having malnutrition. As a response to stress during, the metabolic changes cause an increase in protein breakdown, which further results in a considerable loss of lean body mass. All these factors increase the risk of malnutrition [1]. Moreover, in such critically ill patients, the clinical outcomes and nutritional status are interrelated. Patients who require intensive care have alterations in both the morphological and functional aspects of the gastrointestinal tract. Up to 60% of these patients experience gastrointestinal dysfunction due to compromised gastrointestinal motility, digestion, or absorption [2, 3].

Optimal nutrition is vital for ensuring better outcomes in the healthcare environment. Critically ill patients require specific care to prevent muscle wasting due to overfeeding or underfeeding [4]. In critical illness, insulin resistance and hyperglycemia

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are common sequelae secondary to stress. Severe illness could exacerbate/hasten cellular damage induced by hyperglycemia. Cellular hypoxia in such patients causes the increased expression of insulin-independent glucose transporters on the membranes of several cell types. The excess circulating glucose causes reperfusion injury and cell damage. Usually, hyperglycemia can be handled with increased insulin doses, but carbohydrates should also be administered accordingly, so that there is no excess load for the insulin to act and glycemic variability is also controlled [5–7].

Hospitalized patients and those who discharged after hospitalization also have high rates of malnutrition. This stressful catabolic state in these critically ill patients could result in various complications, such as a rise in sepsis, an increase in the inflammatory response, hyperglycemia, metabolic deterioration and imbalance resulting in multiple organ failure, and prolonged length of mechanical ventilation, which, in turn, result in extended hospitalization and deterioration in quality of life with high morbidity and mortality [6]. These complications ultimately contribute to increased healthcare costs [8]. The key purpose to provide nutritional support to patients who are critically ill is to avoid malnutrition and the associated complications, by offering suitable dosages of macronutrients and micronutrients. This could help meet the intended/measured requirements, evade difficulties related to nutritional support, reduce nitrogen deficit, and modulate the inflammatory response via the use of diverse substrates [1].

Parenteral nutrition (PN) and enteral nutrition (EN) are modes of supplementing nutrition to critically ill patients. In PN, nutritional feed is administered intravenously, so that nutrients enter directly into the bloodstream without the involvement of the digestive tract. In EN, the food is delivered through a tube, so that it reaches the stomach/small intestine [9].

Enteral nutrition is a dynamic therapy that modulates the immune system positively by reducing stress-induced metabolic feedback. It costs less when compared with parenteral nutrition and is ideal in most cases because of less severe complexities and improved patient outcomes [1]. Findings from various studies indicate that enteral nutrition can maintain the structural integrity of the gastrointestinal mucosa much better than PN. This mode of nutrition helps safeguard the integrity of the gut by stimulating blood flow, releasing endogenous trophic agents, and maintaining tight junctions between intraepithelial cells. The villous height structure and secretory IgA immunocytes structure are also maintained by this mode of nutrition. Tatsumi et al. [10] demonstrated a trend toward reduced mortality upon early initiation of enteral feeds. The beneficial aspects of EN have been summarized in many meta-analyses and trials [11–14]. Similarly, a meta-analysis by Heyland et al. [15] also demonstrated a trend towards reduced mortality upon early initiation of enteral feeds.

The importance of EN as the favorable source of nutrition has been well captured and endorsed by the American Society for Parenteral and Enteral Nutrition/European Society for Clinical Nutrition and Metabolism. However, because of the unavoidable disruptions in feeding and delayed gastric emptying, patients often receive lesser than the prescribed measure of EN. Hence, the enteral feeds must be able to provide calories and proteins in ample amounts to support the increased demands [5].

Among all the macronutrients, carbohydrates are the favored substrates to produce energy, but the quantity and quality of the type of carbohydrates should also be monitored. It is well highlighted that precise techniques to manage hyperglycemia during EN therapy must include the composition of nutrition support formulation and evaluation of the caloric needs. Moreover, pharmacologic agents that are regularly used in clinical practice should also be monitored [16]. Most dietary recommendations focus on the quantity of carbohydrates without looking at their quality. The quality of carbohydrates can be measured by estimating the glycemic index (GI) of the feeds. GI estimation technique is a method to relatively rank the carbohydrates in foods with respect to their effect on blood glucose levels. It has been demonstrated that carbohydrates with low GI value (< 55) cause a lower and slower rise in the blood glucose as well as insulin levels, which is attributed to their slow digestion, absorption, and metabolism [6].

It is, therefore, important to estimate the GI of EN supplements used or the recovery of patients with critical illness. The present study was initiated to estimate the GI of a high-calorie, high-protein nutritional supplement specially formulated for critically ill patients and to support their nutritional demands after discharge.

2 Methodology

2.1 Subjects

Fifteen healthy individuals in the age range of 18–45 years and having a body mass index of ≤ 22.9 kg/m [2], who were willing to consume and test the reference foods, were enrolled in the study. Individuals, who were on special diets such as a ketogenic diet, low-GI diet, weight-loss diet, and cholesterol-restricted or a high-protein diet, with self-reported diabetes, suffering from allergies, who had undergone medical or surgical events in the last 3 months, or who were on

routine medications that could affect their blood glucose levels, its digestion, and absorption were not included in the study. Pregnant and lactating mothers were not involved in the study.

2.2 Ethics approval

All the details of the study protocol were provided and any questions from the participants were duly addressed. The study methodology adhered to the international standards for conducting ethical research with humans and was certified by the Institutional Ethics Review Committee of the Madras Diabetes Research Foundation (MDRF). Written informed consent was taken from all the volunteers who agreed to be a part of this study. The study was registered in the Clinical Trial Registry of India, CTRI/2021/08/035929.

2.3 Test and reference food

2.3.1 Test food

Test food was a high-protein and energy-dense nutritional supplement provided by Dr. Reddy's Laboratories. The nutrition supplement was designed to accommodate the ease of titrations from 1 kcal/mL to 2 kcal/mL for tube feeding. To provide 25 g of available carbohydrates, 51 g of this nutritional supplement (Table 1**)** was mixed in 167 mL of lukewarm water. The estimation of available carbohydrates was done by FAO/WHO 2003 approved difference method.

2.3.2 Reference food

Reference food for the GI study was 27.5 g of glucose monohydrate dissolved in 125 mL of water.

2.4 Procedure for determining GI

Participants were explained the study protocol and were advised to undergo 1 day of testing with the test food and 3 days with the reference food. In order to minimize carry-over effects, at least 3 days of washout period was given between measurements.

Participants came to the center in the morning on the scheduled test day, after 10 to 12 h overnight fast. Details were obtained using a 24-h dietary recall method, and questions were asked on smoking, caffeine-containing drinks, alcohol, and physical activity, to ensure that the participants followed the same diet and had similar physical activity on pretest dates and abstained from smoking and alcohol during the study cycle. Female participants were not tested during their menstrual period dates, and testing was rearranged in such cases.

Subjects who were not comfortable with blood sampling via finger-pricking were asked to perform a practice test to make them familiar with the study procedure and also to control their anxiety, which could affect their blood glucose levels. An automatic lancet device was used to make a finger-prick and collect the fasting blood sample for blood glucose assessment using Hemocue 201^{+}

Glucose analyzer (Hemocue Ltd,A¨ ngelholm, Sweden), and this was considered as a reliable method of blood glucose analysis [17]. The samples for blood glucose estimation were collected twice at an interval of 5 min before consumption of the food. The baseline value was taken as the mean of these two values. Further blood samples were collected at 15,30,45,60,90 and 120 min after consumption of test/reference foods. Subjects were provided with 125 mL of water during the subsequent 2 h for both GI testing. For the finger-prick blood samples, the third finger on the left hand was used for all participants. All instruments used in the study were duly calibrated.

This study was performed according to the GI testing protocol recognized by the Food and Agriculture Organization/World Health Organization [18] as well as the guidelines by the International Dietary Carbohydrate Task Force for GI Methodology [19] and ISO [20], which have been validated and published elsewhere.

Table 1 Nutrient composition of nutritional supplement (test food) used in the study

Nutrients	Unit	100 g
Energy	kcal	440
Protein	g	21
Carbohydrates	g	52
Available carbohydrates[a]	g	48.8
Total sugars	g	8.7
Added sugar (sucrose)	g	0
Fat	g	16
Monounsaturated fatty acids	g	2.4
Polyunsaturated fatty acids	g	0.4
Saturated fatty acid (including MCT)	g	10.8
Cholesterol	mg	< 1
Trans fatty acids	g	< 0.1
Dietary fiber	g	2
Sodium	mg	435
Vitamins		
Vitamin C	mg	11.6
Vitamin B5	mg	1.5
Vitamin E	mg	2.9
Vitamin B6	mg	0.6
Vitamin B2	mg	0.5
Vitamin B1	mg	0.4
Vitamin B3	mg	4.6
Vitamin A	mcg	173.9
Folic acid	mcg	57.9
Vitamin K	mcg	15.9
Biotin	mcg	8.7
Vitamin D	mcg	2.9
Vitamin B12	mcg	0.3
Minerals		
Chloride	mg	521.7
Magnesium	mg	98.6
Iron	mg	4.9
Zinc	mg	3.5
Manganese	mg	1.2
Selenium	mcg	11.6
Calcium	mg	173.9
Chromium	mcg	14.5
Phosphorus	mg	173.9
Copper	mcg	492.8
Iodine	mcg	43.5
Molybdenum	mcg	16.0
Other nutrients		
L-Carnitine	mg	40
L-Taurine	mg	40

[a]Available carbohydrates was estimated using the Food energy—methods of analysis and conversion factors: Report of a technical workshop, Rome, 3–6 December 2002 Rome: FAO, 2003. 87 s

Table 2 Baseline characteristics of the study participants

Characteristics	Mean ± SD (n = 10)
Sex Male n (%)	10 (67%)
Age (years)	25 ± 1
Weight (kg)	57 ± 2
BMI (kg/m^2)	21 ± 0.3
Waist circumference (cm)	73 ± 1
Blood pressure (mmHg) Systolic Diastolic	112 ± 4 73 ± 2
Fasting blood glucose (mg/dl)	83 ± 2

n No. of healthy volunteers who participated in the study; *SD* Standard deviation; *BMI* Body mass index

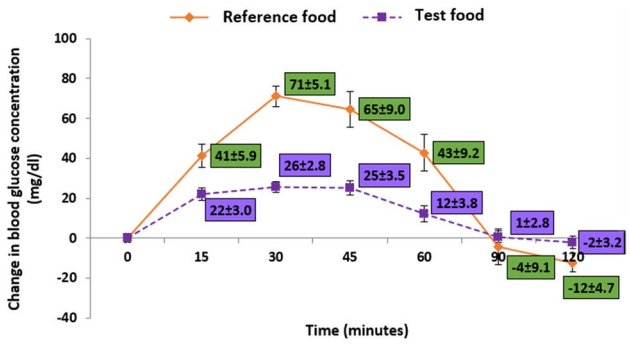

Fig. 1 Change in blood glucose between reference food (glucose) and nutritional supplement (test food) over 2 h

2.5 Data/ statistical analysis

Out of the fifteen participants, one with coefficient of variation (CV) > 30% was identified as an outlier and removed. Four more subjects quit the study due to personal reasons. Hence, data from ten participants were included for further analysis. The trapezoid rule was applied to estimate the incremental area under the curve (IAUC) of blood glucose for the reference and test foods. The area below the fasting baseline was ignored. The IAUC mean and standard errors for the reference and test foods were calculated. Glycemic index value was calculated by expressing each subject's IAUC after the test food as a percentage of the same subject's mean reference IAUC. The mean of the resulting values was taken as the GI of the respective test food and reported as mean and standard errors. The GI values were further tested to see the influence (interaction) by age (years), sex, diet [energy (kcal), protein (g), fat (g), carbohydrates (g), and dietary fiber (g)], and physical activity level, using a generalized linear model using statistical analysis software (version 9.1; SAS Inst., Cary, NC, USA).

$$\text{GIvalue of test food (\%)} = \frac{\text{Blood glucose IAUC value of the test food} \times 100}{\text{IAUC value of the reference food}}$$

3 Results

The baseline characteristics of the study participants are provided in Table 2. The mean age of participants was 25 ± 1 years with a mean BMI of 21 ± 0.3 kg/m^2. The change in blood glucose levels between the reference food (glucose) and the test food over 2 h is depicted in Fig. 1. At the tested nutrient concentration, the change in blood glucose level varied from 15 min up to 120 min. At 120 min, a negative value could be observed pertaining to the blood glucose concentration for both the test food and the reference food. The mean IAUC of the reference food and test food and the GI of the test food are reported in Table 3. As observed, the mean IAUC of the reference food was found to be 3626 ± 269 mg/dL*min

Table 3 Mean IAUC of the reference food and the GI of the test food

Mean IAUC–reference (mg/dL*min)	Mean IAUC–test (mg/dL*min)	GI of the nutritional supplement (test food)
3626 ± 269	1459 ± 132	39 ± 3

IAUC Incremental area under the curve; *GI* Glycemic index

and the mean IAUC of the test food was found to be 1459 ± 132 mg/dL* min; thus, according to the estimated GI test, the GI of the multinutrient supplement was 39 ± 3, placing it in the low-GI food category (a GI value of 55 or less on the glucose reference scale is considered to be low GI for most of the food items) [21, 22]. The nutrient composition of the nutritional supplement (test food) used in this study is listed in Table 1.

4 Discussion

The GI of the nutritional supplement (test food) was found to be low in the present study. The ingredients used to design the nutritional supplement, such as medium-chain triglycerides (MCTs), whey protein concentrate, and maltodextrin, could be the reason for low GI. This nutritional supplement can be used as both tube feed for critically ill patients and as oral feed during convalescence. It is also high in protein and designed to be titrated from 1 kcal/mL to 2 kcal/mL for tube feeding. It is noteworthy to mention that several factors, such as the amount and kind of dietary carbohydrate source, nature of the starch present, quantity of proteins and fat, quality of dietary fiber content, food form, particle size, and method of food processing, affect the blood glucose concentration [8, 23]. Hence, all these factors are considered while planning nutritional interventions to lower the GI of the food, so that the incidences of hyperglycemia are reduced after intake of the dietary/nutritional supplement [24].

Glycemic index is the most reliable predictor of glycemic variations. Foods having GI ≥ 70 on the glucose scale are considered high-GI foods, whereas those that have GI ≤ 55 on the glucose scale are considered low-GI foods. It is important to highlight here that the low-GI foods provoke lesser blood glucose fluctuations than high-GI foods over the day [25].

Standard enteral formulas have intact nutrients usually with carbohydrates in the form of maltodextrin and corn syrup solids, the goal of the standard formula is to provide balanced amounts of macronutrients to meet patient's nutrient requirements [26, 27]. It is important to use most suitable sources of macronutrients in enteral feeds as they vary in chemical forms, molecular sizes, solubility, and quality. These characteristics can affect the osmolarity, absorption, utilization rate, and tolerance of the nutrients, which may directly affect patient recovery [27]. The nutrient composition of the present formulation is meant to match that recommended dietary allowance of the patient thus filling the nutrient gap while tube feeding.

Evolving research emphasizes the importance of GI in the Indian context. Studies also highlight that the GI value of foods should be considered while deciding for carbohydrates in any diet. The quantity of carbohydrate consumed influences blood glucose levels and insulin responses. This is because high-GI carbohydrate sources are quickly broken down during digestion and release glucose quickly into the bloodstream, whereas the reverse is true for low-GI carbohydrate sources where glucose is released gradually into the bloodstream [28].

The GI is calculated as the percentage of IAUC for blood glucose response after consumption of a test food divided by the IAUC of a reference food containing the same amount of available carbohydrate [29]. Several benefits are reported with the use of low-GI supplements, which are found to have a beneficial effect on the lipid profile. Low-GI feeds also relate with decreased chronic inflammation, improved insulin sensitivity, and improved fibrinolytic activity. Moreover, low-GI value in the nutritional feeds proves to be beneficial over a diet based on mere carbohydrate quantity intake computation [6].

We hypothesized that this composition (Table 1) is the reason for low GI, and our study findings agree with the findings of Bhoite et al. [30] where the test food was reconstituted and consumed with water. GI value was reported to be not influenced by individual parameters, such as age (years), sex, diet (energy [kcal], protein [g], fat [g], carbohydrates [g], and dietary fiber [g]), and level of physical activity. The GI value is actually influenced by cooking methods, time taken for chewing, and chemical structure of carbohydrates, along with the content of other nutrients like fat, protein, and dietary fiber [31].

The nutritional supplement (test food) was designed to cater to the needs of critically ill patients and to support their early recovery. The ingredients that were used in the formulation of the product have been selected based on the overall health benefits they confer. Whey protein was included in the test food, as it is a rich source of amino acids and can directly trigger beta cells to secrete insulin, which promotes reduction in postprandial glycemia [32]. It was demonstrated by another study that the consumption of whey protein did not reduce the renal function when type 2 diabetes patients with microalbuminuria were put on a one-year weight-loss program [33].

Gastrointestinal dysfunction is frequent in critically ill patients and is linked with worse clinical outcomes, and hence, it cannot be overlooked [34]. The designed product had MCTs that are readily absorbed into the bloodstream from the gastrointestinal tract. Additionally, these triglycerides exert anti-inflammatory and metabolic benefits such as augmentation of beta cell secretion of insulin in response to glucose, improved insulin sensitivity, and reduced inflammation [35, 36].

In recent years, it has been well acknowledged that the ability of proteins to decrease postprandial glycemia can vary. Especially, milk protein has shown to accelerate an increase in postprandial insulin response with a subsequent reduction in postprandial blood glucose levels. The whey fraction of dairy protein was found to contain predominating insulinotropic secretagogue in some studies, which investigated its insulinotropic effect [37]. The GI value of the test food was found to be low, which may be attributed to the ingredients present in it, one of the predominant reasons being the presence of fair amounts of whey protein.

The test food also contained a good combination of other ingredients targeted to provide specialized nutrition therapy to critically ill patients (Table 1). For such patients, it has been shown to provide a combination of trace minerals that include selenium and antioxidant vitamins. Findings from the meta-analysis of 11 clinical trials reported that the overall use of antioxidants was associated with a significant reduction in mortality [relative risk (RR), 0.65; 95% confidence interval (CI) 0.44–0.97, $p = 0.03$]. The nutritional supplement used had omega-3 fatty acids, which are known to be rapidly absorbed into the cell membranes, influencing many aspects of membrane stability and fluidity. They may also play a significant role in cell mobility and cell-signaling pathways [38].

Special nutritional therapies that provide high-fat, low-carbohydrate nutritional regimen could be helpful for patients with conditions requiring ventilator support, such as for patients with acute respiratory failure. Moreover, the kind of fatty acids provided is also seen to have an impact on recovery [38]. Findings from one of the open-label, randomized trials conducted on 107 critically ill patients reported that the enteral low-carbohydrate formulas demonstrated a trend toward a reasonably reduced mean glucose and significantly lower insulin requirements as compared with standard feeding, but had no effect on glucose variability or time-in target range [39]. Nevertheless, it is important to mention that low-GI diets have beneficial effects on chronic disease progression and on the overall health, and they help in decreasing the disease symptoms. Low GI foods are known to improve glycemic control and insulin sensitivity [38].

In the Indian setting with high carbohydrate diets, a glycemia-targeted specialized nutrition, which is low in GI and contains optimal protein, is acknowledged as an important aspect of the nutritional management of critically ill dysglycemic patients (includingboth diabetic and nondiabetic dysglycemic patients). It is by far established that feeds comprising complex or slowly digestible carbohydrates with monounsaturated fatty acids (MUFAs) help in optimizing glycemic value in critical care settings [6].

5 Conclusion

The three primary groups of macronutrients and source of energy are carbohydrates, proteins, and fats. Consuming proper proportion of these macronutrients is vital for sustaining caloric sufficiency, protein sparing, and to achieve balance in nutrition. For patients in whom control of glucose levels and nutritional assistance are warranted, glycemia-targeted specialized nutrition could be helpful. However, such nutritional supplements must encompass slowly digestible carbohydrates and MUFAs. Recent evidence has shown that such supplements are correlated with better glycemic control and improved insulin resistance when compared with a normal nutritional formula/supplement in critically ill patients.

One of the important aspects in critical care is the selection of proper nutritional strategies. It has been well documented that the combination of nutrients can significantly lower the length of hospital stay, days on ventilator, and reduce infections for both critically ill and postsurgical patients. The supplement used in the present study had a good combination of nutrients like antioxidants, vitamins, minerals, fatty acids, and proteins that could help support the

nutritional needs of critically ill patients with a low-GI load. Such products not only help in faster recovery, but also in controlling glucose levels, especially in critical care settings in those with diabetes. The formulation used in the current study may help in meeting the nutritional requirements of patients who need enteral feeds during and beyond hospitalization and also post discharge. The low glycemic index of the dietary formulation indicates its potential use in criically ill patients who are at risk of hyperglycemic shock. However, long-term interventional studies with such products are warranted, which may help in understanding the benefits of such supplements in critically ill patients.

6 Limitation of the study

GI is measured as the area under the 2 h post prandial glycemic response. However, the utility low GI foods or products on the daily 24 h glycemic response / excursion and further influence on the metabolic health need to be evaluated with long term randomised controlled clinical trials.

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Declarations

Competing interests Rachana Bhoite, Varalakshmi Lalithya Pratti and Vinita Satyavrat are employees of Dr Reddy's Laboratories Pvt Ltd and do not declare any conflict of interest. Rest of the authors do not have any competing interests.

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