

# Efficacy of a Diabetes Specific Nutritional Supplement (DSNS) on Glycemic Response in Prediabetic Adults: A Two-Armed, Open-Labelled Randomized Controlled Study

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## Abstract

It is well known that Diabetes Specific Nutritional Supplements (DSNSs) are linked to improved glycemic control in individuals with diabetes. However, data on efficacy of DSNSs in prediabetics is limited. This was a two-armed, open-labelled, randomized controlled six-week study on 199 prediabetics [30 - 65 years; Glycosylated Hemoglobin (HbA1c) 5.7% - 6.4% and/or Fasting Blood Glucose (FBG) 100-125 mg/dl]. Two parallel phases were conducted: Acute Blood Glucose Response (ABGR) and Intervention phase. Prediabetic participants were randomized into test (n = 100) and control (n = 99). The primary objective was to assess the ABGR of DSNS versus an isocaloric snack, measured by incremental Area under the Curve (iAUC). Test and control received 60 g of DSNS and 56 g of isocaloric snack (cornflakes) respectively, both in 250 ml double-toned milk on visit days 1, 15, 29 and 43. Postprandial Blood Glucose (PPG) was estimated at 30, 60, 90, 120, 150 and 180 minutes. During the 4 weeks intervention phase, the test group received DSNS with lifestyle counselling (DSNS + LC) and was compared with the control receiving lifestyle counselling alone (LC alone). Impact was studied on FBG, HbA1C, anthropometry, body composition, blood pressure, nutrient intake, and physical activity. The impact of DSNS was also studied using CGM between two 14-day phases: CGM1 baseline (days 1 - 14) and CGM2 endline (days 28 - 42). DSNS showed significantly lower PPG versus isocaloric snack at 30 (p < 0.0001), 60 (p < 0.0001), 90 (p < 0.0001), 120 (p < 0.05) and 150 (p < 0.05) minutes on

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all visit days. iAUC for 0 - 180 minutes was significantly lower ( $p < 0.0001$ ) for DSNS as compared to control for all visit days. Post 4-week intervention, both DSNS + LC and LC alone reported significant reductions in FBG, BMI, waist circumference, and BP versus baseline. DSNS + LC reported a significant reduction in weight from baseline. Significantly higher intakes of protein, calcium, iron, vitamin B<sub>12</sub>, and chromium were reported by DSNS + LC versus LC alone. No other significant changes were reported between groups. It may be concluded that DSNS may be considered as a snack for prediabetic or hyperglycemic individuals requiring nutritional support for improved glycemic control.

## Keywords

Diabetes Specific Nutritional Supplement, Prediabetes, Acute Blood Glucose Response, Incremental Area under Curve, Lifestyle Counselling

## 1. Introduction

Prediabetes is characterized as an intermediary stage with glycemic parameters above normal but below the diabetes threshold [1]-[4]. According to the American Diabetes Association, prediabetes is diagnosed with impaired glucose tolerance (2 hours after 75 g oral glucose load: 140 - 199 mg/dL)/or glycosylated hemoglobin (HbA1C: 5.7% - 6.4%) or fasting blood glucose (FBG: 100 - 125 mg/dL) [3] [5].

Globally, 10.5% of the adult population has diabetes, with another half unaware that they are living with the condition. This number is projected to rise to 643 million by 2030 [6]. The global prevalence of Impaired Fasting Glucose (IFG) in 2021 was 5.8% and is projected to rise to 6.5% in 2045 [7]. The prevalence of diabetes in India is 11.4% and prediabetes is 15.3% [8]. About 24.5% of the population is diagnosed with impaired fasting glucose with a conversion rate of 5% - 10% of developing diabetes [9] [10]. Besides being a precursor for Type 2 Diabetes Mellitus (T2DM), prediabetes is a strong predictor of cardiovascular disease, including hypertension and hyperlipidemia [11] [12], renal diseases [13], retinopathy [14], neuropathy [15], and all-cause mortality [12].

Lifestyle modifications and anti-diabetic drug treatment are general methods used for treatment of diabetes [3] [16]. However, lifestyle modifications including diet and physical activity form the first line of treatment for reducing the incidence of diabetes [17]-[21], prediabetes [22]-[24], and improving impaired glucose tolerance by 27% - 58% [25] [26]. Pharmacological treatment (mainly metformin) has also shown beneficial results in reversing hyperglycemia [18]. Evidence has shown that lifestyle modification that includes weight loss and exercise had a larger benefit than metformin in prediabetics [4] [24] [27] [28]. Over the years, studies have shown that dietary modifications and increased physical activity slow down the progression of individuals with prediabetes [29] [30]. How-

ever, compliance with lifestyle modifications for a longer period of time can be a crucial problem [31]-[33], especially in developing countries.

Lifestyle Counselling (LC) is an integral part of Medical Nutrition Therapy (MNT) for prevention and management of diabetes and prediabetes, with goals of promoting and supporting healthy eating patterns, maintaining the pleasure of eating, improving sleep quality, and providing the individuals with the necessary support for healthy lifestyle [5] [34] [35]. Indian diets are generally characterized as high in saturated fat, trans fat, and refined carbohydrates [36]-[38]. Evidence from a recent systematic review has shown that Diabetes Specific Nutritional Supplement (DSNS) as a meal/snack replacement led to reduced glycemic and insulin excursions when compared to standard formulas and other foods. These also showed improvements in lipid profile and cardiometabolic indicators [39].

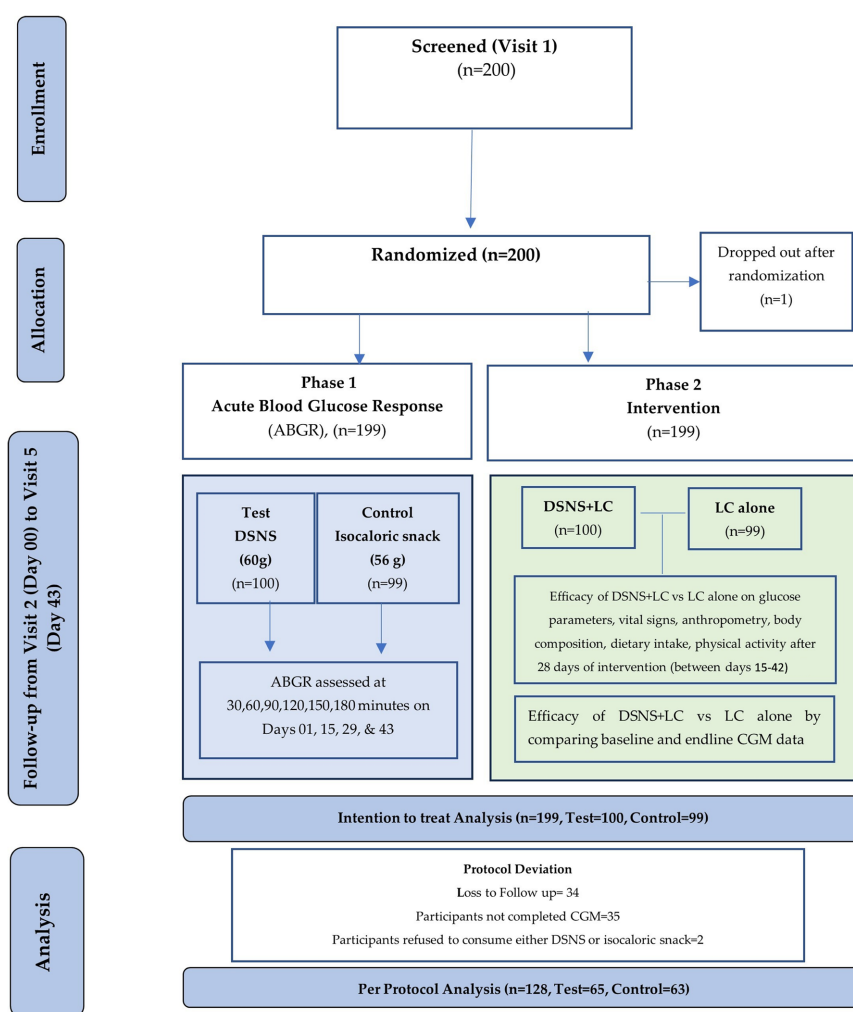
DSNSs are usually low in carbohydrates, high in Monounsaturated Fatty Acids (MUFA), protein, fiber, and rich in micronutrients, thus have low Glycemic Index (GI), which renders them suitable for individuals with diabetes or prediabetes, at risk of hyperglycemia. The DSNSs are mostly rich in micronutrients and could subtly shift the daily nutrient intake to the recommended levels aiding in glycemic control [40]-[44]. The majority of the studies on prediabetics were focused on single or a limited combination of nutrients [45]-[50] with limited data on multiple micronutrient-fortified supplements.

There is enough evidence reporting that DSNS significantly improved glycemic control, and reduced HbA1c, body weight, and waist circumference, among overweight and obese diabetic participants [26] [44] [51]-[57]. Studies have shown that DSNSs reduce post-prandial elevation in diabetic subjects as measured by incremental Area under Curve (iAUC) [58]-[62]. The Area under the Curve (AUC) is the geometric mean value to quantify the total increased blood glucose after consuming any food over time [63]. It is recognized as an important measure to understand acute blood glucose responses after consuming a food or meal in diabetic research [5] [63]. Evidence has shown that iAUC curve is lower for high fiber or low carbohydrate meals as compared to standard meals indicating lower blood glucose elevation [64], suggesting it to be used as an important measure in assessing efficacy of DSNSs. However, studies on efficacy of DSNSs on health status of prediabetic individuals are limited [26] [58] [65] [66]. The primary objective of the present study was to assess the ABGR of a DSNS versus an isocaloric snack, as measured by iAUC in prediabetic adults. Secondary objectives included studying the efficacy of DSNS + LC versus LC alone post four weeks on FBG, anthropometry, body composition, blood pressure, nutrient intake, physical activity, and continuous glucose monitoring indicators.

## 2. Methodology

This was a two-armed, open-labelled, randomized, controlled six-week, single-center study conducted among 199 prediabetic participants. The study was conducted

according to the principles and requirements of the Declaration of Helsinki and was consistent with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidance on Good Clinical Practice (2019) [67] and Indian Council of Medical Research ethical guidelines. The study was reviewed and approved by the Institutional Ethics Committee of the study site. All participants provided written informed consent. The study was explained in detail along with potential benefits and risks to them and their families. The study was registered at Clinical Trials Registry India with registration number CTRI/2023/02/049511 (Available at <https://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=79873&EncHid=&userName=CTRI/2023/02/049511>). The flow chart for study design is shown in **Figure 1**.



**Figure 1.** Flow chart of study design. N = total number of participants, n = number of participants in each group. DSNS: Diabetes Specific Nutritional Supplement; LC: Lifestyle Specific Counselling; CGM: Continuous Glucose Monitoring; iAUC: incremental Area under Curve; ITT: Intention to Treat Analysis; PP: Per Protocol.

## 2.1. Study Design and Participants

Prediabetic participants (n = 200), both males and females (non-pregnant/

non-lactating), between 30 - 65 years of age were recruited in the study. Prediabetes was diagnosed on HbA1C  $\geq 5.7\%$  to  $\leq 6.4\%$  and/or fasting blood glucose between 100 - 125 mg/dl [5] [27]. The participants who were not receiving any anti-diabetic medication and willing to consent were recruited in the study. Participants who had BMI  $< 18.0$  and  $> 32.5$  kg/m<sup>2</sup>, or had any acute infections, eating disorders, or were taking any medication that could have profoundly affected blood glucose, were habitual substance abuse (alcohol, smoking, tobacco) consumers or had any known history of kidney or liver diseases in past 3 months were excluded at the screening.

The sample size was calculated considering an average 10% change in iAUC as outcome, 80% power and an alpha of 0.05 and with a dropout rate of 10%, making a total sample size to be 126 (n = 63 in each arm of the study). In total, 1286 participants were screened, out of which 992 did not meet the inclusion/exclusion criteria. Considering dropouts, two hundred participants were finally recruited after receiving consent for the study. They were randomized into test and control groups according to a schedule generated using SAS® statistical software (Version: 9.4; SAS Institute Inc., USA). One participant from the control group dropped out after randomization. Thus, a total of 199 participants [test (n = 100) and control (n = 99)] participated in this parallel phase study (Figure 1). The study was conducted in two parallel phases for 6 weeks: Acute Blood Glucose Response (ABGR) and Intervention phase including Continuous Glucose Monitoring (CGM). The same participants were involved in both phases (Figure 1).

## 2.2. Study Product

The test DSNS is a low GI [68] nutrition supplement (Horlicks Diabetes Plus provided by Hindustan Unilever Limited). It is a dual fiber blend (Nutriose® and Fibersol®) formulation containing 22% soluble fiber and with a high MUFA composition (70% of total fatty acids delivering ~18% of energy). It delivers 13 vitamins and 7 minerals ( $\geq 15\%$  RDA) along with the three macronutrients and fiber (refer Table S1 for nutrient Composition of DSNS). The carbohydrate delivers 40%, fiber 12%, protein 23% and fat 25% of total energy. This formula has been designed in line with the ICMR-INDIAB 2021 recommendations for Type 2 Diabetes (T2D) remission and prevention of progression to T2D in prediabetic and Normal Glucose Tolerance (NGT) individuals [38].

## 2.3. Acute Blood Glucose Response (ABGR) Phase

ABGR phase was conducted on four visit days during the study. During each visit, participants reported at the clinical site on the previous day evening and were provided with a standard dinner. It was ensured that the time of food administration was kept nearly the same for all the participants (window period  $\pm 1$  hour). Participants were to consume their meal at the latest by 10 pm and were required to stay overnight on-site to maintain fasting for nearly 10 hours. On

visit days 1, 15, 29, and 43, FBG was obtained by withdrawing fingertip capillary blood through finger prick method and using validated Hemocue 201+. The FBG sample was collected prior to product administration [15 mins ( $\pm 2$  mins)]. Pre-weighed 60 g DSNS in 250 ml of double toned milk was provided to the test group ( $n = 100$ ). Isocaloric snack of 56 g of cornflakes in 250 ml of double toned milk was provided to the control group ( $n = 99$ ). The participants were instructed to consume the same within 15-minutes. Participants did not consume anything for the next 180 min (till the last 180 min. blood sample was drawn). After administration of test product/isocaloric snack, estimation of Postprandial Glucose (PPG) was performed at 30, 60, 90, 120, 150 and 180 min ( $\pm 2$  minutes) and it was recorded. The details of the test (DSNS) and control (isocaloric snack) products are presented in **Table 1**.

**Table 1.** Nutrient composition of DSNS and isocaloric snack.

Nutrients	Acute blood glucose response <sup>a</sup> phase		Intervention phase
	DSNS (60 g)*	Isocaloric snack (56 g cornflakes)*	DSNS (60 g)**
Energy (Kcal)	331.1	329.5	213.6
Protein (g)	20.3	12.0	12.0
Fat (g)	9.8	4.3	6.0
Carbohydrate (g)	33.8	61.1	21.3
Fibre (g)	13.2	1.4	13.2

Note: <sup>a</sup>Assessed on days 1, 15, 29 and 43. \*In 250 mL double toned milk. \*\*In 200 ml warm water. DSNS is a micronutrient fortified supplement rich in vitamins and minerals.

Initially, for the ABGR phase, the DSNS (60 g) was administered in water and isocaloric snack of 28 g of cornflakes in 200 ml of toned milk. During the first day (visit 2) for the first set of participants ( $n = 57$ ; not included in the analysis for ABGR phase), the study team received feedback that participants felt hungry even after consuming the test and control products, likely due to the overnight fast. Also, the participants could not consume anything for the next 180 mins post the product administration. Hence, to support study compliance, smooth ethical conduct, and to improve the wholesomeness of both test and control snacks, the DSNS (60 g) was agreed to be reconstituted in 250 ml double toned milk. To match the energy delivery in control group, 56 g of cornflakes were administered in 250 ml double toned milk. This was well accepted by the following study participants.

## 2.4. Intervention Phase

### 2.4.1. DSNS + LC versus LC Alone

This phase was conducted to assess the impact of the DSNS along with lifestyle counselling (DSNS + LC) versus lifestyle counselling alone (LC alone) in predia-

betic adults (**Figure 2**) post 4 weeks of intervention. At the baseline, data on FBG, Hb1Ac, body weight, height, BMI, body composition, blood pressure, along with demography, medical history, 24 hours dietary recall and physical activity questionnaire were collected. The actual intervention phase for DSNS + LC versus LC alone was for 4 weeks (28 days) from day 15 to day 42 with three visits in between visit 3 (day 15), visit 4 (day 29) and visit 5 (day 43, endline). The test group participants received DSNS + LC while the control group received LC alone during the intervention phase. All subjects were reassessed on the above parameters on visits days which coincided with their ABGR assessments visits.

The participants in DSNS + LC group were provided with a 14 day supply of DSNS sachets and counselled on method of reconstitution for consumption at home (**Table 1**) on day 15 and reconfirmed on Day 29. The participants were instructed to consume the DSNS twice a day (30 g each time with 200 ml warm water)—before breakfast and during early evening (between lunch and dinner). Shakers were provided to participants to ensure accurate dilution and compliance with consumption. The compliance was ensured by regular telephonic follow-ups and collecting empty sachets by the study staff before the next batch of sachets was handed over to the participants on day 28 (visit 4). The second batch of empty sachets was collected on day 42 (visit 5). The LC sessions were conducted twice (on days 15 and 29), for all participants during the intervention phase. The product compliance was 100% among study completers. The LC sessions focused on the importance of having a balanced diet, carbohydrate sources, reducing simple sugars and fats, increasing protein and fiber intake along with increasing intakes of fruits and vegetables. The sessions also emphasized daily walk at least for 30 minutes.

Body weight was measured to the nearest 0.1 kg using digital weighing scale (BodySCAN™ HBF 214 AP, Omron). Height was measured using a stadiometer (26SM, Biocon) to the nearest 0.1 cm. Body Mass Index (BMI) was calculated as

Visit 1	Visit 2 (Day 00 & 01)		Visit 3 (Day 14 & 15)		Visit 4 (Day 28 & 29)		Visit 5 (Day 42 & 43)
	Week 1 Day 01-07	Week 2 Day 08-14	Week 3 Day 15-21	Week 4 Day 22-28	Week 5 Day 29-35	Week 6 Day 36-42	End of the study
	CGM 1 (Baseline)		No CGM		CGM 2 (Endline)		
Screening & Randomization	Test (n=100)		Test (DSNS+LC) (n=86)		Test (DSNS+LC) (n=69)		Test (DSNS+LC) (n=65)
	Loss to Follow up = 21 (T 8, C 13) Incomplete CGM data=12 (T 6, C 6) Refused to consume DSNS/isocaloric snack=2 (C 2)		Loss to Follow up=10 (T 4, C 6) Incomplete CGM data=20 (T 13, C 7)		Loss to Follow up=3 (T 2, C 1) Incomplete CGM data=3 (T 2, C 1)		
	Control (n=99)		Control (LC alone) (n=78)		Control (LC alone) (n=65)		Control (LC alone) (n=63)
			Supplementation and lifestyle counselling				
T: test, C: control, CGM: Continuous Glucose Monitoring							

**Figure 2.** Intervention phase of the study.

weight (kg)/height (m<sup>2</sup>). Waist Circumference (WC) was measured midway between the iliac crest and the lowermost margin of the ribs, with the subject breathing normally using a non-stretchable tape. Body fat percentage (%) and skeletal mass (kg) were estimated using BodySCAN™ HBF-214 Body Composition Monitor (Omron). Systolic and diastolic blood pressure was measured using calibrated digital BP apparatus (BP 02XL, Dr. Morepen). Fasting blood glucose and HbA1c were assessed using venous blood samples on visit 1 and visit 5 (day 43). Twenty-four-hour dietary recalls were collected using a standard questionnaire. Information on physical activity was collected using modified Madras Diabetes Research Foundation physical activity questionnaire (MPAQ) [69].

#### **2.4.2. Continuous Glucose Monitoring (CGM)**

Impact of DSNS on the ambulatory glucose profile was studied using a CGM device between two 14-day phases: CGM1 phase (baseline, days 1 - 14) and CGM2 phase (endline, days 28 - 42). The CGM system used was the Free Style Libre Pro (manufactured by Abbott Healthcare Pvt Ltd) and assessed the interstitial fluid glucose concentration. The CGM 1 phase was designed as the baseline for the 4-week intervention to elicit any differences in the CGM outcomes before and during/after the 4-week intervention (**Figure 2**). Randomized participants reported at the study site on day 0 and the CGM device was inserted in the back of the upper arm post dinner for all study participants. They were asked to continue wearing the device for the next 14 days. Participants in both the groups were instructed to continue with their habitual diet and routine physical activity for this CGM1 baseline. The CGM device was removed for all the study participants on Day 14 at bedtime (visit 3) providing a 14-day CGM1 phase data (baseline). All participants received lifestyle counselling on Day 15. In addition to LC, the test group was also provided the DSNS for daily consumption for the next 14 days. During this period, participants were not wearing any CGM device. All study participants reported back on day 29 (visit 4) for the CGM2 baseline.

On day 28, the participants reported back to the study site and a new CGM device was inserted post dinner (visit 4), for all participants. Again, the participants in both groups received lifestyle counselling and the test group was given the DSNS for daily consumption for the next 14 days. All the participants reported back on day 42 (visit 5) for the endline visit and CGM removal. CGM 1 phase (days 1 - 14) and CGM 2 phase (days 29 - 42) records were compared to assess the efficacy of intervention on mean blood glucose, estimated HbA1c, and Time in Range (TIR), among DSNS + LC as well as LC alone groups.

#### **2.5. Data Analysis**

The statistical analysis was done by using SAS® statistical software (Version: 9.4 or higher; SAS Institute Inc., USA). Intention to treat analysis was conducted for 199 participants [test (n = 100) and control (n = 99)] who participated in this parallel phase study. During the study period, 35 participants in the test and 37 participants in the control group did not complete the study (reasons for dropout

as listed in **Figure 2**). Consequently, a per protocol analysis was conducted, encompassing 65 participants in the test, and 63 in control group (**Figure 1**).

Continuous variables were summarized using tables of descriptive statistics: number of participants with recorded observations, mean, standard deviation, median, minimum, and maximum. Categorical variables were summarized using counts and percentages. Least square means with standard error were computed, wherever necessary. For continuous variables, the within-treatment analyses were conducted to compare baseline to post-intervention data using paired t-test. The data between the groups for various parameters was analyzed using an independent t-test. Mean glucose concentrations and TIR values during the CGM1 and 2 were obtained from the CGM device report. Using 54 - 140 mg/dl as normal range for CGM interstitial values, percent TIR was calculated. Estimated HbA1c% was calculated using mean glucose (mg/dl) values into a formula [ $e\text{HbA1c} = 3.38 + 0.023453 (\text{mean glucose})$ ] [70]. The nutrient intake of foods was calculated using IFCT 2017 [71] and food atlas (MDRF) [72]. The mean intakes and nutrient adequacy of major nutrients was compared with Recommended Dietary Allowances (RDAs) given by Indian Council of Medical Research (ICMR), RDA 2024 [73]. Percent energy contribution from macronutrients was also calculated. ANCOVA was used for assessing the differences between the two groups in various nutrient intakes and adequacies changes from baseline to endline. The physical activities are classified into sedentary, moderate, and vigorous categories in the MPAQ [69]. We have used modified MAPQ, thus changes in physical activities under each category were calculated as mean duration (minutes) per day. Safety data was analyzed for the safety population defined as all enrolled participants who received at least one of the test products or isocaloric meals. Adverse Events were summarized with a number and the percentage. All statistical tests of hypothesis employed a level of significance of 0.05.

### 3. Results

All participants were between the age range of 30 - 63 years with a mean age of 44.2 (8.52) years and mean BMI of 25.9 (3.81) kg/m<sup>2</sup> in DSNS + LC and 25.9 (3.84) kg/m<sup>2</sup> in LC alone group. There were 124 males and 75 females in the study. All participants reported to have an HbA1c  $\geq 5.7 - \leq 6.4\%$ . However, it was reported that 42% (n = 84) of prediabetic subjects had FBG between 100 - 125 mg/dl. Almost 28% (55) and 30% (61) participants had FBG < 100 mg/dl and >125 mg/dl respectively. There were no significant differences in anthropometric and body composition parameters between the two groups as shown in **Table 2** at baseline.

#### 3.1. Acute Blood Glucose Response Phase

##### 3.1.1. Post-Prandial Blood Glucose (PPG)

DSNS group showed significantly lower PPG versus isocaloric snack on all visit days at 30 (p < 0.0001), 60 (p < 0.0001), 90 (p < 0.0001), 120 (p < 0.05) and 150 (p < 0.05) minutes. As per Intent to Treat (ITT) analysis, PPG response from

**Table 2.** Baseline characteristics of the participants.

	DSNS + LC (n = 100)	LC alone (n = 99)	p-values
Age, mean, (SD) years	45.2 (8.42)	43.3 (8.42)	0.1098
<b>Gender<sup>#</sup></b>			
Males, n (%)	66 (66.00)	58 (58.6)	0.3078
Females, n (%)	34 (34.00)	41 (41.4)	
Weight, mean (SD), kg <sup>a</sup>	67.3 (10.87)	66.7 (9.83)	0.5853
Height, mean (SD), cm <sup>a</sup>	161.3 (9.43)	160.7(8.33)	0.679
BMI, mean (SD), kg/m <sup>2a</sup>	25.9 (3.81)	25.9 (3.84)	0.9397
Waist circumference, mean (SD), cm <sup>a</sup>	93.6 (9.39)	91.9 (10.48)	0.2402
Fat percentage, mean (SD), % <sup>a</sup>	30.0 (7.28)	31.0 (7.18)	0.3241
Skeletal mass, mean (SD), % <sup>a</sup>	28.9 (4.85)	28.3 (4.80)	0.3721
Diastolic Blood pressure, mean, (SD), mmHg	79.3 (2.25)	79.2 (2.16)	0.7429
Systolic Blood Pressure, mean (SD), mmHg	118.4 (3.04)	118.4 (2.97)	0.8946
Fasting Blood Glucose, mean (SD), mg/dL	116.7 (2.38)	113.3 (2.39)	0.3101
HbA1C %, mean (SD)	5.97 (0.19)	5.95 (0.19)	0.5212

Note: <sup>a</sup>Data from visit 2. <sup>#</sup>Wilcoxon rank test of significance was used for comparing gender differences in the groups. All other parameters were compared using unpaired t-test, at p < 0.05 level of significance.

0 to 180 minutes after DSNS and isocaloric snack consumption by the participants in DSNS and control groups, respectively, on days 1, 15, 29, 43 is shown in **Figure 3**.

The maximum glucose peak was achieved at 60 minutes for both the groups on all the days. However, it was significantly lower in the DSNS group as compared to control group at all the days [day 1 (<0.0001), day 15 (<0.0001), day 29 (<0.0001) and day 43 (<0.0001)]. The differences in PPG levels reduced between DSNS and control group at 180 minutes for all the four days. The Per Protocol (PP) data showed similar results. Detailed data is given in **Table S2**.

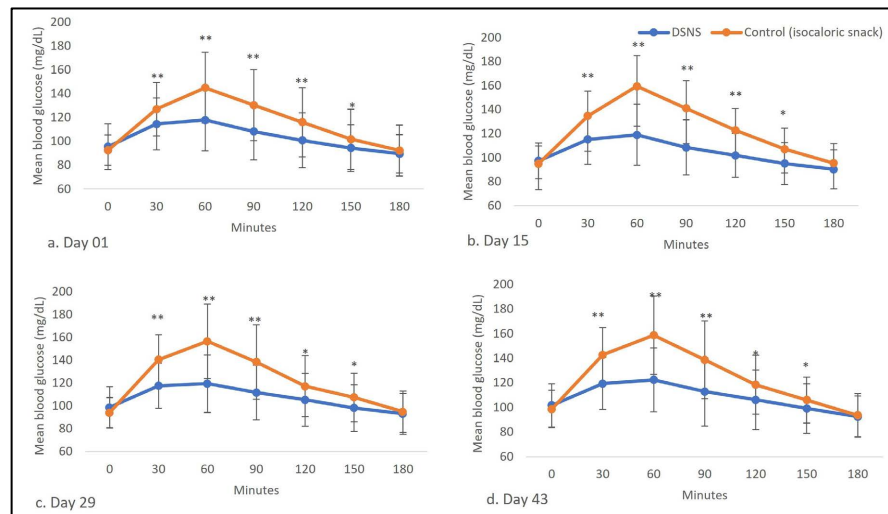
### 3.1.2. Incremental Area under the Curve (iAUC)

The iAUC was significantly lower in DSNS group versus the control group at day 1 (<0.0001), day 15 (<0.0001), day 29 (<0.0001), and day 43 (<0.0001) as per ITT analysis (**Figure 4**). Similar results were obtained from PP data. Detailed data provided in **Table S3**.

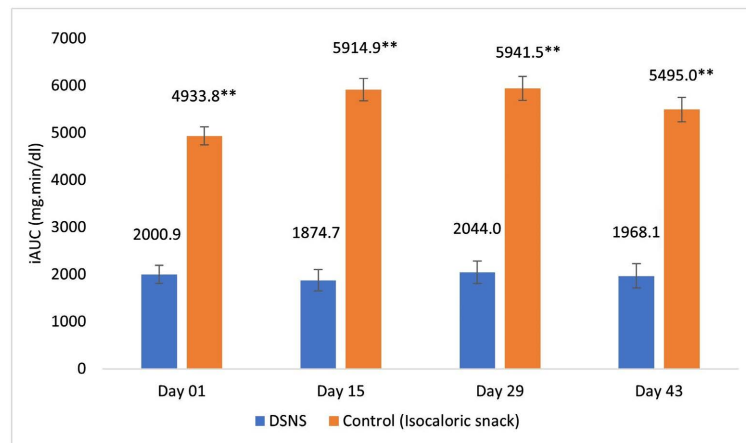
## 3.2. Intervention Phase

### 3.2.1. Changes in Mean FBG, Anthropometric Markers, Body Composition, Blood Pressure and HbA1C

At baseline, no significant differences were observed in any of the parameters between the two groups as per ITT analysis. Post intervention, FBG, waist circumference, systolic and diastolic blood pressure reduced from baseline significantly



**Figure 3.** Post-prandial glucose levels at 0, 30, 60, 90, 120, 150 and 180 minutes on day 1, day 15, day 29 and day 43 in DSNS and control groups. Significant difference between the two groups was calculated using independent t-test at \* $p < 0.05$  and \*\* $p < 0.0001$ .



**Figure 4.** Comparison of iAUC at days 1, 15, 29 and 43 between DSNS and control (isocaloric snack); values are least square of means with standard error bars. \*\*Significant difference between the two groups using analysis of variance at  $p < 0.0001$ .

after 4 weeks of intervention for both the groups with the mean (SD) change being more pronounced in DSNS + LC group versus the LC alone group [FBG: DSNS + LC:  $-25.3$  (26.51) mg/dl,  $p < 0.0001$ ; LC alone:  $-24.4$  (21.66) mg/dl,  $p < 0.0001$ ; waist circumference: DSNS + LC:  $-1.13$  (1.86) cm,  $p < 0.0001$ ; LC alone:  $-0.88$  (1.86) cm,  $p = 0.0004$ ; Systolic BP: DSNS + LC:  $-3.3$  (4.63) mm Hg,  $p < 0.0001$ ; LC alone:  $-2.5$  (4.51) mm Hg,  $p < 0.0001$ ; Diastolic BP: DSNS + LC:  $-3.1$  (3.63) mm Hg,  $p < 0.0001$ ; LC alone:  $-2.6$  (3.72) mm Hg,  $p < 0.0001$ ]. A reduction in weight and percent body fat from baseline was reported by both the DSNS + LC and LC alone groups. While the change in weight was significant for DSNS + LC group [DSNS + LC:  $-0.4$  (1.27)  $p = 0.0104$ , LC alone:  $-1.33$  (6.27), kg/m<sup>2</sup>,  $p > 0.05$ ], the change in percent body fat was significant for LC alone group [DSNS + LC:  $-1.02$  (4.34)%,  $p = 0.058$ ; LC alone:  $-0.98$  (3.5)%,  $p <$

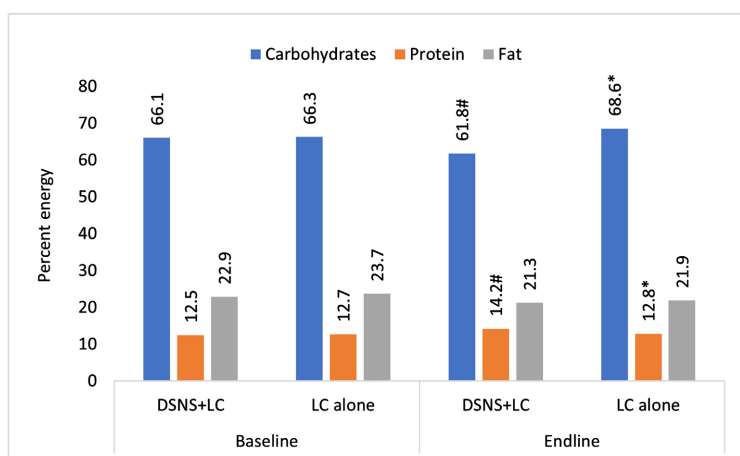
0.028]. Mean (SD) reductions in BMI were significant for both the groups [DSNS + LC:  $-0.29$  (0.74)  $p = -0.0022$ , LC alone:  $-0.33$  (0.74),  $\text{kg/m}^2$ ,  $p = 0.0007$ ]. Percent skeletal mass and Hb1AC did not show any significant changes after 4 weeks intervention in either of the groups. There were no significant differences observed between the test and control groups for any of the measures. The results were observed to be similar in PP analysis. Details are given in **Table S4**.

### 3.2.2. Changes in Dietary Intake and Physical Activity

The dietary intake of participants was assessed at baseline (day 1) and at the end of the study (day 43) using 24-hour recall method.

#### Macronutrients: Changes in percent energy contribution and nutrient adequacy

From the dietary data, average nutrient intake among the participants was computed. The percentage energy contribution from carbohydrate, protein and fat was similar between DSNS + LC and LC alone group at baseline. Post intervention, DSNS + LC group reported a significant reduction in the contribution of energy from carbohydrates, (DSNS + LC:  $-5.3$  (9.22)%, LC alone:  $1.6$  (24.44)%,  $p = 0.0349$ ), and a significant increase in protein energy percent (DSNS + LC:  $1.5$  (1.51)%, LC alone:  $0.03$  (1.37)%,  $p < 0.0001$ ) compared to LC alone group, shown in **Figure 5**. There were no significant changes reported in fat energy percent.



**Figure 5.** Comparison between DSNS-LC and LC groups for intake of proportion of energy contribution from carbohydrates, protein and fat at baseline and endline. \*Significant difference between the groups using independent t-test at  $p < 0.05$ . #Significant differences between baseline and endline within the group using paired t-test at  $p < 0.05$ .

Mean protein intake increased significantly ( $p < 0.05$ ) in DSNS + LC group post intervention from baseline [50.4 (20.24) g] to endline [55.3 (15.96) g]; while there were no significant changes in the energy, protein, carbohydrate, and fat intakes in LC alone group as compared to baseline. Post intervention, percentage adequacy for protein intake increased in DSNS + LC group as compared to LC

alone group (DSNS + LC: 10.3 (41.83)%, LC alone: -7.2 (31.64)%,  $p < 0.001$ ). On adjusting the change from baseline, the percent adequacy for fibre intake also improved in DSNS + LC, compared to LC alone group (DSNS + LC: 30.2 (13.10)%, LC alone: -7 (13.30)%,  $p = 0.0513$ ).

#### **Micronutrients: Changes in mean intake and percent adequacy**

Micronutrient intake data was collected and analyzed for calcium, iron, vitamin B12 and chromium. Post intervention, the mean intakes of calcium, iron, vitamin B12, and chromium were significantly ( $p < 0.0001$  for all) higher in DSNS + LC as compared to LC alone group (**Table 3**).

Percent adequacies of calcium, iron, vitamin B12, and chromium were found to be inadequate at baseline for both the groups. The percent adequacies for intakes of calcium, iron, vitamin B12, and chromium, not only increased substantially ( $p < 0.0001$  for all) in DSNS + LC group post intervention as compared to baseline but were also significantly ( $p < 0.0001$  for all) higher than LC alone group at endline (**Table 3**). The participants in the DSNS + LC group displayed significantly augmented nutrient intake at the endline compared to baseline levels. Similar results were obtained from per-protocol analysis.

#### **Changes in physical activity**

At baseline, majority of the participants were sedentary (DSNS + LC: 97%, LC alone: 97%) and engaged in light physical activities (DSNS + LC: 44%, LC alone: 47%). Only 13% of participants in DSNS + LC and 19% in LC alone groups were engaged in moderate activities. Following the lifestyle counseling sessions, a significant increase in the proportion of participants engaged in moderate activities was observed in both groups (DSNS + LC: 98%,  $p < 0.0001$ ; LC alone: 100%,  $p < 0.0001$ ). There was also a significant rise in the time (mean) spent on moderate activities, with participants in the DSNS + LC group increasing by 33.6 (15.47) minutes ( $p < 0.005$ ) and those in the LC alone group increasing by 30 (18.71) minutes ( $p = 0.0007$ ) as compared to their respective baseline. However, no significant differences in physical activity patterns were noted between the two groups. Data from ITT and PP analysis of physical activity pattern of prediabetic participants is shown in **Table S5**.

#### **3.2.3. Changes in Continuous Glucose Monitoring (CGM) Indicators**

The comparison between baseline and endline CGM data suggested that 4 weeks intervention (both DSNS + LC and LC alone) did not show any substantial changes in glycemic parameters in prediabetic individuals using a CGM device in prediabetics. Data not shown in the paper.

### **3.3. Safety**

Safety data was analyzed for all participants who received either the DSNS or isocaloric snack. Only two minor adverse events (1%), one in DSNS + LC and one in LC alone group were reported. Both AEs were of mild intensity. Both subjects experienced discomfort and mild diarrhoea after consumption of test products. Their vital signs were within normal limits and both the participants

**Table 3.** Mean intakes and % mean adequacies of DSNS + LC and LC alone group at endline and baseline, as per ITT analysis.

Nutrient		DSNS + LC, Mean (SD)			LC alone, Mean (SD)			Between groups comparison for adjusted change from baseline		
		Baseline (n = 100)	Endline (n = 65)	Change from baseline	Baseline (99)	Endline (63)	Change from baseline	DSNS + LC LSM(SE)	LC alone LSM (SE)	p value
Energy	Mean intake (Kcal)	1620.6 (630.95)	1568.0 (460.92)	-7.6 (642.93)	1431.2 (469.84)	1269.0 (351.19)	-11.8.9 (467.55)*	65.3 (49.80)	-194.2 (50.60)	0.0004
	% nutrient adequacy	83.3 (33.06)	80.7 (20.31)	-0.9 (33.79)	74.8 (24.36)	66.3 (15.82)	-7 (24.03)*	2.6 (2.25)	-10.7 (2.28)	<0.0001
Carbohydrate	Mean intake (g)	267.4 (109.78)	248.2 (86.99)	-17.9 (118.7)	237.1 (82.85)	219.9 (93.63)	-13.5 (102.2)	-5.8 (10.90)	-26.1 (11.10)	0.1990
	% nutrient adequacy	205.7 (84.44)	190.9 (66.92)	-13.8 (91.29)	182.4 (63.73)	168.6 (72.03)	-10.4 (78.63)	-4.5 (8.40)	-20.1 (8.54)	0.1990
Protein	Mean intake (g)	50.4 (20.24)	55.3 (15.96)	5.4 (21.21)*	45.6 (16.30)	40.8 (12.38)	-3.6 (16.39)	7.5 (1.72)	-5.8 (1.75)	<0.0001
	% nutrient adequacy	98.1 (37.97)	108.1 (27.57)	10.3 (41.83)	89.9 (31.48)	80.4 (21.79)	-7.2 (31.64)	14.4 (3.06)	-11.9 (3.11)	<0.0001
Fat	Mean intake (g)	45.0 (57.99)	36.2 (10.24)	-5.2 (54.49)	39.8 (50.85)	30.5 (9.37)	-6.8 (44.00)	-3.25 (1.21)	-8.85 (1.22)	0.0014
	% nutrient adequacy	196.4 (266.75)	157.5 (43.37)	-27.8 (270.04)	176.4 (233.12)	134.7 (217.97)	-34.9 (217.97)	-20.5 (5.14)	-42.5 (5.22)	0.0032
Fiber	Mean intake (g)	44.6 (22.71)	50.7 (16.7)	4.8 (26.58)	37.3 (15.17)	39.7 (41.37)	2.6 (43.30)	8.7 (3.95)	-1.5 (4.02)	0.0769
	% nutrient adequacy	158.1 (82.72)	179.5 (52.73)	15.5 (98.77)	133.5 (53.04)	141.5 (138.26)	8.2 (146.33)	30.2 (13.10)	-7.0 (13.30)	0.0513
Calcium	Mean intake (mg)	243.2 (143.96)	583.9 (92.66)	7.9 (2.63)**	255.7 (162.90)	243.6 (109.90)	-2.6 (133.85)	353.5 (11.70)	6.1 (11.90)	<0.0001
	% nutrient adequacy	24.3 (14.4)	58.4 (9.27)	36.2 (13.07)**	25.6 (16.3)	24.4 (10.99)	-0.3 (13.38)	35.3 (1.17)	0.6 (1.19)	<0.0001
Iron	Mean intake (mg)	3.2 (3.99)	9.6 (2.30)	7.9 (2.63)**	3.0 (3.40)	2.2 (2.18)	2.2 (2.18)	7.5 (0.27)	-0.1 (0.28)	<0.0001
	% nutrient adequacy	15.5 (20.1)	44.4 (14.34)	36.4 (15.22)**	13.9 (16.81)	10.1 (10.65)	-2.2 (16.44)	34.7 (1.55)	-0.5 (1.57)	<0.0001
Vitamin B12	Mean Intake (mcg)	0.8 (0.54)	2.5 (0.34)	1.7 (0.48)**	0.9 (0.68)	0.8 (0.41)	-0.07 (0.56)	1.7 (0.04)	-0.03 (0.05)	<0.0001
	% nutrient adequacy	36.7 (24.53)	41.5 (31.04)	77.2 (21.93)**	111.5 (18.71)	36.1 (15.32)	-3.2 (25.25)	75.4 (2.00)	-1.3 (2.03)	<0.0001
Chromium	Mean intake (mcg)	0.03 (0.09)	12.8 (1.61)	12.7 (1.61)**	0.02 (0.016)	0.02 (0.013)	-0.0025 (0.018)	12.7 (0.14)	-0.01 (0.15)	<0.0001
	% nutrient adequacy	0.06 (0.2)	25.5 (3.22)	25.5 (3.22)**	0.04 (0.03)	0.04 (0.03)	0 (0)	25.5 (0.29)	-0.01 (0.29)	<0.0001

Note: Values are Mean (SD) for baseline and endline. % nutrient adequacies were computed by comparing the nutrient intake values with RDA 2024 (ICMR), p-value for within group was calculated using paired t-test. Least square mean (SE) was used to compare the mean change from baseline between groups by ANCOVA, where p-value is significant at \* < 0.05 and \*\* < 0.0001.

felt comfortable after taking a rest. No other participant reported any other adverse events either after consuming the DSNS or isocaloric snack.

#### 4. Discussion

According to Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) nationwide survey report, overall weighted prevalence of prediabetes is 15.3% and diabetes 11.4% [8]. The diabetic Indian population had an average glycosylated hemoglobin of 8.56%, FBG of 172 mg/dL, and PPG of 253 mg/dL. There is a substantial body of evidence reporting the positive role of DSNS in diabetic populations, specifically in reducing PPG levels [39] [74], influencing glycemic variability [55], and lowering HbA1C [57]. However, studies on efficacy of DSNSs on health status of prediabetic individuals are limited [26] [58] [65] [66]. To the best of our knowledge, ours is the first study investigating the efficacy of a DSNS on glycemic response in prediabetics in the Indian context. The strength of this study was its parallel phase study design including the acute blood glucose response of DSNS as well as the intervention phase including 4-weeks intervention and impact assessment of the DSNS on multiple parameters including anthropometry, body composition, nutrient intake, BP and CGM.

In the present study, ABGR for DSNS and isocaloric snack was measured with DSNS reporting significantly lower PPG versus isocaloric snack at 30 ( $p < 0.0001$ ), 60 ( $p < 0.0001$ ), 90 ( $p < 0.0001$ ), 120 ( $p < 0.05$ ) and 150 ( $p < 0.05$ ) minutes on all visit days. iAUC for 0-180 minutes was significantly lower ( $p < 0.0001$ ) for DSNS as compared to control for all visit days. The peak PPG at 60 minutes were significantly lower for DSNS than isocaloric snack on all the days, suggesting that elevation in blood sugar levels would be much lower after consuming DSNS (60 g with 250 mL double toned milk) as compared to standard breakfast (56 g cornflakes with 250 mL double toned milk) (Figure 3 and Figure 4). These findings corroborate with a recent study conducted in Japanese ( $n = 20$ , prediabetics) individuals [58]. In this study, an energy dense, low carbohydrate, and high fibre Oral Nutritional Supplement (ONS) was given to participants on two separate days and it was observed that iAUC of blood glucose levels for 120 minutes was significantly lower after ONS ingestion ( $2207 \pm 391$  mg/dL.min) as compared to standard formula ( $3735 \pm 391$  mg/dL.min,  $p < 0.001$ ) [58].

The DSNS used in the present study is a high fiber supplement containing 22% soluble fiber and with a high Monounsaturated Fatty Acids (MUFA) composition (70% of total fatty acids delivering ~18% of energy). Carbohydrates contribute 40%, protein 23%, and fat 25% of total energy. The high amounts of soluble fiber and MUFA may be contributing to better glycemic control.

PPG and FBG are main contributors to overall glycemic control among T2DM or prediabetic patients [75] [76]. Elevated PPG levels are risk factors for cardiovascular diseases and diabetic complications [12]-[15] [36] [77], especially in those with higher HbA1C %. Controlling PPG response in the overweight and obese population, who are also at risk for T2DM, is crucial for preventing the onset. Evi-

dence indicates that DSNS controls elevation in PPG response and lowers iAUC levels among diabetic patients [52] [59] [61] [62]. A recent study on 66 prediabetic Indians aged 30-66 years observed reduction in post-prandial hyperglycemia and reversal to normoglycemia after consuming 30g almond premeal before breakfast for three months [78]. Previous studies have consistently shown that lifestyle modifications, and certain pharmacological treatments, could effectively facilitate the reversal of prediabetes to normoglycemic levels, thereby preventing its progression to diabetes and improved outcomes [3] [18] [22] [24] [29] [79]. A study by Amer *et al.* (2020) among Saudi prediabetic patients (n = 180), reported significant reversal to normal glucose levels with intensive lifestyle guidance, however the challenge was to sustain interest in adopting lifestyle changes for a longer duration of time [80]. Therefore, compliance with nutrition counselling for a longer duration of time is imperative. The patients who had more nutrition counselling visits in a year had lower mean HbA1c levels as compared to patients with fewer visits per year [81] [82]. A recent study reported a 46% reduction in prevalence of prediabetes after 6 months of intervention, however, this decline was not maintained at 12-month follow-up [65]. Another study on Swedish prediabetic individuals reported that cardiometabolic risk variables effects were controlled only as long as the lifestyle modifications were followed [33].

To maintain cardiometabolic health, it is important to reduce the glycemic and metabolic variabilities. Sustained hyperglycemia is a high-risk state for diabetes and cardiovascular diseases. Reversal to normoglycemia is associated with a significantly reduced risk of future diabetes [17]. It is well established that HbA1C levels are the result of a combination of both FBG and PPG levels, therefore treatment may also influence FPG-PPG relationship [83]. In the present study, lower spike in PPG levels after ingesting DSNS at all the four time points validated the use of DSNS as an alternative to isocaloric high carbohydrate, low fiber breakfast. The parallel intervention phase has shown that the participants who consumed DSNS for 28 days along with lifestyle counselling had significantly higher reductions in FBG, weight, BMI, waist circumference and systolic and diastolic blood pressure as compared to only lifestyle counselling group. While increase in moderate activities during the four-week intervention proved useful in both the groups, the reductions in weight, BMI, and waist circumference were more pronounced in the DSNS + LC group compared to the LC alone group.

The dietary intakes of various nutrients by the prediabetic participants were highly inadequate at baseline in both the groups. DSNS used in our study, is rich in protein, fiber, MUFA and micronutrients. The participants consuming DSNS had shown significant increase in percent nutrient adequacy versus RDA post intervention. The LC alone group did not report any improvements in intakes of protein, iron, calcium, vitamin B12, and chromium, despite lifestyle counselling focusing on importance of nutrient-rich and balanced diets.

The CGM did not show any changes in the glycemic outcomes in the present

study. This could be attributed to the short duration of the study which was possibly not substantial enough to demonstrate significant changes in HbA1C, mean glucose levels and body composition after DSNS consumption in prediabetes. Studies in T2DM patients have demonstrated that mere use of intermittent CGM for 12 weeks had reduced HbA1C by 1% among poorly controlled individuals [84]. Another study on prediabetic and diabetic patients showed positive changes in body composition and behavioral changes among participants regarding goal setting, increased exercise sessions and self-monitoring immediately and after 1 month, however, did not report any changes in HbA1C levels [85]. Studies have demonstrated the use of CGM as behaviour modification tool for improving diet and exercise routine in T2DM patients [86]-[90]. However, the data on use of CGM by prediabetes is still not defined. Future research is needed to evaluate the accuracy and efficacy of CGM among prediabetics.

In the present study, the DSNS was well tolerated and helped prediabetic individuals to meet nutrient requirements along with the improvement in fasting blood glucose levels and lowering the peak PPG levels after consumption.

## 5. Conclusion

The consumption of DSNS effectively controls postprandial glucose peaks and results in lower iAUC levels. Daily intake of DSNS, combined with lifestyle changes, is associated with significant reductions in body weight, BMI, and waist circumference. This study supports the use of DSNS as a snack for prediabetic or hyperglycemic individuals requiring nutritional support for improved glycemic control. However, long-term intervention studies could substantiate efficacy of DSNS on HbA1c and other metabolic outcomes in prediabetic individuals.

## 6. Salient Features of the Present Study

- The first study to investigate the efficacy of a DSNS on glycemic response in prediabetics in Indian context (to the best of our knowledge).
- DSNS showed significantly lower PPG and iAUC as compared to isocaloric snack at four different time points.
- Daily consumption of DSNS as snack along with life counselling showed significant changes in FBG, weight, BMI, waist circumference, and blood pressure from baseline in prediabetic participants.
- Low GI DSNS with a high fiber and MUFA helped prediabetic participants to improve the intake of protein, fibre, iron, calcium, vitamin B12, and chromium.

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### **Authors' Contributions**

D.K., K.J.R., H.S.G., J.B. and M.P. were primarily involved in the conceptualization of the study; S.S. and P.J. were involved in the data collection and conduct of the study. K.J.R., H.S.G. and J.B. were involved in the quality checks and data verification. D.K., K.J.R., and H.S.G. were responsible for the scientific research. J.B. was involved in operational decision-making during the conduct of the study. J.G. was responsible for statistical analyses of results. D.K., K.J.R. and H.S.G. interpreted the study results and participated in data curation. D.K., K.J.R. and H.S.G. 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 the Clinical Trials Registry India (CTRI/2023/02/049511).

### **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 D.K.

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## Conflicts of Interest

D.K., K.J.R., J.B., M.P. and H.S.G. declare potential conflicts of interest as either employees or consultants of HUL (Nutrition), the study sponsor. No other author declares any conflict of interest.

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## Supplementary

**Table S1.** Nutrient composition of Diabetic Specific Nutritional Supplement (DSNS).

Nutrients	Units	Per 100 g	Per 60 g
Energy	Kcal	356	213.6
Protein	g	20	12
<i>%En from protein</i>	%	22.5	
Fat	g	10	6
<i>%En from fat</i>	%	25.3	
<i>%En from MUFA</i>	%	18	
<i>MUFA as % of total fat</i>	%	70	
Carbohydrates	g	35.5	21.3
<i>%En from CHO</i>	%	40	
Total dietary fiber	g	22	13.2
<i>%En from fiber</i>	%	12.4	
Total sugar	g	28	16.8
Added sucrose	g	0	0
Sodium	mg	500	300
<b>Micronutrients</b>			
Calcium	mg	617	370.2
Iron	mg	12.96	7.776
Zinc	mg	4.25	2.55
Selenium	mcg	42	25.2
Copper	mg	0.425	0.255
Magnesium	mg	160	96
Chromium	mcg	21.6	12.96
Vitamin A	mcg	556	333.6
Vitamin D	mcg	6.17	3.702
Vitamin E	mg	12.3	7.38
Vitamin K	mcg	13.6	8.16
Vitamin B1	mg	1.11	0.666
Vitamin B2	mg	1.2	0.72
Vitamin B6	mg	1.6	0.96
Vitamin B12	mcg	2.96	1.776
Folic acid	mcg	222	133.2
Dietary folate	mcg	370.74	222.444
Niacin	mg	14.8	8.88
Vitamin C	mg	55.5	33.3
Pantothenic acid	mg	3.09	1.854
Biotin	mcg	18.5	11.1

**Table S2.** Post-prandial glucose (mg/dl) at 0, 30, 60, 90, 120, 150, 180 minutes after consuming either DSNS or isocaloric snack during ABGR phase of the study on days 1, 15, 29 and 43: Intention to Treat (ITT) and Per Protocol (PP) analysis.

	ITT					PP				
	DSNS		Control (isocaloric snack)		p-value	DSNS		Control (isocaloric snack)		p-value
Day 1	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
0	95.5	19.35	92.5	12.79	0.2105	97.6	22.37	91.9	12.55	0.0756
30	114.6	21.81	127	22.46	0.0001	116.1	24.63	129.4	22.33	0.0016
60	117.9	26.01	144.9	29.73	<0.0001	120.8	28.7	148.2	29.71	<0.0001
90	108.3	23.82	130.4	29.92	<0.0001	111.9	27.11	134.3	29.48	<0.0001
120	100.8	23.05	116	28.99	<0.0001	103.5	26.27	119.1	25.65	<0.0001
150	94.5	19.55	101.8	25.27	0.0237	96.9	22.18	101.8	20.69	0.1959
180	89.6	16.09	92.3	21.3	0.3117	91.3	18.29	92	17.29	0.834
<b>Day 15</b>										
0	97.4	14.91	95	12.52	0.2611	98.8	15.71	93.9	12.63	0.0539
30	115.3	20.86	134.8	21.39	<0.0001	117.1	20.47	134.2	21.13	<0.0001
60	119	25.41	159.5	29.24	<0.0001	120.5	25.68	158.9	28.14	<0.0001
90	108.5	22.96	141.2	33.11	<0.0001	110	24.42	139.9	31.24	<0.0001
120	101.9	18.28	122.8	29.5	<0.0001	102.1	19.63	120.7	26.69	<0.0001
150	95.2	17.51	107.1	22.45	0.0002	96	18.66	105.1	19.26	0.0072
180	90.4	16.24	95.4	19.98	0.077	91.8	17.25	93.4	17.68	0.5491
<b>Day 29</b>										
0	98.7	18.06	94.1	13.21	0.0974	99.4	18.27	94.5	13.2	0.0888
30	117.7	19.73	140.6	21.72	<0.0001	118.5	20.03	141.1	21.82	<0.0001
60	119.6	25.21	156.7	32.58	<0.0001	120.4	25.71	157.7	32.55	<0.0001
90	111.74	24	138.5	33	<0.0001	112.5	24.46	139.5	32.64	<0.0001
120	105.3	23.14	117.3	26.77	0.0065	106.1	23.58	117.8	26.97	0.0097
150	98.2	20.3	107.5	21.22	0.0107	98.7	20.58	107.6	21.54	0.0184
180	93.2	17.99	95	18.25	0.5706	93.8	18.3	95.2	18.4	0.6723
<b>Day 43</b>										
0	101.8	17.59	98.7	15.14	0.2901	101.8	17.59	98.7	15.14	0.2901
30	119.4	21.14	142.7	22.18	<0.0001	119.4	21.14	142.7	22.18	<0.0001
60	122.4	25.87	158.7	31.77	<0.0001	122.4	25.87	158.7	31.77	<0.0001
90	112.9	27.93	138.7	31.6	<0.0001	112.9	27.93	138.7	31.6	<0.0001
120	106.2	24.19	118.4	23.87	0.0048	106.2	24.19	118.4	23.87	0.0048
150	99.2	20.12	106	18.7	0.0492	99.2	20.12	106	18.7	0.0492
180	92.5	16.74	93.7	17.44	0.7058	92.5	16.74	93.7	17.44	0.7058

Note: All values are mean and SD (Standard Deviation). Significant difference between the two groups was calculated using independent t-test at  $p < 0.05$  and  $p < 0.0001$ .

**Table S3.** Comparison of iAUC at days 1, 15, 29 and 43 between DSNS and control (isocaloric snack): I Intention to Treat (ITT) and Per Protocol (PP) analysis.

ITT	DSNS			Control (isocaloric snack)			p-value
	n	Mean	SE	N	Mean	SE	
Day 1	100	2000.9	193.87	99	4933.8	194.85	<0.0001
Day 15	86	1874.7	224.24	78	5914.9	235.46	<0.0001
Day 29	86	2044.0	238.377	78	5941.5	250.3	<0.0001
Day 43	86	1968.1	254.45	78	5495.0	257.726	<0.0001
<b>PP</b>							
Day 1	65	2098.3	233.81	63	5361.0	237.495	<0.0001
Day 15	65	1831.7	236.64	63	5838.7	240.391	<0.0001
Day 29	65	2075.5	262.89	63	5893.8	267.031	<0.0001
Day 43	65	1975.0	272.217	63	5340.9	276.504	<0.0001

Note: Values are least square of means with standard error bars. p-value is calculated between the two groups using analysis of variance at  $p < 0.0001$ .

**Table S4.** ITT and PP analysis of change blood pressure, FBG, HbA1C, anthropometry of participants between baseline and end-line for both DSNS + LC and LC alone groups.

		ITT					PP				
		n	DSNS + LC	n	LC alone	p-value between groups	n	DSNS + LC	n	LC alone	p-value between groups
SBP (mmHg)	Baseline	100	118.4 (3.04)	99	118.4	0.8946	65	118.5 (3.06)	63	118.2 (2.84)	0.5848
	Endline	67	115.1 (4.14)	64	115.7	0.4440	65	115.0 (4.14)	63	115.8 (3.83)	0.2918
	Change from baseline		-3.3 (4.63)		-2.5 (4.51)	0.3485		-3.5 (4.57)		-2.4 (4.49)	0.1997
	p-value		<0.0001		<0.0001			<0.0001		<0.0001	
DBP (mmHg)	Baseline	100	79.3 (2.05)	99	79.2 (2.16)	0.7429	65	79.2 (1.99)	63	79.1 (2.26)	0.8157
	Endline	67	76.1 (3.6)	64	76.6 (2.88)	0.4548	65	76.1 (3.62)	63	76.5 (2.90)	0.4272
	Change from baseline		-3.1 (3.63)		-2.6 (3.72)	0.4136		-3.2 (3.63)		-2.6 (3.74)	0.3994
	p-value		<0.0001		<0.0001			<0.0001		<0.0001	
FBG venous blood (mg/dL)	Baseline	100	116.69 (2.38)	99	113.26 (2.39)	0.3101	65	121.6 (2.87)	63	116.5 (2.91)	0.2128
	Endline	65	96.26 (1.76)	63	92.08 (1.79)	0.0988	65	96.3 (1.76)	63	92.1 (1.79)	0.0988
	Change from baseline		-25.31 (26.51)		-24.37 (21.66)			-25.3 (26.51)		-24.37 (21.66)	
	p-value		<0.0001		<0.0001			<0.0001		<0.0001	

## Continued

HbA1C (%)	Baseline	100	5.97 (0.19)	99	5.95 (0.19)	0.5212	65	5.96 (0.20)	63	5.95 (0.20)	0.7865
	Endline	67	5.99 (0.59)	63	5.93 (0.32)	0.4770	65	5.99 (0.59)	63	5.93 (0.32)	0.4770
	Change from baseline		0.034 (0.57)		-0.017 (0.34)	0.5403		0.034 (0.57)		0.017 (0.34)	0.5403
	p-value		0.634		0.6937			0.6340		0.6937	
BMI (kg/m <sup>2</sup> )	Baseline	100	25.9 (3.81)	99	25.9 (3.84)	0.9397	65	26.0 (3.98)	63	25.7 (4.05)	0.9030
	Endline	67	25.6 (3.83)	63	25.6 (4.2)	0.9100	65	25.7 (3.88)	63	25.5 (4.24)	0.8469
	Change from baseline		-0.29 (0.741)		-0.33 (0.744)	0.7488		0.29 (0.75)		0.34 (0.74)	0.6945
	p-value		0.0022		0.0007			0.0029		0.0006	
Body fat (%)	Baseline	100	30 (7.28)	99	31 (7.18)	0.3241	65	31.1 (7.63)	63	31.8 (7.32)	0.5646
	Endline	67	29.9 (6.87)	64	30.9 (7.73)	0.4344	65	30 (6.93)	63	30.8 (7.75)	0.5470
	Change from baseline		-1.02 (4.34)		-0.98 (3.5)	0.9544		-1.04 (4.41)		-1.02 (3.51)	0.9764
	p-value		0.0583		0.0280			0.0613		0.0243	
Skeletal mass (%)	Baseline	100	28.9 (4.85)	99	27.7 (4.80)	0.3721	65	28.1 (5.05)	63	27.6 (4.86)	0.5203
	Endline	67	27.9 (4.55)	64	27.7 (4.89)	0.7928	65	27.8 (4.57)	63	27.7 (4.91)	0.9477
	Change from baseline		-0.36 (2.99)		0.12 (2.59)	0.3247		-0.37 (3.04)		0.14 (2.61)	0.3106
	p-value		0.3231		0.7114			0.3252		0.3106	
Waist circumference (cm)	Baseline	100	93.6 (9.39)	99	91.9 (10.48)	0.2402	65	92.7 (9.43)	63	91.8 (10.44)	0.5975
	Endline	67	91.7 (8.85)	64	90.9 (10.52)	0.6334	65	91.6 (8.94)	63	90.9 (10.60)	0.6948
	Change from baseline		-1.13 (1.86)		-0.88 (1.86)	0.4278		-1.15 (1.89)		-0.9 (1.86)	0.4543
	p-value		<0.0001		0.0004			0.0001		0.0003	
Body weight (kg)	Baseline	100	67.3 (10.87)	99	66.7 (9.83)	0.6879	65	67.2 (11.03)	63	66.2 (10.17)	0.5853
	Endline	67	66.8 (10.65)	64	64.7 (11.24)	0.2807	65	66.8 (10.8)	63	64.9 (11.26)	0.3086
	Change from baseline		-0.41 (1.27)		-1.33 (6.27)	0.2515		-0.4 (1.28)		-1.4 (6.31)	0.2375
	p-value		0.0104		0.0941			0.0144		0.0906	

Note: p-value for within group was calculated using paired t-test and p-value for between groups was calculated using unpaired t-test, significant at  $p < 0.05$  and  $p < 0.0001$ .

**Table S5.** ITT and PP analysis of changes in type and minutes spent engaging in various kinds of physical activities among the participants in the two groups between baseline and endline.

Intention to Treat (ITT) analysis										
DSNS + LC					LC alone					
	n	Engaged in any activity (%)	Minutes spent in activity		n	Engaged in any activity	Minutes spent in activity		Between the two groups	
			Mean	SD			Mean	SD	95% CI	p-value
<b>Sedentary activities (ITT)</b>										
Baseline	100	97 (97%)	107.9	64.3	99	96 (97%)	112.8	76.6	(-24.90, 15.25)	0.6362
Endline	65	62 (95%)	96.7	71.9	63	63 (100%)	89.8	59.4	(-16.48, 30.18)	0.5621
Change from baseline			-12.7	46.12			-9.9	26.27	(-16.08, 10.44)	0.6744
p-value within group		0.5881	0.0335			0.1631	0.0039			
<b>Light activities (ITT)</b>										
Baseline	100	44 (44%)	26.1	15.73	99	47 (47%)	30.5	20.44	(-12.03, 3.24)	0.2557
Endline	65	36 (55%)	23.2	8.88	63	38 (60%)	27.8	12.93	(-9.74, 0.60)	0.0822
Change from baseline			2.7	5.83			1.6	4.56	(-1.55, 3.65)	0.4232
p-value within group		0.1528	0.0181			0.1106	0.0465			
<b>Moderate activities (ITT)</b>										
Baseline	100	13 (13%)	32.3	18.33	99	19 (19%)	38.7	25.43	(-23.18, 10.42)	0.4444
Endline	65	64 (98%)	37.6	16.35	63	63 (100%)	38.5	13.73	(-6.22, 4.39)	0.7338
Change from baseline			33.6	15.47			30	18.71	(-14.79, 21.94)	0.6844
p-value within group		<0.0001	0.0012			<0.0001	0.0007			
<b>Vigorous activities (ITT)</b>										
Baseline	100	3 (3%)	23.2	5.77	99	2 (2%)	10	0	(-0.36, 27.03)	0.0534
Endline	65	4 (6%)	35	27.39	63	6 (10%)	20.8	12.01	(-14.52, 42.85)	0.2877
Change from baseline			55	NA			5	NA	NA	NA
p-value within group		0.3152	NA			0.0316	NA			

## Continued

Per Protocol (PP)										
Sedentary activities (PP)										
Baseline	65	62 (95%)	109.4	65.91	63	63 (100%)	99.8	69.18	(-14.26, 33.60)	0.4251
Endline	65	62 (95%)	96.7	71.9	63	63 (100%)	89.8	59.4	(-16.48, 30.18)	0.5621
Change from baseline			-12.7	46.12			-9.9	26.27	(-16.08, 10.44)	0.6744
p-value within group		1	0.0335			1	0.0039			
Light activities (PP)										
Baseline	65	30 (46%)	21.3	8.09	63	34 (54%)	27.3	13.99	(-11.83, -0.21)	0.0426
Endline	65	36 (55%)	23.2	8.88	63	38 (60%)	27.8	12.93	(-9.74, 0.60)	0.0822
Change from baseline			2.7	5.83			1.6	4.56	(-1.55, 3.65)	0.4232
p-value within group		0.2925	0.0181			0.0035	0.0465			
Moderate activities (PP)										
Baseline	65	7 (11%)	35	23.45	63	10 (16%)	29.5	14.03	(-13.82, 24.82)	0.553
Endline	65	64 (98%)	37.6	16.35	63	63 (100%)	38.5	13.73	(-6.22, 4.39)	0.7338
Change from baseline			33.6	15.47			30	18.71	(-14.79, 21.94)	0.6844
p-value within group		<0.0001	0.0012			<0.0001	0.0007			
Vigorous activities (PP)										
Baseline	65	1 (2%)	20	NA	63	1 (2%)	10	NA	NA	NA
Endline	65	4 (6%)	35	27.39	63	6 (10%)	20.8	12.01	(-14.52, 42.85)	0.2877
Change from baseline			55	NA			5	NA	NA	NA
p-value within group		0.1657	NA			0.0518	NA			

Note: p-value is calculated using unpaired t-test between the two groups, and within the groups. Chi-square test is used to calculate difference between proportion of participants engaged in various kinds of activities at baseline and endline, p-value significant at <0.05 and <0.0001.