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Glycemic Indices of Multiple Oral Nutritional Supplements: A Randomized Cross-Over Study in Indian Adults

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Abstract

Background: A randomized cross-over study was conducted to assess the glycemic index (GI) of seven Oral Nutritional Supplements (ONSs). These ONSs are designed to support the nutritional requirements of different age-groups, physiological states, or health conditions among Indian adults. **Methods:** The study had two phases viz., phase1 (n = 18) studied two ONSs: A1 and B1 and phase 2 (n = 20) studied five ONSs: A2, B2, C2, D2 & E2. The subjects were healthy, non-diabetic adults, aged between 20 - 44 years with a mean Body Mass Index of 21.2 ± 1.52 kg/m^2 (Phase 1) and 21.0 ± 1.45 kg/m^2 (Phase 2). All these ONSs were compared with reference drinks (glucose). The carbohydrates in one serving of each ONS were matched to carbohydrates from 25 grams of glucose following ISO 2010 guidelines. Capillary blood was assessed for blood glucose response at baseline, 15, 30, 45, 60, 90 and 120 minutes. GI was calculated as the incremental area under the curve (iAUC) for the test drinks and expressed as a percentage of the average iAUC from glucose. **Results:** Phase 1 indicated that the high fiber diabetes-specific nutrition supplement A1 with higher protein (23% energy), higher fat (25% energy) and reduced carbohydrates (40% energy) had a significantly (p = 0.002) lower GI [34 (±6)] as compared to B1 [63 (±7)] (protein 19%, fat 7% and carbohydrates 60% energy) even with similar amount (22%) and type of fiber. Phase 2 reported that all test products [A2 (32 ± 5), B2 (37 ± 4), C2 (31 ± 5), D2 (31 ± 5) and E2 (55 ± 4)] had a low GI. As compared to phase 1, ONSs in phase 2 had lower fiber content (1.6% - 4.6% energy). **Conclusion:** The glycemic index of oral nutrition supplements is influenced not only by their

fiber content, but also by the overall macronutrient composition including protein (≥17% energy), fat (≥10% - 27% energy) and carbohydrates (40% - 57.5% energy).

Keywords

Glycemic Index, Oral Nutritional Supplements, Incremental Area under the Curve, Diabetes

1. Introduction

Rapid urbanization and lifestyle changes have led to developmental transition, facing a double burden of malnutrition in low middle-income countries like India [1] [2]. The coexistence of pre-transition diseases like undernutrition and infectious diseases as well as post-transition, lifestyle related degenerative diseases such as obesity, hypertension, cardiovascular disease, cancer, and diabetes are widespread in India [3] [4]. Diabetes is one of the fastest growing global health emergencies of the 21st century [5] [6]. In 2021, the countries with the highest number of adults with diabetes were China, India, and Pakistan. Moreover, the majority of people with undiagnosed diabetes come from countries with the highest diabetes prevalence namely China, India and Indonesia [6]. Prediabetes is an intermediate state of hyperglycemia with glycemic parameters above normal, but below the diabetes threshold [7]. According to a recent National Non-communicable Disease Monitoring Survey (NNMS), the prevalence of diabetes and impaired fasting blood glucose (IFG) in India was 9.3% and 24.5%, respectively [8]. Impaired Glucose Intolerance (IGT) remains a high risk for developing diabetes, with a yearly conversion rate of 5% - 10% [7]. However, prediabetes should not be seen as a path to diabetes but rather as a window of opportunity to prevent diabetes [9]. In a country like India, with a sizeable population of patients with diabetes, there is a need to reiterate the necessity of identifying prediabetes and planning for lifestyle modifications [9] [10].

Lifestyle modification of diabetes involves changes in dietary intake, food choices and selection, and physical activity [11] [12] [13] [14]. FAO/WHO Expert Consultation in 1997 had suggested that the concept of Glycemic Index (GI) is very relevant in identifying and choosing foods for better management of blood glucose [15]. The Glycemic Index is defined as the percentage of glucose response elicited by 50 g of available carbohydrate of a test food compared with reference food (glucose or white bread) [16] [17]. A GI value ≥70 is considered high, 56 - 69 (inclusive) medium and ≤55 low, where glucose is equal to 100 [18]. This can be considered as a helpful means to identify the most appropriate carbohydrate containing foods. High GI foods rapidly increased glucose level after a meal compared to low GI foods [16] [19] [20]. Many studies had demonstrated that intake of low GI diet can not only improve glycemic control but also provide benefits with prevention of diabetes and coronary heart disease [21] [22]

[23].

Understanding the GI of foods will be relevant not only for known diabetics or prediabetics, but for a large percentage of undetected hyperglycemic individuals [24]. The expert panel of the International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC) confirmed that considering the high prevalence of diabetes and prediabetes globally and consistent scientific evidence, there is a pressing need to disseminate information on GI among the general population and health professionals, through communication channels including food composition tables and labels on products as well as national dietary guidelines [16].

Oral Nutritional Supplements are designed to support the nutritional requirements for specific ages, genders, physiological stages, or health conditions. They are either powders which need to be reconstituted to drinks or as ready-to-drink formulations, typically containing a balanced mix of energy, protein, fat, and micronutrients [25] [26]. The consumption of the ONSs for people who cannot meet their nutritional requirement has increased over the years [27] [28] [29]. However, with an increasing prevalence of IGT and diabetes in India, it is important to understand the impact of the macronutrient composition of these ONSs on the blood glucose response. While a few studies have previously reported the GI of supplements available in the Indian market [27] [30] [31] [32], our study, to the best of our knowledge, represents the first comprehensive examination of the GI of a diverse range of ONSs tailored for meeting nutritional requirements for different populations. This research aims to better understand the specific role of macronutrients in influencing the GI of these supplements.

2. Methodology

2.1. Ethical Considerations

This study adhered to the guidelines as outlined in the Declaration of Helsinki, ICH guidance on Good Clinical Practice and ICMR Ethical Guidelines. The study protocol and all its amendments and written informed consent forms were reviewed and approved by the Institutional Ethics Committee of Om Children Hospital (ECR/1168/Inst/GI/2018) prior to the commencement of the study. The study personnel discussed and addressed any questions or concerns with the participants prior to study. All participants voluntarily signed the informed consent forms after reading them prior to enrollment and had received a copy of the signed document. The study was conducted in two phases. Each phase was registered with the Clinical Trials Registry-India. Phase 1 and phase 2 were registered on January 2022 (CTRI/2022/01/039765) and July 2022 (CTRI/2022/07/044082), respectively. Phase 1 was initiated in February 2022 and completed in April 2022; Phase 2 was initiated in July 2022 and completed in September 2022. The study flow is shown in **Figure 1** CONSORT diagram [33] for both the phases.

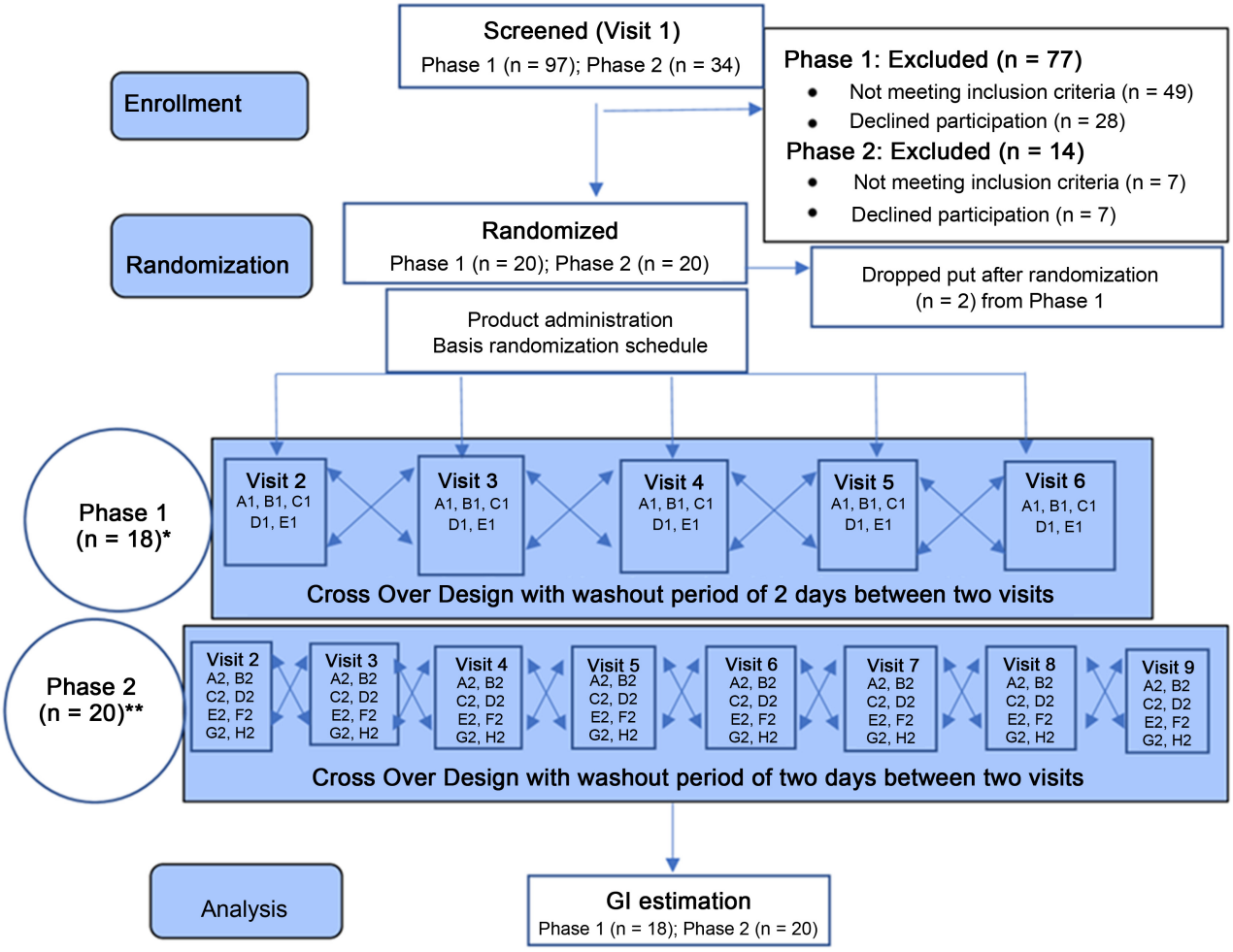

Figure 1. Consort Diagram representing flow of study in Phase 1 and Phase 2.

2.2. Study Design

The objective of the study was to assess the GI of multiple ONSs and understand the role of macronutrient composition of the same. GI was assessed for a total of seven ONSs and compared with reference (Glucon D). ONSs were referred to as test drinks (Phase1: A1, B1; Phase 2: A2, B2, C2, D2, E2). Phase 1 was a double-blind, randomized, cross-over study carried out with two test drinks (A1 and B1) and three reference drinks (C1, D1, E1). Phase 2 was a randomized, cross-over, open-label study wherein five test drinks (A2, B2, C2, D2, E2) were assessed and compared with reference drinks (F2, G2, H2). Both phases followed the International Organization for Standardization (ISO) 2010 guidelines for GI determination of food products [34].

2.2.1. Inclusion and Exclusion Criteria

The participants were included in the study if they had 1) Fasting Blood Glucose (FBG) <100 mg/dL; 2) HbA1c level <5.7%; 3) Body Mass Index (BMI) 18.5 to 22.9 kg/m^2 (both inclusive); 4) had good general health as determined by the investigator based on medical history and vital signs; 5) were willing and ability to

follow the study protocol; 6) ability to understand and provide written informed consent; 7) were willing to refrain from vigorous physical exercise during the study.

The participants were excluded if they 1) had any known food allergy or intolerance to any food or beverages; 2) were taking any medication in the past one week; 3) had any chronic disease or illness in the past three months (e.g., congestive cardiac failure, hepatitis, hypotensive episodes etc.); 4) reported with recent history of dehydration from diarrhea, vomiting or any other reason within a period of 24-hours prior to the study; 5) had participated in any clinical trial within the past 90 days; 6) suffered from blood loss more than 450 mL; 7) were on an unusual diet, special diet, for whatever reason e.g., high protein diet, low sodium diet, for two weeks prior to receiving any reference/test product; 8) performed vigorous physical exercise in the morning on dosing day; 9) were pregnant/lactating; 10) tested positive for HIV; 11) had a current or recent history (within one year of screening) of alcohol (14 units a week on a regular basis) or other substance abuse; 12) were nicotine users/smokers or had quit smoking during the past 3 months; 13) had history of Hepatitis B or C virus.

The participants were instructed to refrain from alcohol consumption, to follow all study directions, return for all specified visits and not take any medication without informing the study staff. After initial screening in the visit 1, eligible participants were informed of their next scheduled date for visits.

2.2.2. Study Participants

Twenty healthy, adults male and female (non-pregnant/non-lactating) participants were enrolled in both the phases to ensure at least 10 participants per phase completed the study as per ISO recommendations [34]. Both the phases included males and non-pregnant/non-lactating females between the ages of ≥18 to ≤45 years. Potential participants from phase 1 (n = 97) and phase 2 (n = 34) were screened at Visit 1 to enroll 20 participants in each phase. During screening, participants were assessed for signs/symptoms and exposure history of COVID-19 and pre-entry scrutiny log for COVID-19. Participants were acclimatized to the environmental conditions and room temperature for at least 15 minutes prior to clinical assessments. Demographical data (age, gender, race, BMI) was collected. Physical examination and vital measurements (temperature, heart rate, blood pressure and respiratory rate) were conducted and recorded along with medical history, medication use (prescription and over the counter) over the past four weeks and history of drug/alcohol abuse. FBG and HbA1c were measured using venous blood for all the participants. In addition, an HIV test was also performed. Approximately 7 ml blood was collected for the three biochemical estimations. Urine pregnancy testing was performed in women of child-bearing age. A total of 18 participants in phase 1 and 20 participants in phase 2 completed the study.

2.2.3. Study Intervention

For phase 1, eligible participants (n = 18) were randomly assigned to one of five

randomization sequences. Each sequence determined whether they would receive either the test or reference drinks. Similarly, in phase 2, eligible participants (n = 20), eight randomization sequences were used to allocate participants to either the test or reference drinks during each visit. The randomization procedure was generated by a biostatistician from a third-party research organization, Cliantha Research, using SAS® statistical software (Version: 9.4; SAS Institute Inc., USA). Only the unblinded pharmacist and quality assurance personnel handled the test products and were not further involved in the study.

Based on scheduled randomization sequence, each participant was randomized to receive either a test or a reference drink during each follow up visit. Participants reported back to the study site on visit 2. All participants consumed a standard dinner before 10 pm (within a ±1 hour window period). They stayed at the site and followed overnight fasting for 10 - 12 hours. The next morning, FBG assessment was performed by withdrawing fingertip capillary blood through finger stick/prick method and using validated Hemocue 201+ prior to 15 minutes (±2 minutes) of the product administration. Participants were instructed to consume the full amount of product, as per scheduled randomization within 10 minutes. All subjects were given products between 8:00 - 9:00 am. Post product administration, assessment of post prandial blood glucose (PPG) was performed at time points at 0, 15, 30, 45, 60, 90 and 120 minutes (±2 minutes window period was for all timepoints except 0 minutes where window period was of +2 minutes). Before the finger-prick the participants were encouraged to warm their hands to improve the blood flow and the third finger of left hand was pricked. To avoid diluting the blood with plasma, blood was extracted from the fingertip without squeezing. Validated Hemocue Glucose 201+ Glucometer was QC checked. It was ensured that the same operator used the same glucometer equipment on the same participants throughout the study. HbA1c was measured using the enzymatic method and was performed on the Architect ci 4100 & Alinity ci series instrument (Abbott Laboratories) with automated analysis. Standard lunch was provided to the participants after 2 hours of dosing. Thereafter the participants were allowed to leave and asked to revisit after a 2-day period for the next visit. This period served as a wash out period between the measurements to minimize carry-over effects. This process was followed till visit 6 for phase 1 and till visit 9 for phase 2, as shown in CONSORT diagram (**Figure 1**).

Satiety score assessment was performed in phase 1, using the 5-point Likert visual analogue scale (VAS) for hunger and fullness (extremely hungry, semi-hungry, no feeling, semi-full, extremely full) with scores ranging from 1 to 5, respectively. Satiety data was collected at baseline (at -5 minutes before product consumption) and at 35, 65, 95, 125, 150 and 180-minutes post product consumption and satiety scores were calculated.

2.2.4. Test and Reference Products

The ONSs in phase 1 were: 1) Diabetes-Specific Nutrition Supplement (DSNS)

A1 (Horlicks Diabetes Plus) and 2) a high fiber adult supplement B1 (Horlicks Cardia+, a superseded supplement). References were three samples of glucose monohydrate (C1, D1, E1). The five ONSs in phase 2 were: a) Protein supplement vanilla (A2) b) Protein supplement chocolate (B2) c) Maternal supplement vanilla (C2) d) Maternal supplement kesar (D2) e) micronutrient rich malt-based supplement (E2). A2 and B2 were different flavors of a protein supplement (Horlicks Protein Plus vanilla & chocolate respectively) with minor differences in protein source. C2 and D2 were identical formulations of a maternal supplement (Horlicks Mothers Plus varied only in flavor vanilla and kesar, respectively), therefore GI of each flavor was tested in 2 groups of 10 participants each. E2 was a micronutrient rich malt based ONS supplement for children (Horlicks). References were three samples of glucose monohydrate (F2, G2, H2) in phase 2. All ONSs were under the brand name Horlicks and were provided by Hindustan Unilever Limited (HUL). The reference was Glucon D (from Zydus Wellness Products Limited).

Both A1 and B1 were high fiber formulations with matched level (22%) and type of soluble fiber but with varying levels of carbohydrate, protein, and fat. Formula A1 was revised from B1 basis ICMR-INDIAB 2021 recommendations for type 2 diabetes (T2D) remission and prevention of progression to T2D in prediabetic and normal glucose tolerance (NGT) individuals [13]. These revisions involved reducing the carbohydrate content (from 60% to 40% of energy), increasing the protein content (from 19% to 23% of energy), and raising the fat content (from 7% to 25% of energy). The fiber levels and type remained the same (22%, soluble). Monounsaturated fatty acid (MUFA) was added in A1 as 70% of total fat content (≈18% of energy). Energy percent contribution of all test products is shown in Table 1.

2.2.5. GI Determination

GI is expressed as a percentage of the incremental area under the glycemic response curve (iAUC) induced by a portion of food containing 50 g or 25 g available carbohydrate in comparison with the AUC generated by a standard

Table 1. Energy percent distribution of each macronutrient for test products in Phase 1 and Phase 2.

	Test Products						
	Phase 1		Phase 2				
	A1	B1	A2a	B2a	C2b	D2b	E2c
Carbohydrate (%)	40.0	60.0	52.4	52.4	57.5	57.5	57.5
Protein (%)	22.5	19.1	36.4	36.4	25.1	25.1	16.5
Fat (%)	25.3	7.1	9.6	9.6	12.8	12.8	27
Fiber (%)	12.4	13.8	1.6	1.6	4.6	4.6	-

a. A2 and B2 had minor differences in protein source; b. C2 and D2 had an identical macronutrient composition; c. Supplement as consumed in toned milk (200 ml).

reference food of 50 g or 25 g glucose or white bread in the same participant [17] [34]. In the present study, glycemic response curve was generated by administering foods equivalent to 25 g of carbohydrates.

For phase 1, to achieve 25 g carbohydrate, 70.8 g A1, 52.3 g B1, and 27.5 g reference products (C1, D1, E1) were consumed with 250 mL of water (Table 1). For phase 2, to achieve 25 g carbohydrate, 50.7 g A2, 50.6 g B2, 50.46 g C2, 50.69 g D2 were consumed with 250 mL of water (Table 2). As test formulation E2 is a micronutrient rich malt based ONS supplement for children to be consumed in milk, the GI of test product E2 was determined using milk (27 g added to 200 ml milk). The reference products F2, G2 and H2 were consumed with 250 mL of water.

Safety of test products were assessed in terms of overall well-being of the participant throughout the study and adverse events reported by participants or assessed by investigators using a questionnaire.

2.3. Statistical Analysis

Statistical analysis was performed using R version 4.1.1. The analyses were conducted separately for phases 1 and 2. Baseline characteristics of the participants were summarized descriptively. The mean blood glucose concentration for each product was plotted over time and reported as mean ± SD. It was observed that there were no significant differences in three reference products used in each phase, therefore their average (R1 and R2 in phase 1 and phase 2, respectively) was used for comparison with the test drinks in both the phases using repeated measures ANOVA at each time point in both the phases. Between-product differences in phase 1 were compared at each timepoint using the paired t-test. Using the blood glucose concentration data, the iAUC was calculated for each participant and product using the trapezoid rule. The iAUC for each product is reported as mean ± SE. The average iAUC of the reference product consumed by a participant across the 3 days was used in the comparison. For an individual participant, GI of each test product was computed using the formula:

Table 2. Baseline characteristics of participants in Phase 1 and Phase 2, Mean (SD).

Characteristics	Phase 1	Phase 2	*p*-value
N	18	20	
Age	34.2 (7.67)	34.3 (7.19)	0.967
Weight (kg)	55.5 (4.99)	55.1 (6.21)	0.829
Height (cm)	162 (8.44)	161.1 (9.76)	0.764
BMI (kg/m^2)	21.2 (1.52)	21.0 (1.45)	0.681
FBG (mg/dL)	80.2 (6.12)	84.5 (5.67)	0.031[a]
HbA1C (%)	5.3 (0.22)	5.1 (0.23)	0.010[a]

[a]Values were statistically significant at $p < 0.05$ using t-test between phase 1 and phase 2 for baseline characteristics.

$$I_{G,t} = \left(A_t / \bar{A}_{ref} \right) \times 100$$

where, A_t is the iAUC of the test product, $\bar{A}_{ref}$ is the average iAUC of the reference product across the 3 days when it was administered. The GI of each test product was expressed as mean ± SE and was rounded to the nearest whole number. The mean GI of the test products in phase 1 and phase 2 were compared using the paired t-test. Statistical analysis for satiety assessment was performed at each timepoint to detect significant changes from baseline in each of the test products, using the paired t-test. All comparisons were performed at the 5% level of significance.

3. Results

In each phase of the study, 20 eligible participants were enrolled. Each participant was randomly assigned to one of five products (phase 1) or eight products (phase 2) as per the cross-over design shown in Figure 1. Finally, 18 participants in phase 1 and 20 participants in phase 2 completed the study.

3.1. Baseline Characteristics

All study participants were healthy with ages between 20 - 44 years in both the phases; mean BMI was 21.2 ± 1.52 kg/m^2 in phase 1 and 21.0 ± 1.45 kg/m^2 in phase 2 and 50% of the participants were females in both the phases. All female participants were non-pregnant, non-lactating at the time of study intervention. Mean FBG and HbA1C were in the safe range for all the participants in both the phases. Details of baseline characteristics are presented in Table 2.

3.2. Blood Glucose Response

Figure 2(a) shows post-prandial glucose (PPG) response from 0 to 120 minutes for all drinks studied in phase 1. There was no significant difference in PPG levels between the three reference drinks (C1, D1, E1) at any time point ($p < 0.05$), therefore the average values of these three reference drinks were calculated (R1) and used for comparison with the two test drinks (A1 and B1). The blood glucose response for glucose (R1) and both test drinks peaked at 30 minutes and PPG values were significantly lower in both the tests drinks (A1 and B1) as compared to reference drink (R1, $p < 0.001$) shown in Table 3. It was also observed that both A1 and B1 had significantly lower values than R1 reference glucose values at all time points 15 ($p < 0.001$), 30 ($p < 0.001$), 45 ($p < 0.001$), 60 ($p < 0.001$) and 120 minutes ($p < 0.001$) except at 90 minutes ($p = 0.204$). There were significant differences in the blood glucose response between the two test drinks (A1 and B1) in Phase1 at 15 minutes ($p = 0.016$), 30 minutes ($p < 0.001$), 45 minutes ($p < 0.001$), 90 minutes ($p = 0.024$) and 120 minutes ($p = 0.049$).

Figure 2(b) shows the PPG response from 0 to 120 minutes for all drinks studied in phase 2. There was no significant difference in PPG levels between the three reference drinks (F2, G2 and H2) at any time point ($p < 0.05$), therefore

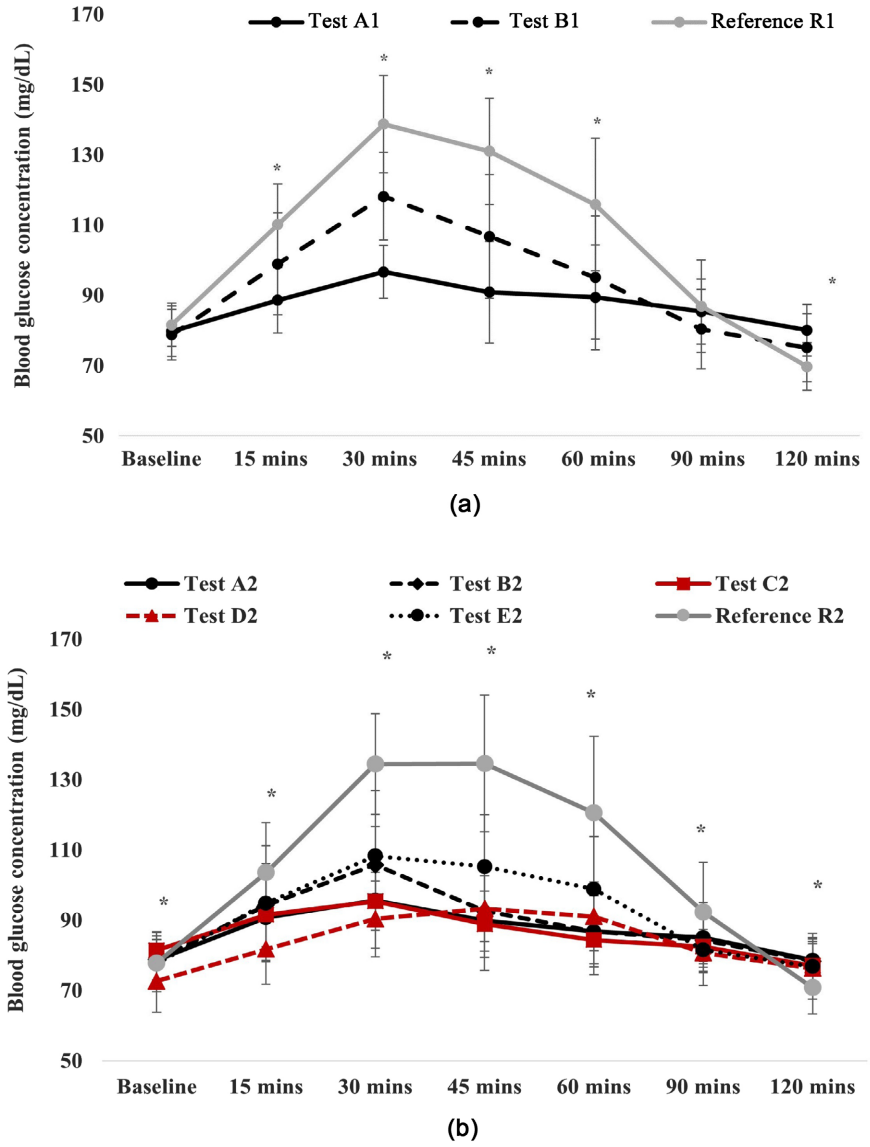

Figure 2. Mean (SD) blood glucose response (a) Phase 1 (b) Phase 2 of test and average reference drinks at baseline and after 15, 30, 45, 60, 90 and 120 minutes of administration. *Values were statistically significant at $p < 0.05$.

the average values of these three reference drinks were calculated (R2). This average R2 has been used for comparison with the five test drinks.

In Phase 2, out of the five, four test drinks (A2, B2, C2, E2) reported peak blood glucose concentrations at 30 minutes and one test drink (D2) at 45 minutes post consumption (Table 3). Except baseline, the blood glucose concentrations were significantly lower in the test drinks (A2, B2, C2, D2 & E2) at all other timepoints [15 ($p = 0.002$), 30 ($p < 0.001$), 45 ($p < 0.001$), (60 ($p < 0.001$), (90 ($p = 0.009$) and 120 minutes ($p = 0.014$)] compared to the blood glucose concentration of reference drink (R2). The details of PPG values of various test drinks and reference drinks are given in **Supplementary** Table S1 (See supplementary materials).

Table 3. Mean (SD/SE) iAUC, PPG, and GI of test products from phase 1 and phase 2.

Test Products	iAUC	Peak Post Prandial Glucose, PPPG (mg/dL)	Glycemic Index, GI
	Phase 1		
A1	1008 (187)[a]	95.8 (7.44)	34 (±6)
B1	1820 (207)[b]	116.9 (12.24)	63 (±7)[a]
Average Reference Drink R1	2997 (257)[c]	137.1 (13.61)[a]	
	Phase 2		
A2	1111 (161)	95.7 (13.63)	32 (±5)
B2	1260 (166)	105.8 (10.92)	37 (±4)
C2	1076 (190)	95.4 (8.30)	31 (±5)
D2	1076 (190)	93.3 (9.36)	31 (±5)
E2	1890 (187)	108.3 (18.65)	55 (±4)[b]
Average Reference Drink R2	3516 (±257)[d]	134.6 (19.46)[b]	-

All values are Mean (SD/SE as applicable). iAUC: incremental area under the 120-min plasma glucose curve, PPPG: peak postprandial glucose, GI: Glycemic Index. Mean with different superscript letters in column are significantly higher ($p < 0.05$) in their respective phases with repeated measures ANOVA or paired t-tests as applicable.

3.3. Incremental Area under Curve (iAUC)

Table 3 and Figure 3(a) show the mean (±SE) incremental area under the curve (iAUC) for test and reference drinks from 0 to 120 minutes for phase 1. The iAUC was significantly different between A1 and B1 [1008 (±187) and 1820 (±207) mg/dL × minutes; $p < 0.001$] respectively. Since the reference products C1, D1 and E1 had similar iAUC values, an average of reference drinks (R1) was taken for ease of interpretation (R1: 2997 ± 257 mg/dL × minutes). Both A1 and B1 had significantly lower iAUC as compared to the average iAUC for reference (R1) post 120 minutes ($p < 0.001$). Figure 3(b) shows the mean (±SE) iAUC for phase 2. Since the reference products F2, G2 and H2 were the same reference drink (glucose) and had similar iAUC values, an average was taken for ease of interpretation (3516 ± 257 mg/dL × minutes). The iAUC for all five test drinks A2, B2, C2, D2 and E2 was significantly lower than the average iAUC for reference drinks ($p < 0.001$).

3.4. Glycemic Index

Mean (±SE) GI of A1 and B1 were 34 (±6) and 63 (±7) respectively, with A1

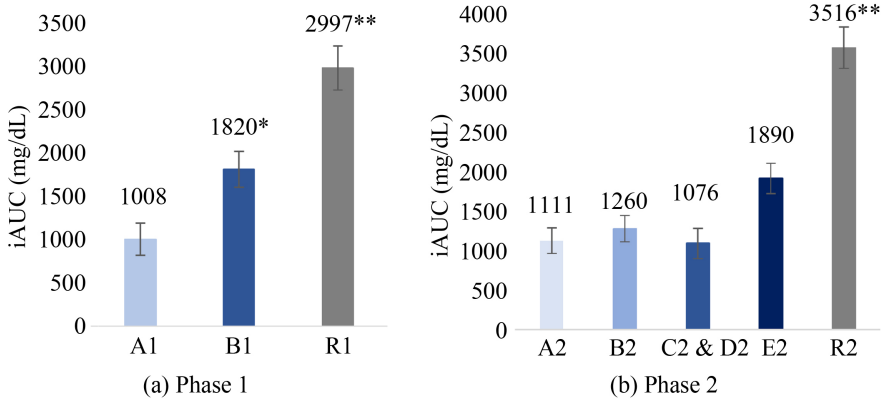

Figure 3. Mean Incremental area Under the Curve (iAUC) (a) Phase 1 (b) Phase 2 for various test and reference drinks; *Values were statistically significant at $p < 0.05$ vs A1; **Values were statistically significant at $p < 0.05$ vs all other products in that phase.

reporting a significantly lower GI compared to B1 ($p = 0.002$). The revised DSNS A1 was found to be low GI (≤55) whereas the formula B1 was medium GI (**Table 3**). Mean (±SE) GI of the high protein supplements, A2 and B2 were 32 (±5) and 37 (±4) respectively. The mean (±SE) GI of maternal supplements C2 and D2 was 31 (±5) as the formulas were identical. The mean (±SE) GI of the micronutrient rich malt-based supplement E2 was 55 (±4). In addition to A1 from phase 1, all test formulations A2, B2, C2, D2 and E2 tested in phase 2 had low GI.

3.5. Safety Endpoints

Only one study participant in phase 1 experienced discomfort and nausea after consumption of test product A1 at Visit 4. After well-being assessment, the participant was fine and didn't complain of any subsequent discomfort or nausea. Product compliance was 100% for both phases 1 and 2 as the product was administered under supervision.

3.6. Satiety

Assessment of satiety scores using the visual analogue scale was performed in phase 1. Following product consumption, the mean satiety score remained above baseline until 180 minutes for A1 and 150 minutes for B1 and was significantly higher than baseline until 125 minutes post consumption of the products ($p < 0.05$).

4. Discussion

With an increasing prevalence of IGT and diabetes, it is important to understand the GI of the oral nutritional supplements (both for diabetic and non-diabetic) on the blood glucose response and the impact of macronutrient composition on the same. Determining GI of foods is important in making informed food choices for better blood glucose management. Thus, the current study aimed to determine the GI of multiple ONSs, including diabetic, maternal, protein and

micronutrient rich supplements and to understand the role of macronutrients composition.

In the present study, all the test drinks were high in protein (17% - 36% energy) and fat (10% - 27% energy). In Phase 1, we studied the GI of two high fiber formulations with matched type and amount of soluble fiber (22%), with varying levels of protein, fat, and carbohydrates (**Table 2**). Carbohydrates in A1 were reduced to 40% energy and increased protein and fat to 23% and 25% of energy respectively, keeping fiber levels and type of fiber, identical to B1. In addition, the monounsaturated fatty acid (MUFA) was added at 70% of total fat levels (≈18% of energy). These revisions in the composition of ONS shifted the medium GI [63 (±7)] B1 to a low GI [34 (±6)] A1. Both the high fiber formulations A1 and B1 reported significantly higher satiety scores as compared to reference (data not shown). In Phase 2, all the test formulations had carbohydrate, protein, and fat energy percent that ranged from 52% - 58%, 17% - 36% and 10% - 27% respectively (**Table 1**). All test products in phase 2 were low GI (**Table 3**). Our finding was in consensus with other studies demonstrating that reducing the amount of carbohydrates in a meal has a favorable effect on PPG levels [35].

Many previous studies have reported the role of fiber content, type of fiber, food form, type of cereals, carbohydrate, protein and fat amount and fat composition etc. have an important effect on GI of foods [36]-[42] and may not necessarily predict glycemic parameters [43] [44] [45] [46].

In one of the initial studies on GI determination, 62 commonly eaten foods were fed individually to groups of 5 - 10 healthy fasting volunteers. Blood glucose levels were measured over 2 hours and expressed as a percentage of the AUC curve when the same amount of carbohydrate was taken as glucose. A significant negative relationship of PPG rise was seen with fat ($p < 0.01$) and protein ($p < 0.001$) but not with fiber or sugar content [17]. Another detailed study observed the relationship between dietary fiber and GI where dietary fiber content and composition of 25 foods were related to their GI. Total dietary fiber was significantly related to GI ($r = 0.461$, $p < 0.05$) but not the soluble fiber ($r = 0.308$) [47]. This is relevant as both the test products from phase 1 (A1 and B1) had the same type and amount of soluble fiber. No simple correlation exists between the fiber content of foods and their GI and that different types of dietary fiber have different effects [48] [49] [50].

Another study assessed the blood glucose response to feeding 50-g carbohydrate portions of white and whole meal bread and white spaghetti. The study reported identical blood glucose rises after white and whole meal bread, but the response after spaghetti was markedly reduced. This result indicates that food form rather than just fiber may be important in determining the glycemic response [41]. A study measured the PPG in patients with T2D in response to isoglucidic portions (50 g available carbohydrate) of three starch-rich foods: 65 g spaghetti, 90 g white bread, and 285 g potatoes. This study highlighted that when a portion of bread replaced spaghetti with the same amount of available carbohydrate, the glycemic response increased by 68%. When spaghetti was replaced

with potatoes, the glycemic response was 48% higher. The differences could not be accounted for by the amount of carbohydrate or dietary fiber as it was similar in the three test meals [40].

The glycemic index of a food is also dependent on the presence of fat [51], protein [52], and anti-nutrients [53] and its interaction with starch digestible enzymes (slow digestible starches and rapid digestible starches) [46]. The inclusion of whey to meals with rapidly digested and absorbed carbohydrates promotes insulin release and reduces PPG excursion [38]. In another study that explored the effects of protein on insulin and glucose response, 14 healthy normal-weight participants were fed test meals containing 0, 15.8, 25.1, 33.6, and 49.9 g protein along with approximately 58 g carbohydrate. Mean areas of the glucose curves above fasting decreased with increasing protein dose. Meals containing protein generated significantly lower ($p < 0.01$) AUC than protein-free meals. It was concluded that co-ingestion of protein with carbohydrate reduces glycemic response [39]. This can modify the gastrointestinal transit time which in turn affects the rates of glucose absorption. Many recent studies demonstrated that fatty acids [54] [55] and amino acids [35] [56] can stimulate secretion of various gut enzymes in the gastrointestinal tract that influence post prandial glucose metabolism [36] [57] [58] [59]. Previous studies have indicated that co-ingestion of fat with carbohydrates had shown a significant reduction in the glucose response and GI [51] [55] [60]. However, a recent study had demonstrated that there is no change in glycemic responses and GI of adding various amounts of fat to carbohydrates, but serum cholesterol levels remained unaffected [36].

Most supplements in this study are reported to be low GI (<55). Our findings are in agreement with the previous data which supports that it is not the total fiber content but the overall composition of the food, especially the macronutrients (protein, fat and carbohydrates) that determine the PPG response. Optimally altering food composition allows low PPG/GI [61] [62]. If food and nutrition industries enable this information around the GI of foods, based on their expertise and experience around science and technology, it will contribute towards the increased awareness and availability of low-GI foods. At a population level, this will allow for selection and prescription of low GI foods.

Strengths and Limitations

The design of this study was strong as it was a randomized, controlled, cross-over trial. The adherence to ISO 2010 guidelines for GI determination and participant enrollment adds credibility to the study's methodology and ensures standardized procedures. A high rate of compliance, completeness of data, and minimal loss to follow-up are strengths of this study. Additionally, this study is comprehensive with a wider application as it includes GI determination of nutrition supplements for different segments of the population available in Indian market (**Box 1**).

- With an increasing prevalence of IGT and diabetes in India, it becomes important to understand the impact of commercially available ONSs on the blood glucose response.
- Determination of GI of foods and the role of macronutrient composition on the same is relevant in making informed food choices for better blood glucose management.
- This study was carried out to determine the GI of multiple ONS with varied ranges of macronutrients. Basis ISO 2010 method, GI was calculated as the iAUC for the test drink and expressed as a percentage of the average iAUC response from glucose.
- Findings from phase 1 reported the mean (±SE) GI of A1 and B1 as 34 (±6) and 63 (±7) respectively. From phase 2, mean (±SE) GI of A2, B2, C2, D2 and E2 was 32 (±5), 37 (±4), 31 (±5), 31 (±5) and 55 (±4) respectively. Except B1, all HFDs tested in this study were low GI (≤55).
- Even with a matched fiber type and amount (as in A1 and B1), it was the high protein and high fat with reduced carbohydrates in A1 that seem to be responsible for lowering the GI.
- Findings from this study are consistent with the previous studies that not just the fiber, it is the overall macronutrient composition specifically higher protein and fat and reduced carbohydrates that play an important role in influencing the GI of nutrition supplements.

Box 1. Summary of study rationale, key study results, and take-home messages.

Findings from this study may have limited generalizability beyond the Indian population as dietary habits, genetics and other factors can vary significantly across different regions and populations affecting the impact of nutrition supplements on glycemic control. Follow up studies are necessary to assess the sustained effects of these nutrition supplements on glycemic control in diabetics and prediabetics. The present study focused on measuring GI after a single dose administration of the supplements. Long-term usage may have different effects on the glycemic control and overall health. Future research is required to understand the potential consequences of extended consumption of these supplements.

5. Conclusion

It may be concluded that it is not just the fiber, but other factors such as the macronutrient composition involving high protein (≥17% energy) and fat (≥10% - 27% energy) coupled with reduced carbohydrates (≈40% - 58% energy) that play an important role in lowering the GI of oral nutrition supplements.

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Authors' Contributions

J.B, M.P. and D.A. were mainly involved in the conceptualization of the study;

D.K., S.S., P.J. and J.B. were involved in its conduct, quality checks and data collection. J.G. was responsible for statistical analyses of results. D.K. and J.B. analyzed and interpreted the study results and participated in data curation. D.K. drafted and led the manuscript for its intellectual content, literature searches, interpretation of data, and graph generation. The final version of the manuscript was carefully reviewed and approved by all authors. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

The study protocol, all amendments, and the informed consent form were reviewed and approved by the Institutional Ethics Committee of Om Children Hospital (ECR/1168/Inst/GI/2018). The study was performed in accordance with the protocol, Good Clinical Practice (GCP) guidelines, local regulations governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki. The study was registered with Clinical Trials Registry India (CTRI/2022/01/039765 and CTRI/2022/07/044082).

Informed Consent Statement

The informed consent form was reviewed and approved by the Institutional Ethics Committee of Om Children Hospital (ECR/1168/Inst/GI/2018). All participants voluntarily gave written informed consent prior to enrollment.

Data Availability Statement

Ethical restrictions imposed by the IEC prevent public sharing of the data for this study. The data used in this publication is owned by HUL (Nutrition). Data access request will be evaluated by HUL (Nutrition) in consideration of IEC requirements. Interested researchers will need to sign a research collaboration agreement with HUL (Nutrition). Requests can be sent to deepti.khanna2@unilever.com.

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Conflicts of Interest

D.K., J.B. M.P. and D.A. declare potential conflicts of interest as employees of HUL (Nutrition), the study sponsor. No other author declares any conflict of interest.

References

[1] Nguyen, P.H., Scott, S., Headey, D., Singh, N., Tran, L.M., Menon, P., *et al.* (2021) The Double Burden of Malnutrition in India: Trends and Inequalities (2006-2016). *PLOS ONE*, **16**, e0247856. https://doi.org/10.1371/journal.pone.0247856

[2] Young, M.F., Nguyen, P., Tran, L.M., Avula, R. and Menon, P. (2020) A Double Edged Sword? Improvements in Economic Conditions over a Decade in India Led

to Declines in Undernutrition as Well as Increases in Overweight among Adolescents and Women. *The Journal of Nutrition*, **150**, 364-372. https://doi.org/10.1093/jn/nxz251

[3] Popkin, B.M., Corvalan, C. and Grummer-Strawn, L.M. (2020) Dynamics of the Double Burden of Malnutrition and the Changing Nutrition Reality. *The Lancet*, **395**, 65-74. https://doi.org/10.1016/S0140-6736(19)32497-3

[4] Dutta, M., Selvamani, Y., Singh, P. and Prashad, L. (2019) The Double Burden of Malnutrition among Adults in India: Evidence from the National Family Health Survey-4 (2015-16). *Epidemiology and Health*, **41**, e2019050. https://doi.org/10.4178/epih.e2019050

[5] Pradeepa, R. and Mohan, V. (2021) Epidemiology of Type 2 Diabetes in India. *Indian Journal of Ophthalmology*, **69**, 2932-2938. https://doi.org/10.4103/ijo.IJO_1627_21

[6] Dainna, J. and Magliano, E.J.B. (2021) IDF Diabetes Atlas 10th Edition Scientific Committee. IDF DIABETES ATLAS [Internet]. International Diabetes Federation, Brussels. https://www.ncbi.nlm.nih.gov/books/NBK581934/

[7] Bansal, N. (2015) Prediabetes Diagnosis and Treatment: A Review. *World Journal of Diabetes*, **6**, 296-303. https://doi.org/10.4239/wjd.v6.i2.296

[8] Mathur, P., Leburu, S. and Kulothungan, V. (2022) Prevalence, Awareness, Treatment and Control of Diabetes in India from the Countrywide National NCD Monitoring Survey. *Frontiers in Public Health*, **10**, Article ID: 748157. https://doi.org/10.3389/fpubh.2022.748157

[9] Das, A.K.M., Ramachandran, A., Kalra, S., Mithal, A., Sahay, R., Tiwaskar, M., Das, S., Baruah, M.P., Jacob, J., Sheikh, S. and Kesavadav, J. (2022) An Expert Group Consensus Statement on "Approach and Management of Prediabetes in India". *Journal of the Association of Physicians of India*, **70**, 69-78. https://doi.org/10.5005/japi-11001-0162

[10] Ramachandran, A., Snehalatha, C., Kapur, A., Vijay, V., Mohan, V., Das, A.K., *et al*. (2001) High Prevalence of Diabetes and Impaired Glucose Tolerance in India: National Urban Diabetes Survey. *Diabetologia*, **44**, 1094-1101. https://doi.org/10.1007/s001250100627

[11] Tuso, P. (2014) Prediabetes and Lifestyle Modification: Time to Prevent a Preventable Disease. *The Permanente Journal*, **18**, 88-93. https://doi.org/10.7812/TPP/14-002

[12] Jose, J. and Thomas, N. (2018) How Should One Tackle Prediabetes in India? *Indian Journal of Medical Research*, **148**, 675-676. https://doi.org/10.4103/ijmr.IJMR_1785_18

[13] Anjana, R.M., Srinivasan, S., Sudha, V., Joshi, S.R., Saboo, B., Tandon, N., *et al*. (2022) Macronutrient Recommendations for Remission and Prevention of Diabetes in Asian Indians Based on a Data-Driven Optimization Model: The ICMR-INDIAB National Study. *Diabetes Care*. https://doi.org/10.2337/figshare.20383599

[14] Garedow, A.W., Jemaneh, T.M., Hailemariam, A.G. and Tesfaye, G.T. (2023) Lifestyle Modification and Medication Use among Diabetes Mellitus Patients Attending Jimma University Medical Center, Jimma Zone, South West Ethiopia. *Scientific Reports*, **13**, Article No. 4956. https://doi.org/10.1038/s41598-023-32145-y

[15] Mann, J., Cummings, J.H., Englyst, H.N., Key, T., Liu, S., Riccardi, G., *et al*. (2007) FAO/WHO Scientific Update on Carbohydrates in Human Nutrition: Conclusions. *European Journal of Clinical Nutrition*, **61**, S132-S137. https://doi.org/10.1038/sj.ejcn.1602943

[16] Augustin, L.S.A., Kendall, C.W.C., Jenkins, D.J.A., Willett, W.C., Astrup, A., Barclay, A.W., *et al*. (2015) Glycemic Index, Glycemic Load and Glycemic Response: An International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC). *Nutrition, Metabolism and Cardiovascular Diseases*, **25**, 795-815. https://doi.org/10.1016/j.numecd.2015.05.005

[17] Jenkins, D.J., Wolever, T.M., Taylor, R.H., Barker, H., Fielden, H., Baldwin, J.M., *et al*. (1981) Glycemic Index of Foods: A Physiological Basis for Carbohydrate Exchange. *The American Journal of Clinical Nutrition*, **34**, 362-366. https://doi.org/10.1093/ajcn/34.3.362

[18] Atkinson, F.S., Foster-Powell, K. and Brand-Miller, J.C. (2008) International Tables of Glycemic Index and Glycemic Load Values: 2008. *Diabetes Care*, **31**, 2281-2283. https://doi.org/10.2337/dc08-1239

[19] Henry, C.J., Quek, R.Y.C., Kaur, B., Shyam, S. and Singh, H.K.G. (2021) A Glycaemic Index Compendium of Non-Western Foods. *Nutrition & Diabetes*, **11**, Article No. 2. https://doi.org/10.1038/s41387-020-00145-w

[20] Schulze, M.B., Liu, S., Rimm, E.B., Manson, J.E., Willett, W.C. and Hu, F.B. (2004) Glycemic Index, Glycemic Load, and Dietary Fiber Intake and Incidence of Type 2 Diabetes in Younger and Middle-Aged Women. *The American Journal of Clinical Nutrition*, **80**, 348-356. https://doi.org/10.1093/ajcn/80.2.348

[21] Della Corte, K., Jalo, E., Kaartinen, N.E., Simpson, L., Taylor, M.A., Muirhead, R., *et al*. (2023) Longitudinal Associations of Dietary Sugars and Glycaemic Index with Indices of Glucose Metabolism and Body Fatness during 3-Year Weight Loss Maintenance: A Preview Sub-Study. *Nutrients*, **15**, Article No. 2083. https://doi.org/10.3390/nu15092083

[22] Jenkins, D.J.A., Dehghan, M., Mente, A., Bangdiwala, S.I., Rangarajan, S., Srichaikul, K., *et al*. (2021) Glycemic Index, Glycemic Load, and Cardiovascular Disease and Mortality. *The New England Journal of Medicine*, **384**, 1312-1322. https://doi.org/10.1056/NEJMoa2007123

[23] Færch, K., Alssema, M., Mela, D.J., Borg, R. and Vistisen, D. (2018) Relative Contributions of Preprandial and Postprandial Glucose Exposures, Glycemic Variability, and Non-Glycemic Factors to HbA1cin Individuals with and without Diabetes. *Nutrition & Diabetes*, **8**, 38. https://doi.org/10.1038/s41387-018-0047-8

[24] ADA (2020) Diabetes Advocacy: Standards of Medical Care in Diabetes-2019. *Diabetes Care*, **43**, S203-S204. https://doi.org/10.2337/dc20-S016

[25] Kang, M.R. (2017) Use of Oral Nutritional Supplements for Patients with Diabetes. *The Journal of Korean Diabetes*, **18**, 181-188. https://doi.org/10.4093/jkd.2017.18.3.181

[26] Taylor, N. (2020) Overview of Oral Nutrition Supplements and Their Use. *British Journal of Community Nursing*, **25**, S12-S15. https://doi.org/10.12968/bjcn.2020.25.Sup8.S12

[27] Tey, S.L., Van Helvoort, A. and Henry, C.J. (2016) Glycaemic Responses to Liquid Food Supplements among Three Asian Ethnic Groups. *European Journal of Nutrition*, **55**, 2493-2498. https://doi.org/10.1007/s00394-015-1072-1

[28] Popkin, B.M. (2017) Relationship between Shifts in Food System Dynamics and Acceleration of the Global Nutrition Transition. *Nutrition Reviews*, **75**, 73-82. https://doi.org/10.1093/nutrit/nuw064

[29] Law, C., Green, R., Kadiyala, S., Shankar, B., Knai, C., Brown, K.A., *et al*. (2019) Purchase Trends of Processed Foods and Beverages in Urban India. *Global Food Security*, **23**, 191-204. https://doi.org/10.1016/j.gfs.2019.05.007

[30] Rachana, B., Vijayalakshmi, P., Ganesh, R., Gopinath, V., Karthikeyan, P., Kavitha, V., *et al*. (2019) Glycemic Index and Response of a Plant Based Nutritional Supplement and Its Subjective Satiety Following Its Use in Indian Adults. *Food and Nutrition Sciences*, **10**, 937-946. https://doi.org/10.4236/fns.2019.108067

[31] Rachana, B., Shobana, S., Lalithya, P.V., Sudha, V., Vinita, S., Gayathri, R., *et al*. (2023) Glycemic Index of a Nutritional Supplement Designed for People with Chronic Kidney Disease. *Food Science & Nutrition*, **11**, 5379-5387. https://doi.org/10.1002/fsn3.3495

[32] Patel, K., Kudrigikar, V., Bachani, D. and Mehta, S. (2023) Glycemic Index of a Diabetes-Specific Nutritional Powder: An Open-Label Study in Healthy Indian Adults. *Food and Nutrition Sciences*, **14**, 200-224. https://doi.org/10.4236/fns.2023.143014

[33] Schulz, K.F., Altman, D.G., Moher, D. and The, C.G. (2010) CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials. *BMC Medicine*, **8**, Article No. 18. https://doi.org/10.1186/1741-7015-8-18

[34] ISO (2010) Food Products—Determination of the Glycaemic Index (GI) and Recommendation for Food Classification. ISO 26642:2010. ISO, Geneva.

[35] Vlachos, D., Malisova, S., Lindberg, F.A. and Karaniki, G. (2020) Glycemic Index (GI) or Glycemic Load (GL) and Dietary Interventions for Optimizing Postprandial Hyperglycemia in Patients with T2 Diabetes: A Review. *Nutrients*, **12**, Article No. 1561. https://doi.org/10.3390/nu12061561

[36] Meng, H., Matthan, N.R., Ausman, L.M. and Lichtenstein, A.H. (2017) Effect of Macronutrients and Fiber on Postprandial Glycemic Responses and Meal Glycemic Index and Glycemic Load Value Determinations. *The American Journal of Clinical Nutrition*, **105**, 842-853. https://doi.org/10.3945/ajcn.116.144162

[37] Roberts, S., Desbrow, B., Grant, G., Anoopkumar-Dukie, S. and Leveritt, M. (2013) Glycemic Response to Carbohydrate and the Effects of Exercise and Protein. *Nutrition*, **29**, 881-885. https://doi.org/10.1016/j.nut.2012.12.022

[38] Frid, A.H., Nilsson, M., Holst, J.J. and Björck, I.M. (2005) Effect of Whey on Blood Glucose and Insulin Responses to Composite Breakfast and Lunch Meals in Type 2 Diabetic Subjects. *The American Journal of Clinical Nutrition*, **82**, 69-75. https://doi.org/10.1093/ajcn/82.1.69

[39] Spiller, G.A., Jensen, C.D., Pattison, T.S., Chuck, C.S., Whittam, J.H. and Scala, J. (1987) Effect of Protein Dose on Serum Glucose and Insulin Response to Sugars. *The American Journal of Clinical Nutrition*, **46**, 474-480. https://doi.org/10.1093/ajcn/46.3.474

[40] Parillo, M., Giacco, R., Riccardi, G., Pacioni, D. and Rivellese, A. (1985) Different Glycaemic Responses to Pasta, Bread, and Potatoes in Diabetic Patients. *Diabetic Medicine*, **2**, 374-377. https://doi.org/10.1111/j.1464-5491.1985.tb00655.x

[41] Jenkins, D.J., Wolever, T.M., Jenkins, A.L., Lee, R., Wong, G.S. and Josse, R. (1983) Glycemic Response to Wheat Products: Reduced Response to Pasta but No Effect of Fiber. *Diabetes Care*, **6**, 155-159. https://doi.org/10.2337/diacare.6.2.155

[42] Jenkins, D.J., Wolever, T.M., Taylor, R.H., Barker, H.M., Fielden, H. and Jenkins, A.L. (1980) Effect of Guar Crispbread with Cereal Products and Leguminous Seeds on Blood Glucose Concentrations of Diabetics. *British Medical Journal*, **281**, 1248-1250. https://doi.org/10.1136/bmj.281.6250.1248

[43] Visuthranukul, C., Sampatanukul, P., Aroonparkmongkol, S., Sirimongkol, P. and Chomtho, S. (2022) Glycemic Index and Glycemic Load of Common Fruit Juices in Thailand. *Journal of Health, Population and Nutrition*, **41**, Article No. 5. https://doi.org/10.1186/s41043-022-00284-z

[44] Zurbau, A., Jenkins, A.L., Jovanovski, E., Au-Yeung, F., Bateman, E.A., Brissette, C., *et al*. (2019) Acute Effect of Equicaloric Meals Varying in Glycemic Index and Glycemic Load on Arterial Stiffness and Glycemia in Healthy Adults: A Randomized Crossover Trial. *European Journal of Clinical Nutrition*, **73**, 79-85. https://doi.org/10.1038/s41430-018-0182-2

[45] Jeong, S., Min Cho, J., Kwon, Y.-I., Kim, S.-C., Yeob Shin, D. and Ho Lee, J. (2019) Chitosan Oligosaccharide (GO2KA1) Improves Postprandial Glycemic Response in Subjects with Impaired Glucose Tolerance and Impaired Fasting Glucose and in Healthy Subjects: A Crossover, Randomized Controlled Trial. *Nutrition & Diabetes*, **9**, Article No. 31. https://doi.org/10.1038/s41387-019-0099-4

[46] Meynier, A., Goux, A., Atkinson, F., Brack, O. and Vinoy, S. (2015) Postprandial Glycaemic Response: How Is It Influenced by Characteristics of Cereal Products? *British Journal of Nutrition*, **113**, 1931-1939. https://doi.org/10.1017/S0007114515001270

[47] Wolever, T.M. (1990) Relationship between Dietary Fiber Content and Composition in Foods and the Glycemic Index. *The American Journal of Clinical Nutrition*, **51**, 72-75. https://doi.org/10.1093/ajcn/51.1.72

[48] Tsitsou, S., Athanasaki, C., Dimitriadis, G. and Papakonstantinou, E. (2023) Acute Effects of Dietary Fiber in Starchy Foods on Glycemic and Insulinemic Responses: A Systematic Review of Randomized Controlled Crossover Trials. *Nutrients*, **15**, Article No. 2383. https://doi.org/10.3390/nu15102383

[49] Hardy, D.S., Garvin, J.T. and Xu, H. (2020) Carbohydrate Quality, Glycemic Index, Glycemic Load and Cardiometabolic Risks in the US, Europe and Asia: A Dose-Response Meta-Analysis. *Nutrition, Metabolism and Cardiovascular Diseases*, **30**, 853-871. https://doi.org/10.1016/j.numecd.2019.12.050

[50] Thorburn, A.W., Brand, J.C. and Truswell, A.S. (1986) The Glycaemic Index of Foods. *The Medical Journal of Australia*, **144**, 580-582. https://doi.org/10.5694/j.1326-5377.1986.tb112314.x

[51] Collier, G. and O'Dea, K. (1983) The Effect of Coingestion of Fat on the Glucose, Insulin, and Gastric Inhibitory Polypeptide Responses to Carbohydrate and Protein. *The American Journal of Clinical Nutrition*, **37**, 941-944. https://doi.org/10.1093/ajcn/37.6.941

[52] Granfeldt, Y., Björck, I. and Hagander, B. (1991) On the Importance of Processing Conditions, Product Thickness and Egg Addition for the Glycaemic and Hormonal Responses to Pasta: A Comparison with Bread Made from "Pasta Ingredients". *European Journal of Clinical Nutrition*, **45**, 489-499.

[53] Thorne, M.J., Thompson, L.U. and Jenkins, D.J. (1983) Factors Affecting Starch Digestibility and the Glycemic Response with Special Reference to Legumes. *The American Journal of Clinical Nutrition*, **38**, 481-488. https://doi.org/10.1093/ajcn/38.3.481

[54] O'Donovan, D., Horowitz, M., Russo, A., Feinle-Bisset, C., Murolo, N., Gentilcore, D., *et al*. (2004) Effects of Lipase Inhibition on Gastric Emptying of, and on the Glycaemic, Insulin and Cardiovascular Responses to, a High-Fat/Carbohydrate Meal in Type 2 Diabetes. *Diabetologia*, **47**, 2208-2214. https://doi.org/10.1007/s00125-004-1591-4

[55] Gentilcore, D., Chaikomin, R., Jones, K.L., Russo, A., Feinle-Bisset, C., Wishart, J.M., *et al*. (2006) Effects of Fat on Gastric Emptying of and the Glycemic, Insulin, and Incretin Responses to a Carbohydrate Meal in Type 2 Diabetes. *The Journal of Clinical Endocrinology & Metabolism*, **91**, 2062-2067. https://doi.org/10.1210/jc.2005-2644

[56] Ma, J., Jesudason, D.R., Stevens, J.E., Keogh, J.B., Jones, K.L., Clifton, P.M., *et al*. (2015) Sustained Effects of a Protein "Preload" on Glycaemia and Gastric Emptying over 4 Weeks in Patients with Type 2 Diabetes: A Randomized Clinical Trial. *Diabetes Research and Clinical Practice*, **108**, e31-e34. https://doi.org/10.1016/j.diabres.2015.02.019

[57] Beglinger, S., Drewe, J., Schirra, J., Göke, B., D'Amato, M. and Beglinger, C. (2010) Role of Fat Hydrolysis in Regulating Glucagon-Like Peptide-1 Secretion. *The Journal of Clinical Endocrinology & Metabolism*, **95**, 879-886. https://doi.org/10.1210/jc.2009-1062

[58] Ryan, A.T., Luscombe-Marsh, N.D., Saies, A.A., Little, T.J., Standfield, S., Horowitz, M., *et al*. (2013) Effects of Intraduodenal Lipid and Protein on Gut Motility and Hormone Release, Glycemia, Appetite, and Energy Intake in Lean Men. *The American Journal of Clinical Nutrition*, **98**, 300-311. https://doi.org/10.3945/ajcn.113.061333

[59] Xie, C., Jones, K.L., Rayner, C.K. and Wu, T. (2020) Enteroendocrine Hormone Secretion and Metabolic Control: Importance of the Region of the Gut Stimulation. *Pharmaceutics*, **12**, Article No. 790. https://doi.org/10.3390/pharmaceutics12090790

[60] MacIntosh, C.G., Holt, S.H. and Brand-Miller, J.C. (2003) The Degree of Fat Saturation Does Not Alter Glycemic, Insulinemic or Satiety Responses to a Starchy Staple in Healthy Men. *The Journal of Nutrition*, **133**, 2577-2580. https://doi.org/10.1093/jn/133.8.2577

[61] Gheldof, N., Francey, C., Rytz, A., Egli, L., Delodder, F., Bovetto, L., *et al*. (2022) Effect of Different Nutritional Supplements on Glucose Response of Complete Meals in Two Crossover Studies. *Nutrients*, **14**, Article No. 2674. https://doi.org/10.3390/nu14132674

[62] Kubota, S., Liu, Y., Iizuka, K., Kuwata, H., Seino, Y. and Yabe, D. (2020) A Review of Recent Findings on Meal Sequence: An Attractive Dietary Approach to Prevention and Management of Type 2 Diabetes. *Nutrients*, **12**, Article No. 2502. https://doi.org/10.3390/nu12092502

Supplementary Materials

Table S1 PPG, iAUC and GI of test and reference products at each time point of the study.

Table S1. PPG, iAUC and GI of various test and reference ONS in Phase 1 and Phase 2.

	Baseline	15 min	30 min	45 min	60 min	90 min	120 min	iAUC	GI
Phase 1									
A1	79.2* (7.07)	87.9 (9.12)	95.8 (7.44)	90.1 (14.19)	88.7 (14.64)	84.7 (9.1)	79.5 (7.17)	1008 (187)	34 (6)
B1	78.2* (7.11)	98 (14.22)	116.9 (12.24	105.7 (17.26)	94.2 (17.21)	79.8 (11.16)	74.6 (9.51)	1820 (207)	63 (7)
R1	81.0 (5.99)	109.0 (11.30)	137.1 (13.61)	129.5 (14.85)	114.6 (18.51)	86.2 (12.91)	69.3 (6.64)	2997 (257)	-
*p-value**	0.457	<0.001	<0.001	<0.001	<0.001	0.204	0.001	<0.001	-
*p-value*** (*A*1 vs *B*1)	0.542	0.016	<0.001	<0.001	0.073	0.024	0.049	<0.001**	0.002**
Phase 2									
A2	78.7 (5.69)	90.8 (12.62)	95.7 (13.63)	89.9 (14.1)	86.8 (12.36)	85.1 (9.93)	78.6 (7.67)	1111 (161)	32 (5)
B2	78.8 (8.03)	94.3 (11.82)	105.8 (10.92)	92.6 (11.46)	86.8 (10.12)	84.3 (7.72)	78.4 (6.31)	1260 (166)	37 (4)
C2	72.7 (8.89)	81.8 (10.02)	90.4 (10.78)	93.3 (9.36)	91.1 (9.80)	80.7 (5.17)	76.3 (8.79)	1076 (190)	31 (5)
D2	81.5 (4.98)	91.6 (10.97)	95.4 (8.30)	88.9 (9.43)	84.4 (6.82)	82.5 (4.90)	77.1 (6.79)	1076 (190)	31 (5)
E2	77.6 (7.93)	94.9 (16.35)	108.3 (18.65)	105.3 (14.76)	98.8 (15.02)	81.6 (10.19)	76.8 (6.53)	1890 (187)	55 (4)
R2	77.9 (6.63)	103.6 (14.24)	134.5 (14.31)	134.6 (19.46)	120.6 (21.78)	92.4 (14.06)	70.9 (7.51)	3516 (1244)	-
*p-value**	0.152	0.002	<0.001	<0.001	<0.001	0.009	0.014	<0.001	-

A1, B1, A2, B2, C2, D2, E2 were test products. R1 and R2 are average of reference products (glucose monohydrate) in Phase 1 and Phase 2 respectively. All values are mean (SD/SE as applicable), *Repeated measures ANOVA between test and reference products at $p < 0.05$; **paired t-test between A1 and B1 in phase 1 at $p < 0.05$.