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Efficacy of a Diabetes Specific Nutrition Supplement on Glycemic, Anthropometric, Dietary and Gut Health Markers in Adults with Type 2 Diabetes: An RCT

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Abstract

With increasing incidence of diabetes, use of diabetes specific nutrition supplements (DSNS) is common for better management of the disease. To study effect of 12-week DSNS supplementation on glycemic markers, anthropometry, lipid profile, SCFAs, and gut microbiome in individuals with diabetes. Markers studied were glycemic [Fasting Blood Glucose (FBG), Post Prandial Glucose (PPG), HbA1c, Incremental Area under curve (iAUC), Mean Amplitude of Glycemic Excursions (MAGE), Time in/above Range (TIR/TAR)], anthropometry [weight, Body Mass Index (BMI), waist circumference (WC)], lipid profile, diet and gut health [plasma short chain fatty acids (SCFAs)]. N = 210 adults were randomized to receive either DSNS with standard care (DSNS + SC; n = 105) or standard care alone (SC alone; n = 105). After 12 weeks, significant differences between DSNS + SC versus SC alone was observed in FBG [−3 ± 6 vs 14 ± 6 mg/dl; p = 0.03], PPG [−35 ± 9 vs −3 ± 9 mg/dl; p = 0.01], weight [−0.6 ± 0.1 vs 0.2 ± 0.1 kg; p = 0.0001], BMI [−0.3 ± 0.1 vs 0.1 ± 0.1 kg/m^2; p = 0.0001] and WC [−0.3 ± 0.2 vs 0.2 ± 0.2 cm; p = 0.01]. HbA1C and low-density lipoprotein (LDL) were significantly reduced in DSNS + SC [−0.2 ± 0.9; p = 0.04 and −5 mg/dl; p = 0.03] respectively with no change in control. Continuous Glucose Monitoring (CGM) reported significant differences between DSNS + SC versus SC alone

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for mean glucose [−12 ± 65 vs 28 ± 93 mg/dl; $p < 0.01$], TAR 180 [−9 ± 42 vs 7 ± 45 mg/dl; $p = 0.04$], TAR 250 [−3 ± 27 vs 9 ± 38 mg/dl; $p = 0.05$], iAUC [−192 (1.1) vs −48 (1.1) mg/dl; $p = 0.03$]. MAGE was significantly reduced for both DSNS + SC (−19 ± 67; $p < 0.001$) and SC alone (−8 ± 70; $p = 0.04$), with reduction being more pronounced for DSNS + SC. DSNS + SC reported a decrease in carbohydrate energy % [−9.4 (−11.3, −7.6) %; $p < 0.0001$] and amount [−47.4 (−67.1, −27.7) g; $p < 0.0001$], increased dietary fiber [9.5 (7.2, 11.8) g; $p < 0.0001$] and protein energy % [0.9 (0.5, 1.3) %; $p < 0.0001$] versus SC alone. DSNS + SC reported significant increases versus SC alone in total (0.3 ng/ml; $p = 0.03$) and individual plasma SCFAs. The consumption of DSNS significantly improves the glycemic, anthropometric, dietary, and gut health markers in diabetes.

Keywords

Diabetes Specific Nutrition Supplement, Standard of Care, Diabetes, Glycemic Markers, HbA1C

1. Introduction

The trade liberalization in India during the mid-1990s was countered by unfavorable shifts in the lifestyle of the Indian population. The changes included increased consumption of refined carbohydrates, added sugars, and high intake of fats, with reduced levels of physical activity among the populace [1]. The consequence was an increase in the prevalence of non-communicable diseases (NCDs) in India. Since then, NCDs have been on the rise in India, with Indians being diagnosed with NCDs approximately a decade earlier than Caucasians, often before the age of 45 [2].

Among the NCDs, the global prevalence of diabetes has steadily gone up, with India contributing to a major part of the burden [3]. In the Southeast Asian countries, India is topmost among 5 countries, for the number of people with diabetes. One in every eleven adults has diabetes (about 90 million) in India and over 1 of every 2 (51.2%) adults living with diabetes are undiagnosed [4]. Currently, India has 101 million people with diabetes and 136 million with prediabetes [5].

The general risk factors for diabetes are physical inactivity, higher BMI, hypertension, dyslipidemia, imbalance in macronutrient intake, unhealthy dietary habits, insulin resistance and family history [3] [6]. The Global Burden of Diseases (GBD) study also identified the risk factors of diabetes such as high body mass index (BMI), dietary factors (diet low in fruits, nuts and seeds, and whole grains), alcohol use, occupational carcinogens, diet high in processed meat, low physical activity and tobacco use [7]. The fluctuations in blood glucose levels—glycemic variability (GV), also known as glycemic excursions, consist of episodes of hypoglycemia and hyperglycemia (including postprandial hypergly-

cemia). Studies indicate that intermittent high blood glucose has a detrimental effect that is worse than constant high blood glucose [8]. These glycemic excursions give rise to macrovascular conditions, such as coronary heart disease, stroke, peripheral arterial disease, and microvascular conditions, including diabetic kidney disease, retinopathy, and peripheral neuropathy [9]. Hence pursuing the best possible therapeutic intervention for glycemic control becomes imperative for persons with diabetes.

Besides medical treatment, an essential component of diabetes management comprises appropriate lifestyle and dietary changes [5] [10] [11]. The food-based dietary management, enhanced with evidence-based products, such as diabetes-specific nutrition supplements (DSNS), can help control the progression and severity of chronic diseases. With a low glycemic index (GI), these formulas match the diabetes dietary recommendations, are palatable and contain fiber, monounsaturated fatty acids (MUFAs) and/or polyunsaturated fatty acids (PUFAs), proteins, vitamins, and minerals in calorie-controlled portions [12] [13]. Elia *et al*. 2005 reported that short- and long-term use of DSNS as oral supplements or tube feeds are associated with improved glycemic control compared with standard formulas [14]. Dietary fiber is also known to increase the production of short chain fatty acids (SCFAs) and an abundance of SCFA-producing bacteria. The SCFAs can improve gut barrier integrity, glucose, and lipid metabolism, and regulate the immune system, the inflammatory response, and blood pressure which may thereby benefit cardio-metabolic health [15].

Efficacy of DSNS on glycemic, anthropometric and lipid profile markers has been reported in adults with prediabetes and diabetes [16]-[21]. This randomized, controlled, open-label, parallel group study was conducted to assess the impact of a DSNS on glycemic markers [fasting blood glucose (FBG), postprandial blood glucose (PPG), HbA1c, 24-hr incremental area under the curve (iAUC), mean amplitude of glycemic excursions (MAGE) and Time in and Above Range (TIR and TAR)], anthropometry [weight, BMI, waist circumference (WC)], lipid profile, dietary characteristics, SCFAs plasma and fecal and impact on gut microbiome in adults with diabetes, post a 12-week supplementation.

2. Methodology

This clinical trial was conducted in South Asian Indian adults with Type 2 Diabetes (T2D). The participants were randomized to receive either a DSNS along with the Standard Care (DSNS + SC; n = 105) or Standard Care alone (SC alone; n = 105). Refer CONSORT flow diagram (**Figure 1**).

This study was conducted at the Madras Diabetes Research Foundation (MDRF) (Chennai, India) between Jan.-Dec. 2023. It was performed in accordance with the protocol, Good Clinical Practice (GCP) guidelines [22], local regulations governing clinical conduct, and the ethical principles that have their origin in the Declaration of Helsinki. The study protocol was approved by the Institutional Ethics Committee of MDRF (Chennai, India), (ECR/194/Inst/TN/2013/RR-19)

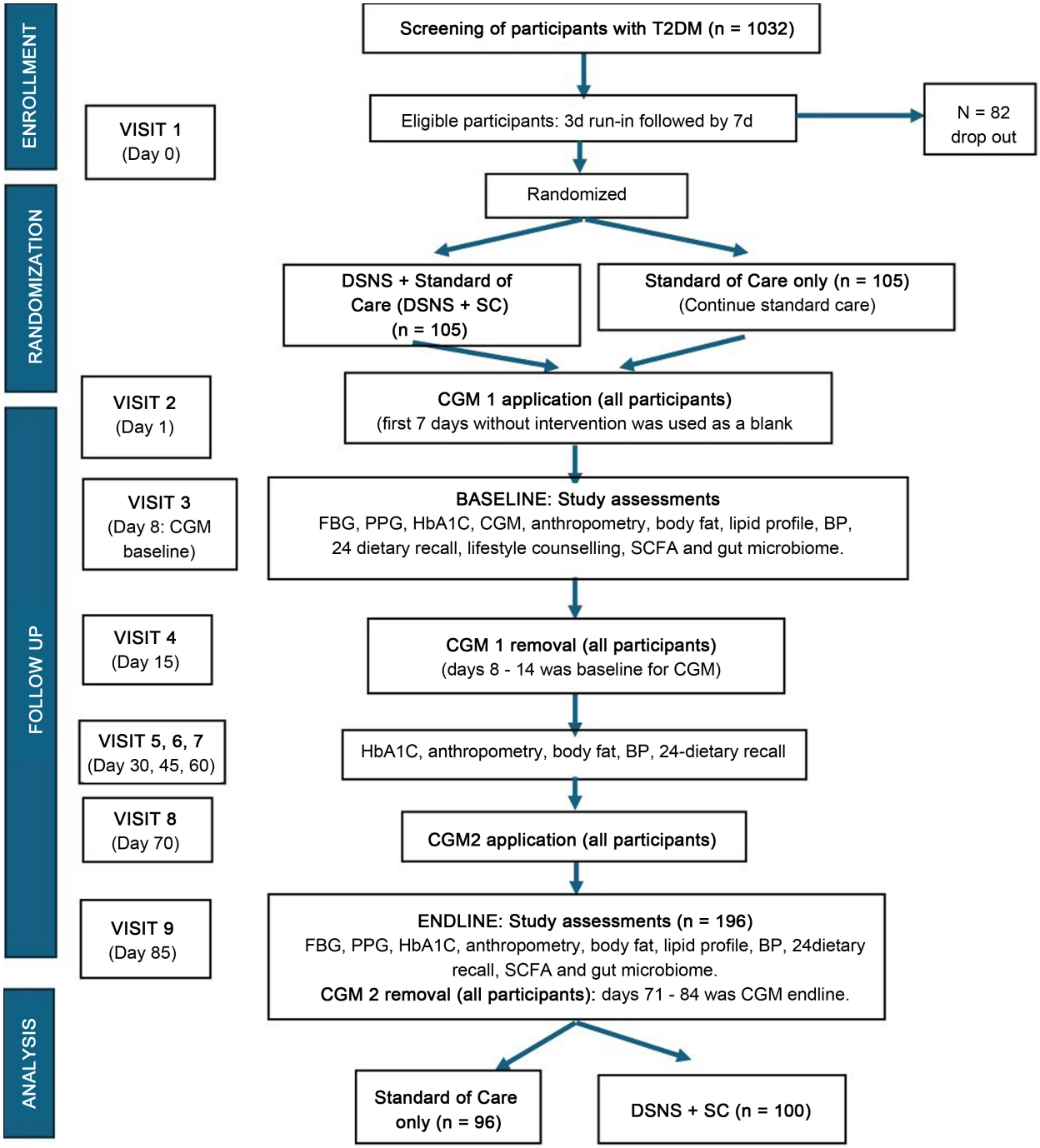


Figure 1. CONSORT 2010 flow diagram.

and protocol code NUN-HFD-003/22 [approval date, 24th November 2022]. The study objectives were explained to all participants, who voluntarily gave written informed consent prior to enrollment. The study was registered with the Clinical Trials Registry-India (CTRI) CTRI/2023/01/049210.

The primary objective was to evaluate the effect of DSNS + SC administered for 12 weeks on glycemic markers-FBG, PPG and HbA1c. Impact of DSNS + SC was also studied using a Continuous Glucose Monitoring (CGM) on measures

iAUC, MAGE and TIR and TAR as compared to the SC alone group. The secondary objectives were impact on body weight, BMI, WC, lipid profile, blood pressure, dietary intakes, and plasma SCFAs post 12 weeks supplementation. As exploratory variables, in a sub-sample [~5% of participants (n = 10: DSNS + SC = 5 and SC alone = 5)] fecal SCFA were assessed at baseline and at the end of the study. Impact of the DSNS was also assessed on gut microbiome in 2% of participants (from DSNS + SC) at baseline and endline. Fecal SCFA and gut microbiota results have not been included in this paper.

Glycemic Index (GI) of the DSNS is 34 making it a low GI [23] nutrition supplement (Horlicks Diabetes Plus provided by Hindustan Unilever Limited). It is a high fiber formula containing 22% soluble fiber and a high monounsaturated fatty acids (MUFA) composition (70% of total fatty acids delivering ~18% of energy). The carbohydrate delivers 40%, protein 23% and fat 25% of total energy. This formula has been designed basis the ICMR-INDIAB 2021 recommendations for T2D remission and prevention of progression to T2D in prediabetic and normal glucose tolerance (NGT) individuals [24]. Nutrition composition of DSNS is provided in **Table S1** (Supplementary material). Participants in the intervention arm, consumed 30 g of powder reconstituted in 200 mL water, twice daily. As a drink, the cost of the DSNS per serve is affordable and within the means of large segments of the diabetic population. The drink was recommended to be consumed in the morning (before breakfast) and at night (before bedtime). For each DSNS + SC participant, a measuring shaker (calibrated to 200 mL) was provided for reconstitution. Compliance was assessed via diary records kept by the participants.

The study included both males and females between 30 - 65 years with T2D established as FBG ≥ 126– ≤ 180 mg/dl, for at least one year. Participants on stable doses of oral hypoglycemic agents (OHA) for at least 3 months, willing to follow study protocol and provide informed consent were included. Participants with BMI < 18.0 kg/m^2 or >32.5 kg/m^2, on insulin injections, having alterations of dosages of OHA in the last 3 months, or suffered any acute infections like viral fever, typhoid, cold, diarrhea, constipation in the last one month or having diabetes induced/related complications, thyroid dysfunction, respiratory disorders, cancer or had a heart attack or stroke or having any eating disorder or lactose intolerance or consuming any herbal/ayurvedic/traditional preparation/nutrition supplements that could profoundly affect blood glucose or had a substance abuse problem (alcohol, smoking, tobacco) or were pregnant or lactating women or planning to relocate in the next 1 year or a long duration of travel out of town or enrolled in any other clinical trial or had participated in a clinical study in the last 3 months or employees of the site conducting the study were all excluded. Participants were instructed to make no major modifications in their routine diet and physical activity and refrain from feasting and fasting during the study period.

Sample size was calculated considering an average 10% reduction in FBG as

the outcome, 80% power, an alpha of 0.05 and a dropout rate of 15%. The required sample size was n = 178. The study recruited n = 210 [2 arms; Intervention arm (DSNS + SC) n = 105, receiving DSNS and control arm (SC alone) n = 105, receiving standard care for diabetes]. Eligible participants from site registers were contacted by phone and invited to attend a medical screening visit after which all participants who met the inclusion criteria were enrolled and randomized using computer generated random numbers into either DSNS + SC or SC alone group.

Eligible participants underwent a three-day run-in phase for the DSNS starting Day 0 (Visit 1) for 3 days. This was followed up by a 7-day washout. Objective of this run in was to assess acceptability, tolerance, and willingness to participate to ensure compliance throughout the study. Participants unwilling to consume the DSNS were considered as drop-outs (n = 82). Participants were randomized to either DSNS + SC or SC alone (**Figure 1**).

Ambulatory Glucose Profile (AGP) was monitored using a CGM device (Free style Libre Pro) for all participants. The participants reported at the study site on Day 1 (Visit 2) for application of the CGM device. The device recorded the glucose levels over 24 hours for a period of 14 days. They were instructed to keep the device on for 14 days. For obtaining a "true blank" baseline, the first 7 days of the CGM were without the DSNS supplementation in the DSNS + SC group. On Day 8 (Visit 3), all other study outcomes were measured so that it acted as the baseline for the remaining study parameters-FBG, PPG, HbA1C, anthropometry, body fat, lipid profile, BP, 24-dietary recall, SCFA and gut microbiome. DSNS consumption was initiated from Day 8 onwards in the intervention arm. The CGM was removed for all participants on Day 15 (Visit 3). It was re-applied in the last 14 days (day 70 - 84). These two phases acted as the baseline and endline for CGM data.

Weight was measured in kilogram using Omron digital weighing scale with a least count of 100 g. Height was measured in centimeters using a stadiometer (SECA Model 214, Seca Gmbh Co, Hamburg, Germany). The BMI was calculated using the formula BMI = Weight/Height^2 (in meters) (kg/m^2). Body fat (total and visceral fat) was determined using a leg-to-leg bioimpedance Omron digital scale (electronic OMRON; 171 Omron HBF 212, Tokyo, Japan). The WC was measured in centimeters using a non-stretchable tape. Systolic and diastolic blood pressure (BP) was measured in mmHg using the digital apparatus (Omron HEM 7120, Tokyo, Japan) once a month during the study period. All measurements were carried out in light clothing and no shoes. All variables were measured at baseline (day 8), day 30, 60 and endline (day 85). The plasma glucose was measured by the glucose oxidase peroxidase method; HbA1c was measured by high-performance liquid chromatography (HPLC) using a Variant machine (Bio-Rad, Hercules, CA, USA); serum cholesterol by the cholesterol oxidase peroxidase-4-aminophenazone, serum triglycerides by the glycerol phosphate oxidase-peroxidase-4-aminophenazone, high-density lipoprotein cholesterol (HDL)

directly with polyethylene glycol pre-treated enzymes using a Hitachi 912 Auto analyzer (Roche Diagnostics, GmbH, Mannheim, Germany) utilizing kits supplied by Boehringer Mannheim (Mannheim, Germany) and low-density lipoprotein (LDL) cholesterol was calculated using the Fried Wald formula in subjects with triglycerides ≤400 mg/d. A Free Style Libre Pro (manufactured by Abbott Healthcare Pvt. Ltd.) as a CGM device was used to assesses the interstitial fluid glucose concentration. 8 - 10 ml of blood was collected and analyzed for FBG and PPG (mg/dL), HbA1C [mmol/mol (%)], total cholesterol (mg/dL), triglyceride (mg/dL), LDL (mg/dL) and HDL (mg/dL) at baseline and at the end of 12 weeks.

Plasma SCFA at baseline and endline was analyzed using Gas Chromatography and Mass Spectrometry (GC-MS); AGILENT GCMS/MS 700D autoanalyzer, Acquity Labs. The amounts of SCFA have been reported as mmol/l. The amount of SCFA and the proportion and differences between the SCFA were used. Adverse events (AEs) were monitored at periodic intervals during the study. AE were recorded for both test and control arm participants.

Statistical Analysis

Statistical analyses were performed using SAS 9.4 (SAS Institute Inc.). Continuous variables were presented as mean ± SD, and categorical variables as percentages (n%). For variables with substantial variation, least square means with standard errors were provided. Baseline differences between the intervention and control groups were assessed using chi-square tests for categorical variables and independent two-sided t-tests for continuous variables. Changes within each group over time were evaluated using paired t-tests, while differences between groups were analyzed using generalized linear models.

The CGM data was presented in various ways including mean glucose levels, iAUC, and MAGE. The percent time each participant was within specific glucose ranges (e.g., 70 - 180 mg/dL or 3.9 - 10.0 mmol/L), hypoglycemia (<70 mg/dL or <3.9 mmol/L), and hyperglycemia (>180 mg/dL or >10.0 mmol/L) was also assessed. The mean 24-hour interstitial glucose (MIG) concentration was used to calculate iAUC, while MAGE was computed using a validated algorithm to measure glycemic variability.

3. Results

A total of 1,032 diabetic participants were screened, out of which 210 were randomly and equally assigned to one of the two study groups: DSNS + SC or SC alone. Refer to CONSORT Flow Diagram [25] (**Figure 1**).

3.1. Participant Characteristics and Demographics

At baseline, there were no significant differences between the two groups for gender distribution, body weight, BMI, WC, BP, FBG, PPG, lipid profile and dietary intake (**Table 1**). Both the groups were largely comparable at baseline.

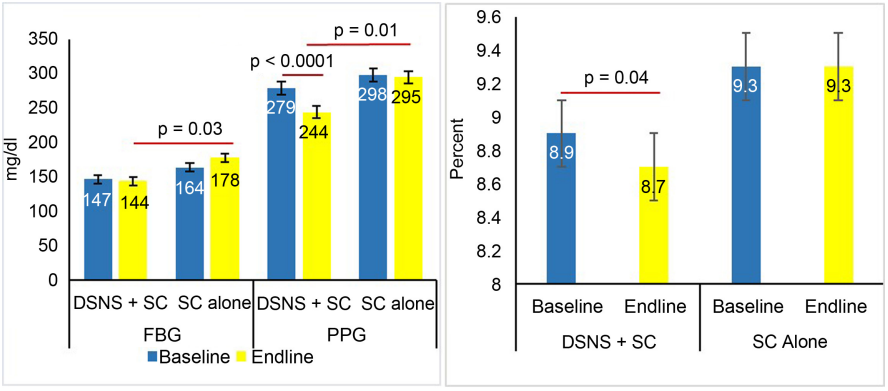
3.2. Glycemic Markers

3.2.1. Blood Biomarkers

After 12 weeks of consumption, the FBG, in the DSNS + SC exhibited a significant decrease as compared to the SC alone. While the SC alone showed an increase in FBG, the DSNS + SC showed a reduction or relatively well maintained FBG resulting in an overall decrease of 17.4 mg/dl. A similar response was noted for PPG also, which demonstrated a significant decrease (−31.8 mg/dl, $p < 0.01$) between the groups with DSNS + SC [−35.0 (9.0) mg/dl; $p < 0.001$] reporting a much higher reduction as compared to the SC alone [−3.0 (9.0) mg/dl; $p = 0.61$], at the end of 12 weeks consumption (Figure 2). HbA1C reduced significantly only in the DSNS + SC [−0.2 (0.1)%; $p = 0.04$], with SC alone reporting no change at all. There was no significant change observed between the groups (Figure 2).

Table 1. Baseline characteristics of the study participants (n = 210)-Intention to treat.

Variables	Units	DSNS + SC (n = 100)	SC alone (n = 96)	p-value
Age	Years	50.0 ± 9.0	53.0 ± 8.0	0.01
Male		44.0 (44.0)	45.0 (47.0)	0.69
Body weight	kg	69.1 ± 13.3	66.8 ± 13.5	0.22
Body mass index	kg/m^2	27.8 ± 4.2	27.2 ± 4.8	0.33
Waist circumference	cm	95.0 ± 10.2	93.4 ± 11.3	0.32
Systolic blood pressure	mmHg	125.0 ± 17.0	129.0 ± 17.0	0.06
Diastolic blood pressure	mmHg	81.0 ± 11.0	82.0 ± 9.0	0.47
Fasting blood glucose	mg/dL	148.0 ± 51.0	163.0 ± 68.0	0.08
Post prandial plasma glucose	mg/dL	280.0 ± 76.0	298.0 ± 93.0	0.14
Glycosylated hemoglobin HbA1c	%	8.9 ± 1.6	9.3 ± 1.7	0.06
Total Cholesterol	mg/dL	200.0 ± 47.0	200.0 ± 51.0	0.99
Triglyceride	mg/dL	5.0 (0.1)	5.0 (0.1)	0.93
High density lipoprotein cholesterol	mg/dL	46.0 ± 11.0	44.0 ± 12.0	0.35
Low density lipoprotein cholesterol		123.0 ± 40.0	120.0 ± 39.0	0.54
TC/HDL ratio	mg/dL	4.6 ± 1.4	4.7 ± 1.2	0.50
LDL/HDL ratio		2.8 ± 1.1	2.8 ± 1.0	0.86
Total energy	Kcal	1576.0 ± 484.0	1493.0 ± 331.0	0.16
Carbohydrates	g	251.0 ± 81.0	232.0 ± 53.0	0.05
Carbohydrates	%E	64.1 ± 5.8	63.0 ± 5.6	0.19
Total dietary fibre	g	24.7 ± 7.6	23.0 ± 7.0	0.22
Protein	g	49.0 ± 16.0	47.0 ± 13.0	0.33
Protein	%E	12.3 ± 1.5	12.4 ± 1.4	0.72
Total fat	g	45.0 ± 15.0	45.0 ± 15.0	0.68
Total fat	%E	25.6 ± 4.6	27.0 ± 4.6	0.05



(a) (b)

Figure 2. Differences in glycemic markers between groups (a) FBG and PPG (b) HbA1C. Data presented as Least Square Mean (LSM) ± Standard Error of Mean (SEM). p-value < 0.05 considered as significant using Generalized Linear Model (GLM). p-value < 0.05 considered as significant using paired t-test. Significant values are indicated between and within groups with red lines and p values indicated above.

3.2.2. CGM Markers

The comparison of CGM baseline (days 8 - 14) was made with CGM endline (days 78 - 84). The MIG in the first week of supplementation (days 8 - 14) showed highly significant differences between the two groups ($p = 0.0004$) along with TAR 180 ($p = 0.01$) and TAR 250 ($p < 0.0001$) TIR 70-180 ($p = 0.002$) (Table S2). Significant differences were reported for DSNS + SC and SC alone for MIG, iAUC, TAR 180, TAR 250 and MAGE. TIR 70-180 was observed to significant in the DSNS + SC [9 ± 40; $p = 0.0001$] and SC alone [−6 ± 42 mg/dl $p = 0.02$], however no differences between groups were observed. For MIG, while there was a significant reduction reported by DSNS + SC (−12.0 ± 65.0, $p = 0.001$), the SC alone reported a significant increase (28.0 ± 93.0, $p < 0.0001$) (Figure 3). Similarly, for TAR measures, for TAR 180 and 250, DSNS + SC reported a significant decrease [(−9.0% ± 42.0%, $p = 0.0001$) and (−3.0% ± 27.0%, $p = 0.04$)] respectively, with SC alone reporting a significant increase for both the measures. (Table S3). Both DSNS + SC and SC alone reported a significant reduction in the MAGE from baseline with DSNS + SC reporting a higher reduction (−19.0 ± 67.0, $p < 0.0001$) versus SC alone (−8.0 ± 70, $p = 0.04$). The iAUC reported significant differences between the groups ($p = 0.03$) with DSNS + SC reporting significantly lower iAUC (−192.0 (1.1), $p < 0.0001$) than that reported by control [−48 (1.1), $p = 0.03$] (Figure 3).

3.3. Anthropometric Markers and Blood Pressure

There were significant differences in weight [−0.8 (−1.2, −0.5) kgs; $p < 0.0001$] and BMI [−0.4 (−0.6, −0.2) kg/m^2; $p < 0.0001$] reported between the groups. The DSNS + SC reported a significant reduction versus baseline for both weight [−0.6 ± 0.1 kg; $p < 0.0001$] and BMI [−0.3 ± 0.1; $p < 0.0001$]. In addition, WC also reported significant differences between the groups [−0.5 (−1.0, −0.1) cm; $p = 0.01$] with DSNS + SC reporting a reduction and control reporting a minor

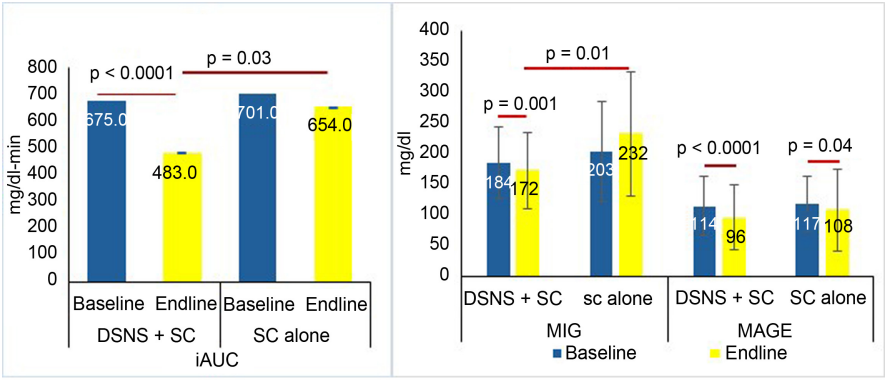


Figure 3. Differences in CGM markers between groups for days 8 - 14 for both CGM phases (a) iAUC (b) MIG and MAGE. (a) Data presented as Log transferred (standard error). And (b) Data presented as Mean ± Standard Deviation (SD). Significant values are indicated between and within groups with red lines.

increase. No changes were reported in the blood pressure (Table S4).

3.4. Lipid Profile

The key lipid profile markers studied were total cholesterol (TC), triglyceride, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), TC/HDL ratio and LDL/HDL ratio. Post supplementation, only the DSNS + SC reported a significant reduction in the LDL [−5.0 (3.0) mg/dL; $p = 0.03$] with control reporting no significant changes. No significant differences were reported for any other lipid profile measures (Table S4).

3.5. Dietary Characteristics

At baseline the 24-hour diet recall showed no differences in total energy, carbohydrate, protein and fat between the two groups. At endline, DSNS + SC showed significant reduction in carbohydrate intake [47.4 g (−67.1, −27.7); $p \leq 0.0001$], percent energy from carbohydrate [−9.4 (−11.3, −7.6); $p < 0.0001$] and fiber intake [9.5 (7.2, 11.8); $p < 0.0001$]. The protein intake was noted to be significantly higher in the DSNS + SC [4.0 (1.0) g; $p = 0.002$)] (Figure 4). While fat intake increased significantly ($p = 0.01$) in the SC alone (Table S5).

3.6. Plasma SCFAs

A total of eight short chain fatty acids (SCFAs) were assessed in the plasma at baseline and endline. All SCFA's except one (valeric acid) reported significant increase in the DSNS + SC as compared to baseline [Acetic acid: 0.2 (0.1) ng/ml, $p < 0.0001$; Propionic acid: 0.1 (0.1) ng/ml, $p < 0.0001$; Isobutyric acid: 0.3 (0.1) ng/ml, $p = 0.001$; Butyric acid: 0.1 (0.03) ng/ml, $p < 0.0001$; Isovaleric acid: 0.2 (0.1) ng/ml, $p < 0.0001$; 2-Methyl butyric acid: 0.2 (0.1) ng/ml, $p = 0.0004$ and Hexanoic acid: −0.2 (0.03) ng/ml, $p < 0.0001$. The SC alone reported no significant differences from baseline for any of the SCFAs except for hexanoic acid.

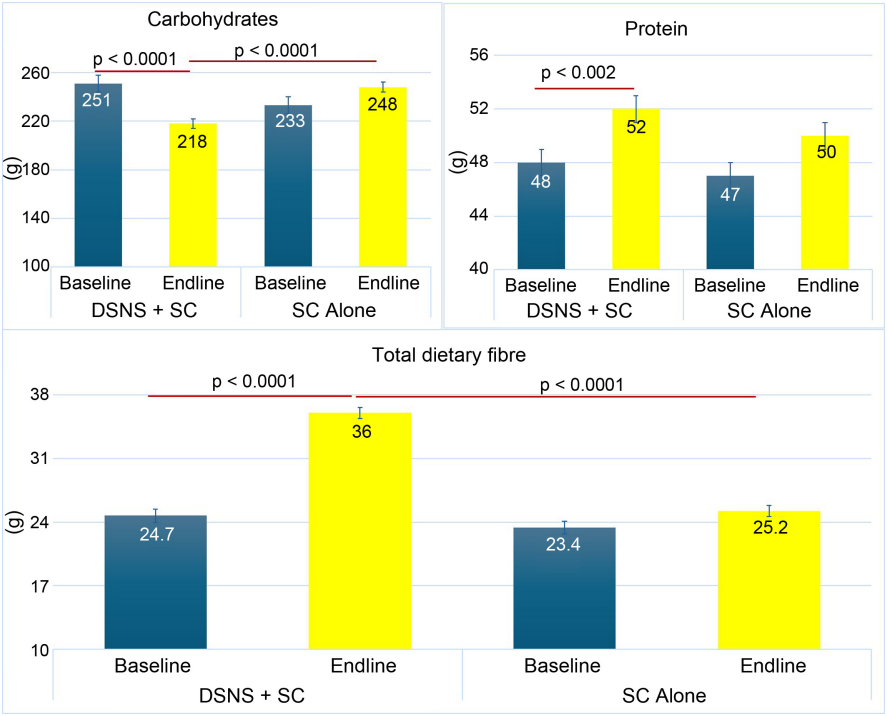


Figure 4. Dietary intake between groups at baseline and endline. Data are shown as Mean + SEM values. Total carbohydrate intake (g/day), total protein intake (g/day), total fat intake (g/day), total fibre intake (g/day). Significant values are indicated between and within groups with red lines. Differences in CG.

Table 2. Changes in plasma SCFA between groups (n = 192).

SCFA (ng/ml)*	DSNS + SC$ (n = 97)				SC alone (n = 95)				Between-group difference (95% CI)	Between-group p-value**
	Baseline (n = 97)	End of 12 weeks	Change	p-value	Baseline (n = 95)	End of 12 weeks	Change (n = 95)	p-value		
Acetic acid	4.6 (0.1)	4.8 (0.1)	0.2 (0.1)	0.0001	4.7 (0.1)	4.6 (0.1)	−0.1 (0.1)	0.74	0.3 (0.1, 0.5)	**0.04**
Propionic acid	3.2 (0.03)	3.3 (0.1)	0.1 (0.1)	<0.0001	3.3 (0.03)	3.1 (0.1)	−0.2 (0.1)	0.73	0.3 (0.1, 0.4)	**0.002**
Iso butyric acid	3.1 (0.1)	3.4 (0.1)	0.3 (0.1)	0.001	3.0 (0.1)	3.2 (0.1)	0.2 (0.1)	0.16	0.1 (−0.1, 0.3)	0.10
Butyric acid	2.6 (0.02)	2.7 (0.03)	0.1 (0.03)	<0.0001	2.8 (0.02)	2.8 (0.03)	0.0 (0.03)	0.13	0.1 (0.0, 0.2)	**0.02**
Iso valeric acid	2.7 (0.1)	2.9 (0.1)	0.2 (0.1)	<0.0001	2.7 (0.1)	2.7 (0.1)	0.0 (0.1)	0.44	0.2 (0.0, 0.4)	**0.002**
2-Methyl Butyric acid	2.3 (0.1)	2.5 (0.04)	0.2 (0.1)	0.0004	2.3 (0.1)	2.3 (0.1)	0.0 (0.1)	0.56	0.2 (0.0, 0.4)	**0.01**
Valeric acid	1.9 (0.02)	1.8 (0.03)	−0.1 (0.04)	0.58	1.8 (0.1)	1.8 (0.03)	0.0 (0.1)	0.52	−0.1 (−0.3, 0.0)	0.80
Hexanoic acid	2.3 (0.03)	2.1 (0.03)	−0.2 (0.03)	<0.0001	2.4 (0.03)	2.2 (0.03)	−0.2 (0.1)	0.0003	0.0 (−0.1, 0.1)	0.45
Sum of SCFA	4.7 (0.1)	4.8 (0.1)	0.2 (0.1)	<0.0001	4.8 (0.04)	4.7 (0.1)	−0.1 (0.1)	0.73	0.3 (0.1, 0.5)	**0.03**

*Data presented as Log mean (standard error); DSNS + SC taken nutritional beverage 2 times in a day. **p-Value < 0.05 considered as significant using Generalized Linear Model (GLM). p-Value < 0.05 considered as significant using paired t test. $Nutritional beverage (30 g) twice a day (before breakfast and before bedtime).

The DSNS + SC also reported significantly higher levels of SCFA as compared to SC alone for acetic acid: 0.3 (0.1, 0.5) ng/ml, p = 0.04; propionic acid: 0.3 (0.1,

0.4) ng/ml, $p < 0.002$; butyric acid 0.1 (0.0, 0.2); $p = 0.02$; isovaleric acid: 0.2 (0.0, 0.4) ng/ml, $p = 0.002$ and 2-methyl butyric acid: 0.2 (0.0, 0.4) ng/ml, $p = 0.01$ (Table 2). The sum of all SCFAs was also significantly different 0.3 (0.1, 0.5) $p = 0.03$, between the two groups with DSNS + SC reporting significantly higher levels post supplementation.

4. Discussion

In this study, supplementation of a DSNS (low GI, low carbohydrate, high protein, MUFA and fiber) along with standard care (DSNS + SC) was compared with standard care (SC alone). Efficacy of DSNS + SC on was assessed on the glycemic markers [FBG, PPG, HbA1C], anthropometry (weight, BMI, waist circumference), lipid profile, blood pressure, dietary intake and plasma SCFAs post 12 weeks supplementation. In the realm of diabetes management, fiber is a crucial component of a DSNS formulation. Dietary fiber, particularly soluble fiber, is known for its potential benefits in managing T2D. Soluble fiber forms a gel-like substance in the digestive tract, which can slow down the absorption of glucose, thereby helping to stabilize blood sugar levels after meals. Additionally, soluble fiber promotes a feeling of fullness, which can aid in weight management—a essential aspect of diabetes control.

The FBG showed a significant decrease in the DSNS + SC as compared to the SC alone. Despite the emphasis on adherence to the diet and exercise regimen for participants in both the groups, departures from the "standard" regimen cannot be prevented however, the DSNS + SC appears to potentially mitigate any variations in glucose response, controlling the FBG levels even when there are digressions from the "standard" regimen. Possibly the intake of the DSNS at bedtime is offsetting the glucose spikes aiding in the preservation of the FBG unlike in the SC alone where pharmacological intervention with lifestyle counselling seemed slightly weaker in countering the glycemic variations over the 12-week period. DSNS in this study providing 13.2 g of fiber per day, supported the maintenance of blood glucose levels and improved overall glycemic control as reported in previous studies [26] [27]. Postprandial hyperglycemia or spikes in glucose levels after meals poses a significant challenge in diabetes management, as it is closely linked to cardiovascular disease (CVD) and macroangiopathic complications [28]. Attenuating these spikes, especially those occurring two hours after a glucose challenge, is paramount for reducing the risk of CVD. The DSNS demonstrates promising results in this regard, showing a substantial difference in PPG compared to the SC alone, highlighting the efficacy of DSNS in reducing postprandial glucose levels.

The slow gastric emptying of fibre is possibly influencing glucose levels favorably reducing both FBG and PPG. The glycemic control by the fiber is exerted through increasing viscosity, that delays gastric emptying, and the absorption of glucose in the small intestine. Increases in viscosity can decrease conversion of maltodextrin to glucose by up to 35% and slow the interaction between diges-

tive enzymes and nutrients and, consequently, the breakdown of nutrients into components that will be absorbed in the brush border, including glucose [29].

The MIG in the DSNS + SC showed a significant reduction from baseline versus endline. Significant reductions were observed from the first week supplementation itself, indicating long term consumption is useful in controlling glycemic variability. MAGE, a marker for glycemic variability is designed to capture mealtime glucose excursions [30] and a significant indicator in vascular endothelial dysfunction and cardiovascular events in patients with diabetes mellitus [31] [32] The DSNS + SC exhibited higher efficacy with a greater reduction in MAGE versus SC alone. Therefore, there is a potential for the combination of DSNS with SC to slow down cardiovascular complications in patients with diabetes. Notably, in the SC alone, although the pharmacological agents did significantly mitigate MAGE ($p = 0.04$), there was a small significant increase [+10 (2.9), $p = 0.04$] in the levels of MIG over 12 weeks. This rise was not observed in the DSNS + SC where MIG remained static resulting in no significant differences within the group ($p = 0.11$), suggesting that a combination of DSNS (high fiber) with SC can help to control sugar levels, resisting any further upsurges.

Increases in dietary protein are known to promote postprandial insulin secretion that facilitates glucose regulation [33]. This effect is also observed in this study, where a significant increase in dietary protein was observed. The presence of MUFAs in DSNS, known for their ability to improve insulin sensitivity [34] could be another reason for improved glucose regulation. HbA1c levels similarly underwent a significant decrease over the 12-week period in the DSNS + SC, whereas no significant change was observed in the SC. Although the differences between the groups were not significant, these findings reinforce the notion that prolonged use of DSNS can enhance overall glycemic control.

In terms of body weight, while the SC alone showed a small increase in weight, the DSNS + SC showed a decrease in weight. This change may be attributed to alterations in the dietary patterns of the participants. The average 24-hour recall diet collected at different time points revealed that in the DSNS + SC, energy from carbohydrate intake decreased, with a concomitant increase in energy from protein. The primary cause of overweight/obesity is an increase in the energy absorption: energy expenditure ratio. Hence limiting energy absorption is critical to treat overweight/obesity. Fiber consumption may decrease energy absorption by way of diluting a diet's energy availability while maintaining other important nutrients [35]. The high MUFA content of DSNS + SC appears to act on satiety levels [36] along with the high fiber, consequently reducing the quantity of carbohydrates consumed during meals and resulting in weight loss. Dietary protein is an equally satiating macronutrient; its significant increase in the diet could also be the cause of reduction in calorie excesses, specifically from carbohydrates. The protein intake in the DSNS + SC increased by 4 g during the intervention period. Long-term use of the product could benefit weight loss in

individuals with diabetes.

The loss of visceral adipose tissue (VAT) is favored because of its adverse metabolic consequences, namely, the accumulation of VAT leads to inflammation and insulin resistance. The waist circumference, an indirect indicator of visceral fat, significantly reduced over a period of 12 weeks. Although the change seems extremely small, alterations using nutritional supplements alone are nevertheless noteworthy. Long-term use of the product may further decrease WC provided all other factors are well-maintained. LDL is influenced by genetic predisposition, dietary macronutrient intake, and body weight. The reduction in LDLs in the intervention arm is a likely consequence of the decrease in carbohydrate intake and reduced body weight. Thomsen *et al*. [37] indicated that lowered carbohydrate intake had weight-independent beneficial effects, namely, improved glycemic control and decreased circulating and intrahepatic triacylglycerol levels when compared with individuals with T2D on a standard care diet, along with an increase in protein intake and fat may also contribute to these changes. A similar effect was also observed in the DSNS + SC, where the carbohydrate intake in the participant decreased with consumption of DSNS + SC over a period of 12 weeks.

It is well established that gut microbiota in T2D differs from healthy individuals with lower diversity of the microbial community, altering gut homeostasis and contributes to the pathophysiology of T2D [38]. An effect of fiber metabolism in the gut by is the production of SCFAs such as acetate, propionate, and butyrate. They are by-products of bacterial fermentation, produced predominantly in the colon by members of the gut microbiota that use undigested dietary fiber as an energy source. These SCFAs play a vital role in modulating various physiological processes, including glucose metabolism. The interaction between dietary fiber, SCFAs, and diabetes is complex and multifaceted. Studies suggest that SCFAs may exert beneficial effects on glucose homeostasis by improving insulin sensitivity and enhancing glucose uptake in peripheral tissues [37]. The plasma SCFAs acetate, propionate and butyrate were found to be highly significant in the DSNS + SC. The highly significant amounts of plasma SCFA propionate ($p < 0.0001$ in DSNS + SC and $p = 0.002$ between groups) in combination with acetate, known to be involved in the regulation of appetite hormones (decreased ghrelin and elevated PYY), are possibly contributing to increased satiety, resulting in well-maintained energy intake ($p = 0.35$) in the DSNS + SC.

With the addition of the DSNS in the diet, there is a likelihood that the gut microbiome is favorably altered, influencing the plasma levels of important SCFA significantly. These fatty acids are versatile, for instance, acetate serves as an energy source and affects cholesterol and lipid metabolism. Butyrate acts on the gut barrier, gene expression, and colon health [39]. Propionate is important for gluconeogenesis (by down regulation) in the liver [40]. All three exhibit anti-inflammatory properties. Both propionate and acetate are required for appe-

tite regulation as well as lipid and cholesterol metabolism [41]. Increase of these SCFAs in the DSNS + SC indicate their role in the favorable changes in PPG, FBG, and LDL levels. Therefore, the high fiber content in the DSNS proved to be an extremely beneficial component, supporting overall glycemic response of patients with diabetes.

Strength of this study is that this has wider outcomes as it is an RCT which in addition to reporting the efficacy of a DSNS on the glycemic, anthropometric and lipid profile markers, also reports impact on plasma SCFA's. To the best of our knowledge this is the first study reporting improvement in gut health as measured plasma SCFAs using a DSNS. The 10-day run in-wash out period was an effective strategy as it ensured a high rate of compliance and a minimal loss to follow-up. While the study has been conducted on Indian diabetic participants, the results may be generalizable for South Asians owing to similarities in dietary patterns, food choices and genetics. As a limitation, this was 12-week intervention which reported a modest reduction in the HbA1C for the DSNS + SC. A longer intervention may be more effective in observing better improvements in HbA1C.

In summary, this DSNS, with its low GI, optimal blend of high fiber, protein, MUFAs, and low carbohydrate content, initiates a beneficial cascade effect and combined with SC can be a strategy for promoting overall glycemic control, weight management, and enhanced metabolic health. Its versatile nature makes it a convenient option for individuals with diabetes seeking balanced nutrition and improved well-being.

5. Conclusion

In conclusion, the study has demonstrated that after 12 weeks of DSNS + SC use, both FBG and PPG remained lower compared to SC alone, along with improvements in anthropometric parameters. Additionally, HbA1c and LDL levels showed improvements in the intervention group alone while plasma SCFAs improved significantly suggesting improved gut biome and health. These findings suggest promising implications of the DSNS as an adjunct therapy for patients with diabetes on regular oral medications.

6. Salient Features of the Present Study

- This is the first study reporting an improvement in gut health as measured by plasma SCFAs using a DSNS (to the best of our knowledge). Three key SCFAs (acetate, butyrate, propionate) along with the sum of all SCFAs showed a significant increase in the intervention as compared to the control.
- DSNS + SC group reported a significant improvement in all the glycemic markers (FBG, PPG, iAUC, MIG, TIR, TAR, MAGE) as compared to the control group receiving only standard of care.
- DSNS + SC group also reported a significant reduction in weight, BMI and waist circumference as compared to SC group.

- The glycemic markers using CGM showed significant improvement from the first week of supplementation in the DSNS + SC group versus the control group.
- DSNS + SC reported a significant decrease in carbohydrate energy % and its amount, an increase in dietary fiber and as well as an improvement in protein energy % versus SC alone.

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Authors' Contributions

D.K., H.S.G., S.V., G.R., J.B., K.J.R. and M.P, were primarily involved in the design and conceptualization of the study. S.V., G.R., J.G.R., P.K., D.V., A.R.M. and V.M. were involved in data collection, study conduct, protocol execution, quality checks and data verification. A.K. was responsible for the statistical analysis of results. J.B. and D.K. were involved in operational decision making during the conduct of the study. S.V., A.K., G.R., J.R.G., P.K., D.V., A.R.K. and V.M. interpreted the study results and participated in data curation. M.P., D.K., S.V., A.R.M. and V.M. were overall responsible for the conduct of the study ethically and scientifically. H.S.G. drafted and led the manuscript for its intellectual content, literature searches and graph generation. H.S.G. and D.K. jointly led the manuscript creation and carried out interpretations regarding intellectual content. 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

Study was performed in accordance with the protocol, Good Clinical Practice (GCP) guidelines, local regulations governing clinical conduct, and the ethical principles that have their origin in the Declaration of Helsinki. The study protocol was approved by the Institutional Ethics Committee of MDRF (Chennai, India), (ECR/194/Inst/TN/2013/RR-19) and protocol code NUN-HFD-003/22 [approval date, 24th November 2022]. The study objectives were explained to all participants, who voluntarily gave written informed consent prior to enrolment. The study was registered with the Clinical Trials Registry-India (CTRI) CTRI/2023/01/049210 (CTRI).

Informed Consent Statement

The informed consent form was reviewed and approved by the Institutional Ethics Committee of MDRF (Chennai, India). All participants voluntarily gave written informed consent prior to enrolment.

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., H.S.G., K.J.R., J.B., M.P. declare potential conflicts of interest as employees of Hindustan Unilever Limited (HUL), the study sponsor. All other authors declared no potential conflict of interest.

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Supplementary Tables

Table S1. Nutrient composition of diabetic specific nutritional supplement.

Composition	Units	DSNS (100 g)
Energy	kJ (kcal)	1490.2 (356.0)
Protein	g	20.0
Fat	g	10.0
MUFA	g	7.0
Carbohydrates	g	35.5
Total Dietary Fiber	g	22.0

Table S2. Comparison of CGM derived parameters in DSNS + SC versus SC alone post 1 week of DSNS supplementation.

Variables	DSNS + SC (n = 68)	SC alone (n = 69)	p-value
Mean	184 ± 59	203 ± 81	0.0004
Time above 180 range	46 ± 34	53 ± 38	0.01
Time above 250 range	19 ± 25	29 ± 33	<0.0001
Time in 70 - 180 range	51 ± 32	43 ± 35	0.002
#IAUC	675 (1.0)	701 (1.0)	0.40
MAGE	114 ± 49	117 ± 45	0.53

Data presented as Mean ± SD. #Data Presented as Log transferred (standard error). p-value is tested using independent t-test. Calculate as average of Day 8 to Day 14.

Table S3. Comparison of mean change in CGM derived parameters between baseline (days 8 - 14) and endline (days 78 - 84) between the study groups.

Variables	DSNS + SC (n = 68)				SC alone (n = 69)				Between group differences 95% CI	Between group p-value
	Base	End	Change	p-value	Base	End	Change	p-value		
Mean interstitial glucose mg/dl	184 ± 59	172 ± 63	−12 ± 65	0.001	203 ± 81	232 ± 102	28 ± 93	<0.0001	−40.5 (−69.2, −11.8)	0.01
Time above 180 range	46 ± 34	37 ± 38	−9 ± 42	0.0001	53 ± 38	61 ± 40	7 ± 45	0.003	−16.4 (−32.0, −0.8)	0.04
Time above 250 range	19 ± 25	16 ± 27	−3 ± 27	0.04	29 ± 33	38 ± 42	9 ± 38	<0.0001	−11.9 (−23.6, −0.2)	0.05
#iAUC	675 (1.0)	483 (1.0)	−192 (1.1)	<0.0001	701 (1.0)	654 (1.0)	−48 (1.1)	0.54	−176.6 (−336.6, −16.6)	0.03
MAGE	114 ± 49	96 ± 52	−19 ± 67	<0.0001	117 ± 45	108 ± 67	−8 ± 70	0.04	−10.6 (−31.2, 9.9)	0.31

Data presented as Mean ± SD. #Data Presented as Log transferred (standard error). Within group p-value is tested using Paired T-test and between group p-value is tested using GLM. Base and End is calculated average of Day 8 to Day 14.

Table S4. Adjusted mean change in anthropometry & lipid profile (n = 196).

Variables	DSNS + SC[$] (n = 100)		SC alone (n = 96)		Between-group difference (95% CI)	Between-group p-value*
	Change from Baseline.	p-value	Change from Baseline.	p-value		
Glycemic Markers						
Fasting blood glucose (mg/dL)	−3.0 (6)	0.53	14.0 (6)	0.06	−17.4 (−33.3, −1.4)	**0.03**
Post prandial plasma glucose (mg/dl)	−35.0 (9)	**<0.0001**	−3.0 (9)	0.61	−31.8 (−56.1, −7.5)	**0.01**
Glycosylated hemoglobin HbA1c (%)	−0.2 (0.1)	**0.04**	0.0 (0.1)	0.78	−0.2 (−0.6, 0.1)	0.18
Anthropometry and blood pressure						
Body weight (kg)	−0.6 (0.1)	**<0.0001**	0.2 (0.1)	0.07	−0.8 (−1.2, −0.5)	**<0.0001**
Body mass index (kg/m^2)	−0.3 (0.1)	**<0.0001**	0.1 (0.1)	0.08	−0.4 (−0.6, −0.2)	**<0.0001**
Waist circumference (cm)	−0.3 (0.2)	0.09	0.2 (0.2)	0.09	−0.5 (−1.0, −0.1)	**0.01**
Systolic blood pressure (mmHg)	1.0 (1)	0.61	0.0 (1)	0.91	1.1 (−2.9, 5.0)	0.60
Diastolic blood pressure (mmHg)	−1.0 (1)	0.40	1.0 (1)	0.32	−1.6 (−4.0, 1.3)	0.31
Lipid Profile						
Total Cholesterol (mg/dl)	−6.0 (3)	0.08	−3.0 (3)	0.31	−2.5 (−11.8, 7.0)	0.61
[#]Triglyceride (mg/dl)	0.0 (0.0)	0.77	0.0 (0.0)	0.95	0.1 (0.0, 0.2)	0.77
High density lipoprotein cholesterol (mg/dl)	0.0 (1)	0.56	−1.0 (1)	0.10	1.3 (−0.7, 3.2)	0.20
Low density lipoprotein cholesterol (mg/dl)	−5.0 (3)	**0.03**	−1.0 (3)	0.67	−3.7 (−11.0, 3.7)	0.33
TC/HDL ratio	0.1 (0.1)	0.55	0.2 (0.1)	0.21	−0.1 (−0.3, 0.2)	0.68
LDL/HDL Ratio	0.0 (0.1)	0.71	0.1 (0.1)	0.14	−0.1 (−0.3, 0.1)	0.39

Data presented as LS mean ± SEM; [#]Log transferred mean (SEM). Outcome adjusted for Baseline Age. *p-Value < 0.05 considered as significant using Generalized Linear Model (GLM). p-Value < 0.05 considered as significant using paired t test. [$]Nutritional beverage (30 g) twice a day (before breakfast and before bedtime).

Table S5. Adjusted mean change in dietary characteristics (n = 196).

Variables	DSNS + SC[$] (n = 100)		SC alone (n = 96)		Between-group difference (95% CI)	Between-group p-value*
	Change from Baseline	p-value	Change from Baseline	p-value		
Total Energy (Kcal)	36.0 (42)	0.35	108.0 (43)	0.01	−72.3 (−192.6, 48.0)	0.24
Carbohydrates (g)	−33.0 (7)	**<0.0001**	15.0 (7)	0.02	−47.4 (−67.1, −27.7)	**<0.0001**
Carbohydrates (%E)	−9.4 (0.6)	**<0.0001**	0.0 (0.7)	0.99	−9.4 (−11.3, −7.6)	**<0.0001**
Total dietary fibre (g)	11.3 (0.8)	**<0.0001**	1.8 (0.8)	0.06	9.5 (7.2, 11.8)	**<0.0001**
Protein (g)	4.0 (1)	**0.002**	3.0 (1)	0.07	1.1 (−3.0, 5.3)	0.60
Protein (%E)	0.7 (0.1)	**<0.0001**	−0.2 (0.2)	0.31	0.9 (0.5, 1.3)	**<0.0001**
Total Fat (g)	1.0 (2)	0.30	5.0 (2)	0.01	−4.1 (−8.9, 0.7)	0.09
Total Fat (%E)	−0.8 (0.5)	0.14	0.8 (0.6)	0.19	−1.6 (−3.1, −0.1)	0.05

Data presented as LS mean ± SEM; *p-Value < 0.05 considered as significant using Generalized Linear Model (GLM). p-Value < 0.05 considered as significant using paired t test. Outcome adjusted for Baseline Age [$]Nutritional beverage (30 g) twice a day (before breakfast and before bedtime).