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Randomized Controlled Trial

Premeal almond load decreases postprandial glycaemia, adiposity and reversed prediabetes to normoglycemia: A randomized controlled trial☆

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SUMMARY

Background: Asian Indians show rapid conversion from prediabetes to type 2 diabetes (T2D). Novel dietary strategies are needed to arrest this progression, by targeting postprandial hyperglycaemia (PPHG).
Design: We conducted a free-living randomized controlled open-label parallel arm study to evaluate the effect of a premeal load of almonds (20 g) 30 min before major meals on anthropometric, glycaemic, and metabolic parameters over 3 months. Sixty-six participants with prediabetes in the age range of 18–60 yrs were recruited. The study was registered at clinicaltrials.gov (registration no. NCT04769726).
Results: Thirty participants in each arm completed the study. As per 'intention-to-treat' analysis, overall additional mean reductions were statistically significant for body weight, BMI, waist circumference (WC), subscapular and suprailiac skinfolds, and improved handgrip strength (Kg) ($p < 0{\cdot}001$ for all) in the treatment arm *vs.* the control arm (after multiple adjustments). In the blood parameters, the additional mean reduction in the treatment arm *vs.* control arm was statistically significant for fasting and post-75 g oral glucose-load blood glucose, postprandial insulin, HOMA-IR, HbA1c, proinsulin, total cholesterol, and very low-density lipoprotein cholesterol ($p < 0{\cdot}001$ for all). Most importantly, we observed a reversal to normoglycemic state (fasting blood glucose and 2 h post-OGTT glucose levels) in 23.3% (7 out of 30) of participants in the treatment arm which is comparable to that seen with Acarbose treatment (25%).
Conclusion: Incorporation of 20 g of almonds, 30 min before each major meal leads to significant improvement in body weight, WC, glycemia (particularly PPHG), and insulin resistance and shows potential for reversal of prediabetes to normal glucose regulation over 3 months.

1. Introduction

Sustained hyperglycaemia plays an adverse role in the development and progression of microvascular and macrovascular complications in patients with type 2 diabetes (T2D) [1]. Characteristically, the magnitude of postprandial hyperglycaemia (PPHG) in Asian Indians is higher than in other ethnic groups [2,3]. Among lean young adults of 5 different ethnic origins (European Caucasians, Chinese, Southeast Asians, Asian Indians, and Arabic Caucasians), a 75 g white bread carbohydrate challenge showed that Southeast Asians had the highest PPHG and lowest insulin

Abbreviations: PPHG, postprandial hyperglycaemia; T2D, type 2 diabetes; IGT, impaired glucose tolerance; CV, cardiovascular; HbA1C, glycosylated haemoglobin; BMI, body mass index; FBG, fasting blood glucose; OGTT, Oral glucose tolerance test; FFQ, Food frequency questionnaire; SMBG, Self-monitoring of blood glucose; HOMA-βCF, Homeostasis model assessment- β-cell function; ELISA, Enzyme linked immunosorbent assay; EDTA, Ethylenediamine tetraacetic acid; hs-CRP, High sensitivity C-reactive protein; TNF-α, Tumor necrosis factor alpha; DI, Disposition index; GLP-1, Glucagon like peptide; MUFAs, Monounsaturated fatty acids; CCK, Cholecystokinin.

☆ Data described in the manuscript, code book, and analytic code will be made available upon request pending approval of the paper.

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sensitivity; whereas European and Arabic Caucasian participants were the most insulin sensitive and carbohydrate tolerant [4,5].

Of note, PPHG contributes substantially to overall glycemia in patients suffering from mild or moderate hyperglycaemia [6], and has been shown to produce equal or more harmful effects than fasting hyperglycaemia [7]. PPHG occurring in individuals with impaired glucose tolerance (IGT), has been shown to double the risk for cardiovascular (CV) mortality. A meta-analysis (n, 9600 from prospective studies, 1966–1996) showed a progressive relationship between glucose levels and CV risk that extended far below the current thresholds for diabetes [8]. In fact, compared with a fasting plasma glucose level of 4.2 mmol/l (75.6 mg/dL), fasting plasma glucose of 6.1 mmol/l (109.8 mg/dL) and 2 h post–challenge glucose of 7.8 mmol/l (140.4 mg/dL) were associated with a relative CV event risk of 1.3 (95% confidence interval 1.1–1.7) and 1.6 (95% confidence interval 1.2–2.1), respectively. These results are supported by the findings that, even in patients within the range of normal glucose tolerance, the severity of coronary heart disease correlates with higher levels of glycosylated haemoglobin (HbA1c) and post–challenge glucose levels [9]. Importantly, PPHG also appears to be the rate-limiting factor for achieving optimal glycaemic control in T2D [10].

T2D has been increasing worldwide and in India [3]. Asian Indians have an increased risk of T2D at a much lower BMI than whites [11]. An annual progression rate of about 12–18% from IGT to T2D has been seen for south Asians [12–14] which is substantially higher than the progression rate of about 5–11% observed in individuals of white European origin with IGT. Further, Asian Indians are comparatively more insulin resistant and have higher subclinical inflammation than other ethnic groups [15]. Thus, early intervention for the prevention of diabetes from prediabetes is particularly important for this ethnic group.

Dietary carbohydrate intake is a primary determinant of PPHG and thus remains a nutrient of concern for patients with T2D [21]. It is important to consider the macronutrient composition of Indian diets in the context of PPHG and associated metabolic perturbations and insulin resistance [16]. A typical Indian major meal largely comprises of starchy foods, consisting of high amounts of carbohydrates [4,17]. In the STARCH (Study To Assess the dietary CarboHydrate) study, carbohydrates constituted 64.1% of the total energy in Indian patients with T2D [4]. In a study from the UK, in which 7-d weighed intakes in 173 South Asian *vs.* European men aged 40–69 y were measured, starch intake was higher (28.0% *vs.* 21.5% of energy, $p < 0.001$), and higher serum insulin concentrations at 2 h post glucose were associated positively with carbohydrate intake in the former ($p = 0.001$) [17].

Low-carbohydrate diets are effective for improving glycemic control, in addition to reducing body mass and blood lipids [18]. However, there is general apprehension surrounding the adoption of a low-carbohydrate diet given that carbohydrates are commonly substituted with increasing amounts of dietary fat. With this in mind, and considering the relatively poor long-term adherence to restrictive and intensive diets [19], there is a need for alternative strategies that might be effective in reducing exposure to PPHG.

Previously, approaches to reduce PPHG in patients with diabetes have included improving insulin sensitivity (via exercise and weight loss), limiting total carbohydrate intake, and use of postprandial glucose regulator drugs like Acarbose, Nateglinide, Repaglinide, etc. (Table 1) Consumption of tree nuts provides us with novel opportunities for research on PPHG. To date, there are 6 studies (2 studies on healthy participants, 2 studies on patients with T2D, and 2 were conducted on participants with prediabetes) in which the effect of almond consumption on PPHG has been researched [20–25]. Of note, none has been carried out on Asian Indians/South Asians. There is only one study available in which a premeal load of almonds (similar to the present study) was used to see effects on postprandial glucose excursions in participants with prediabetes. In this study, Crouch et al. [23] showed that a premeal load of 15 g of almonds decreased 2 h blood glucose value by 14.1% and isolated 1 h postprandial hyperglycemia by 19.4% in individuals with prediabetes. However, in this study acute response of a premeal load of 15 g of almonds was evaluated and effects on 24 h glycemia and long-term effects were not studied. On the other hand, there are several studies that show that the incorporation of almonds in diets, not as a premeal load, may decrease PPHG [20–23,25]. In our previous study on intervention with almonds (20% of energy/day) over a period of six months, we observed a significant decrease in HbA1c and a small decrease in fasting blood glucose (FBG), but postprandial glucose levels were not measured in that study [26].

Considering the findings of our previous study of 6 months [26] and limited-time study by Crouch et al. [23] we hypothesized that dietary intervention with a premeal load of almonds (before breakfast, lunch and dinner daily) will decrease the glucose and insulin excursions after meals, and thus reduce overall hyperglycemia.

2. Methodology

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and Ethical Guidelines for Biomedical Research for Human Participants as enunciated by the Indian Council of Medical Research, New Delhi, India. All procedures involving human participants/patients were approved by an independent review committee, 'Ethics Committee for Human Research'. Written informed consent forms, approved by the ethics committee, were signed by the participants. The study was initiated in January 2018 and was completed in June 2021. The study was registered at clinicaltrials.gov (registration no. NCT04769726, available at https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S000AO3N&selectaction=Edit&uid=U0000VVL&ts=4&cx=-hrv1fh).

We screened 1317 participants, out of which 1171 were screen failures that did not fulfill the inclusion/exclusion criteria. Sixty-six participants gave their consent for the study and were recruited. Out of sixty-six participants, sixty participants with confirmed prediabetes completed the study (28 males and 38 females, aged between 18 and 60 y). Prediabetes was diagnosed on oral glucose tolerance tests (OGTT) according to the following criteria; FBG $\geq$100 mg/dL and <126 mg/dL and 2 h post-OGTT blood glucose (2 h-POGTTBG) (after ingestion of 75-g anhydrous oral glucose mixed in 200 ml water), 2 h-POGTTBG $\geq$140 mg/dL and<200 mg/dL, the latter criterion being mandatory for inclusion in the study [27]. Those with known diabetes, acute infections, advanced end-organ damage, history of pancreatitis, significant renal and liver disease, recent (<3 months) changes ($\geq$5%) in weight and/or on weight- changing medications, any known allergy to nuts, having uncontrolled hypertension or hypothyroidism were excluded from the study. This study was conducted at National Diabetes, Obesity and Cholesterol Foundation (NDOC, www.n-doc.org), Delhi, India. Out of the 66 recruited, all had IGT, 36 participants only had IGT with normal FBG and 30 had both impaired fasting glucose tolerance (IFG) and IGT.

This was a free-living randomized (using block randomization with variable block size) controlled open- label parallel arm study to evaluate the effects of the premeal load of almonds on hyperglycemia over 3 months. Participants fulfilling the inclusion/exclusion criteria were randomized to either the control arm or the treatment arm after a run-in period of 2 weeks. Participants were given dietary

Table 1
Effect of postprandial glucose regulator drugs and premeal load of almonds on glucose parameters and body weight.

PP regulators	Fasting blood glucose (mg/dL)	Postprandial blood glucose (mg/dL)	Glycosylated Hemoglobin (HbA1c %)	Body weight (kg)	Waist circumference (cm)
Acarbose (T2D) Hanefeld et al. 1991 [51] and Talaviya et al. 2015 [52]	19.4–25.2	↓ 28.0–61.2	0.7–0.8	↓ 1.5	N/A
Acarbose (Prediabetes) Chiasson et al. 2007 [53]	N/A	Mean change than placebo; ↓ 0.6	N/A	Mean change than placebogroup; ↓ 1.2	Mean change than placebogroup; ↓ 0.6
Repaglinide and metformin (T2D) Frandsen et al. 1999, [54] Landgraf et al. 2000 [55], Ma et al. 2014 [56]	↓ 22.7–49.7	↓ 66.1	↓ 1.2–1.1	↓ 1.2 kg	N/A
Nateglinide (Prediabetes) Rury et al. 2010 [57]	Mean change than placebo; ↓ 0.5	Mean change than placebo; ↑ 4.4	Mean change than placebo; ↓ 0.2	No significant change	No significant change
Nateglinide (T2D) Horton SE et al. [58]	↓ 12.6	N/A	↓ 0.5	N/A	N/A
VogliboseT2D Talaviya et al. 2015 [52]	6-month: ↓ 15.7 9-month: ↓ 20.6	6-month: ↓ 32.6 9-month: ↓ 44.1	6-month: ↓ 0.3 9-month: ↓ 1.1	6-month: ↓ 3.0 9-month: ↓ 4.3	–
Premeal load					
Almond (Prediabetes) Crouch et al. 2016 [23]	↓ 2.9	1 h: ↓ 37.1 2 h: ↓ 19.5	N/A	N/A	N/A
Almond (healthy adults) Liu et al. 2017 [59]	N/A	N/A	N/A	week 8: ↓ 0.5 week 16: ↓ 0.6	N/A
Soya-Yogurt (T2D) Chen et al. 2010 [60]	N/A	↓ 18	N/A	N/A	N/A
Almonds along with meals					
Almond (T2D) Gulati et al. 2017, Chen et al. 2017 [61], Li et al. 2010 [62]	↓ 0.4–7.2	N/A	↓ 0.1–0.3	↓ 0.6–0.8	↓ 0.6–1.3
Almond (Prediabetes) Gulati et al. 2022 (current study)	↓ 6.3	↓ 26.8(2.6, 78.9)	↓ 0.4 (0.6–0.3)	↓ 3.9 (4.1, 2.4)	↓ 2.8 (1.2,7.1)

↓ decrease; ↑ Increase; NA, data not available.

advice at the time of enrolment. During the run-in period, all participants consumed a standard diet formulated according to the guidelines for Asian Indians [28], which was continued in the control arm for a further 3 months. Dietary counseling was provided to all participants according to height, weight, and physical activity levels. Instructions were given verbally and in written form and were discussed in detail individually and during group meetings. The general qualitative recommendations for both control and treatment diet arms were to consume a diet rich in vegetables and fruits; select whole-grain, high-fiber foods; select fat-free or low-fat dairy products; and limit foods containing partially hydrogenated vegetable oils; and to curtail consumption of sugar-sweetened beverages. All participants (control and treatment arm) were asked to visit the study site once in 30 days when dietary advice was further reinforced. The participants were advised 45 min of brisk walking daily. Physical activity was assessed using the Global Physical Activity Questionnaire throughout the study during their monthly visits to the study site (not shown in the results). Diet and exercise status was assessed telephonically on a biweekly basis, through text messages and face-to-face interactions (once every month), and by cross-checking with the spouse or a close relative of the subject in both study arms (Fig. 1).

Dietary composition (% energy) was as follows – control diet: carbohydrates, 50; fat, 35; and protein,15; and treatment diet (including preload of almonds): Carbohydrates, 49; fat, 32; and protein, 19. Participants assigned to the treatment arm were given pre-weighed packets of raw unsalted almonds 20 g almonds (about 17–18 in number) and were instructed to take a packet of 20 g almonds 30 min before breakfast, lunch, and dinner, and chew it over 5 min. The nutritional information of 20 g and 60 g almonds has been provided in Table 2. Participants were instructed not to consume any other nuts in the Intervention arm and nuts in any form in the control diet arm. Dietary data were collected using 24 h dietary recall and FFQ at enrolment, baseline, and once every month during the study. The purpose of the FFQ was to check the pattern of food consumption at each point of contact. Diet data collected using 24 h dietary recall (analyzed using software, 'DietCal' version 5.0; Profound Tech Solution; http://dietcal.in/) based on values from the Nutritive Value of Indian Foods [29] are presented in Table 3. Participants' information was recorded in a call log and in case report forms, and regularly reviewed by the study coordinators. Participants were asked to bring empty pouches of the almonds given as an investigation product at the time of their visit to the study site. All the participants in the treatment arm were given a sufficient quota of almond packs to last for 30 days along with some extra packets for their family members to ensure good compliance. Participants met with the investigators monthly to provide updates on diet and lifestyle compliance, and for general check-ups. Acceptability of the diet was good (85%), as almonds were convenient to carry to the workplace, taste good, and are generally considered as nutritious food. Betterment of PPHG was a motivational factor leading to good compliance in most

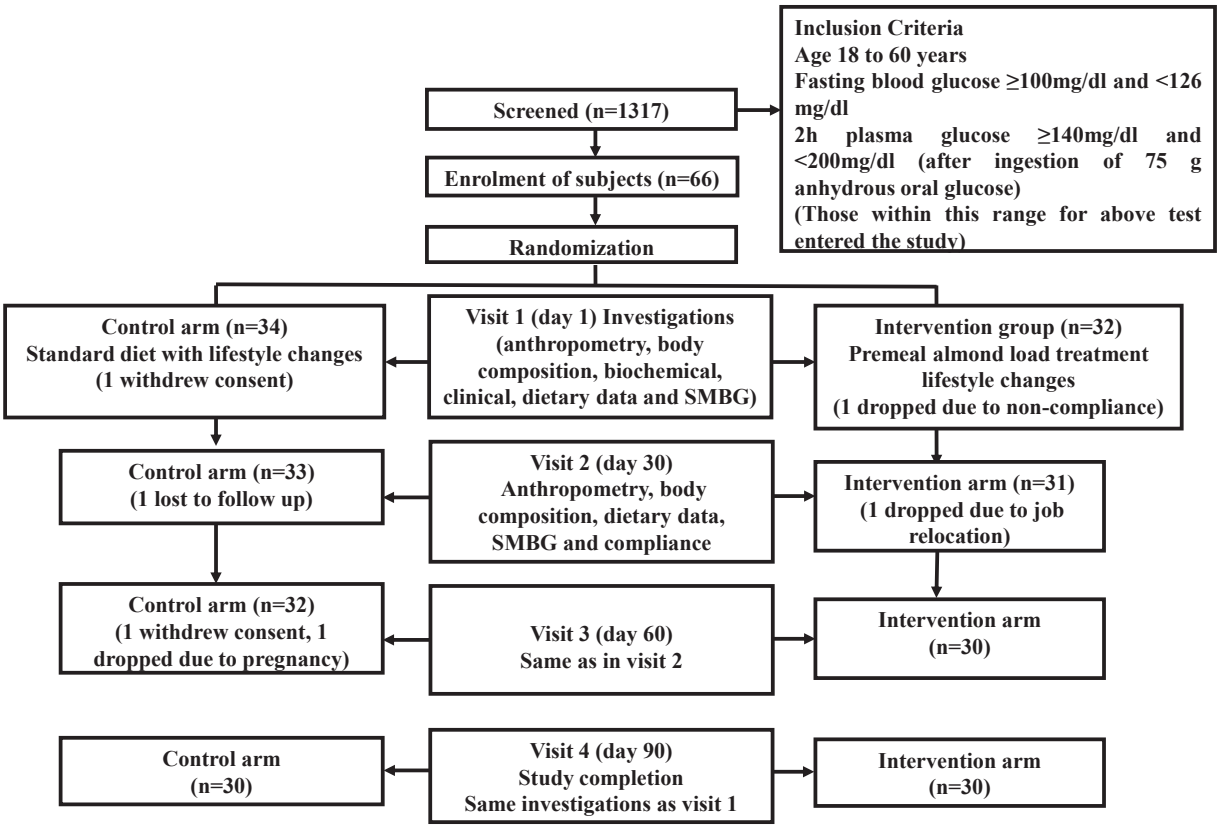

Fig. 1. Flow Diagram of the Study. The flow chart shows 90 days plan for the randomized controlled parallel arm study. After initial screening eligible participants were randomized to premeal almond load treatment and the control diet. They were followed up for 90 days. Participants were asked to record activity, mealtime, and almond preload timings, which was indicated in Fig. 3. There were six dropouts in the study. Out of sixty-six recruited participants, sixty participants completed the study.

Table 2
Nutritional information of 20 g and 60 almonds.

Almond	Energy	Protein	Fat	Carbohydrate	Fiber
20 gm	131	4.2	11.8	2.1	0.3
60 gm	393	12.5	35.4	6.3	0.9

Source: Nutritive value of Indian foods [29].

participants. The diet and exercise records were maintained in a compliance log. Based on this log, compliance ranged from 80 to 90% of days (averaging about 85%). There was no difference in compliance between the treatment and control arms.

Participants were provided with a glucose meter (Contour Plus One blood glucose meter, Ascensia Diabetes Care Holdings AG, Switzerland) to monitor their blood glucose levels during the 3-months intervention period. Instructions were given so that within 90 days of the intervention period, all the participants could record 30 readings of blood glucose in fasting state, 30 readings 2 h after lunch, and 30 readings 2 h after dinner. Data on self-monitoring of blood glucose (SMBG) are presented in Fig. 2. All the participants were given a diary to record their food intake including almond intake, and their blood glucose levels. No adverse effect was reported.

All anthropometric [height, weight, circumferences (waist, hip, mid upper arm) skinfolds], body fat estimation, and biochemical measurements were taken as previously and sum of skinfolds was calculated [30]. Waist circumference was measured midway between the iliac crest and the lowermost margin of the ribs while individual was standing erect. And sum of all truncal and peripheral skinfolds was calculated. The handgrip strength was assessed with Jamar Hydraulic Hand Dynamometer (Sammons Preston, IL, USA) which estimates the muscle strength (in Kg) primarily generated by the flexor muscles of the hand and the forearm. The participants

Table 3
Macronutrient distribution of the control and intervention diets at enrolment, after run-in and during the intervention period (Mean values and standard deviations).

Variable	Enrollment		Day 0 (after run-in period)				During intervention			
	Mean	SD	Control		Intervention		Control		Intervention	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
Energy ((kJ)	5448.8	407.94	5428.3	384.1	5540.0	413.0	5433.8	233.9	5620.0	483.3
Energy (kcal)	1302.3	97.5	1297.4	91.8	1324.1	98.7	1298.7	55.9	1343.2	115.5
Protein (g)	39.1	3.7	47.9	4.6	62.3	3.4	48.3	5.6	64.3	4.1
Protein (%)	12.0		14.8		18.8		14.9		19.1	
Carbohydrate (g)	174.3	20.0	163.2	8.1	162.6	23.4	163.4	8.3	164.4	31.9
Carbohydrate (%)	53.5		50.3		49.1		50.3		49.0	
Fat (g)	49.8	10.8	50.3	10.9	47.2	4.1	50.2	7.0	47.6	11.6
Fat (%)	34.4		34.9		32.1		34.8		31.9	

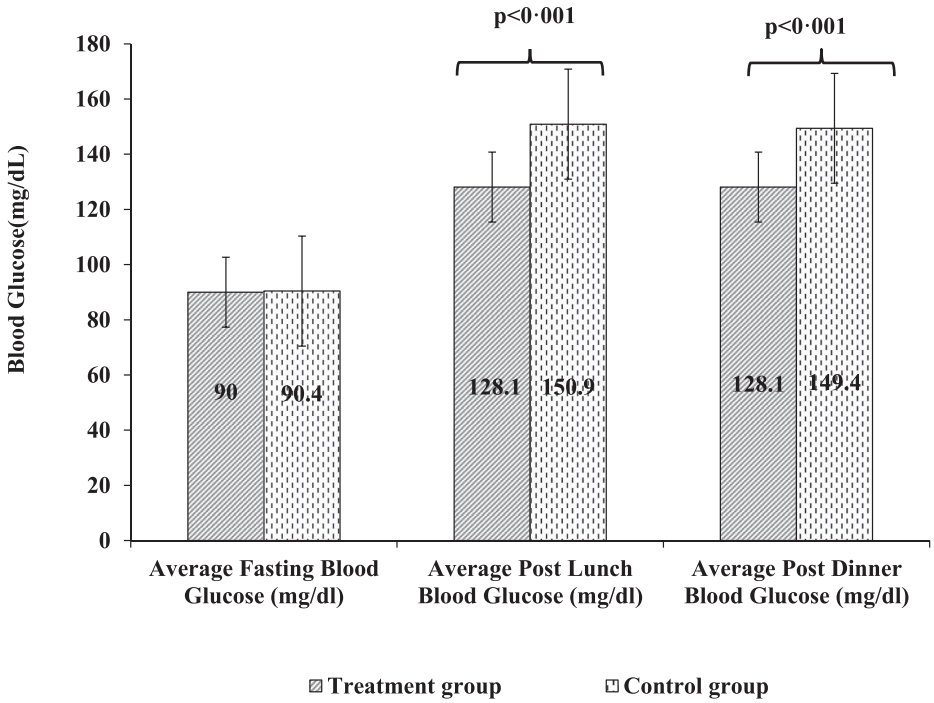

Fig. 2. Comparison of average blood glucose readings. Mean values of average blood glucose reading: fasting, 2 h post lunch, 2 h post-dinner, over 30 days each. The error bars represent the standard error of the mean. Participants were asked to monitor their blood glucose readings every day using a blood glucose meter. which was given to them at the time of recruitment. Participants recorded their food intake, activity, and blood glucose reading in the log given to them. They were told to record 30 readings of fasting blood glucose, 30 readings of 2 h post-lunch glucose level, and 30 readings of 2 h post-dinner blood glucose levels on any day suitable to them over 90 days. An average of 30 readings at each time, over 90 days has been presented in the graph.

were encouraged to produce their maximal grip strength. Three readings were recorded, consisting of a 2-4-s maximal contraction, with a 30-s rest period between each trial. The average of the three readings was taken [31].

Fasting serum insulin was measured using a chemiluminescence immunoassay. The values of FBG and fasting insulin have been used to calculate insulin resistance by homeostasis model assessment (HOMA). The value of HOMA denoting insulin resistance was termed as HOMA-IR and was calculated as: [fasting insulin (mU/mL) X fasting glucose (mmol/L)/22.5]. The value of HOMA denoting β-cell function was termed as HOMA-βCF and was calculated as: [20 X fasting plasma insulin (mIU/mL)/fasting plasma glucose (mmol/L)-3.5]. The disposition index (DI) provides a measure of βCF adjusted for insulin sensitivity and was calculated as: Insulin sensitivity [(22.5/fasting insulin (mU/mL) X fasting glucose (mmol/L)] X HOMA-βCF [32].

HbA1c levels were measured using High-Performance Liquid Chromatography (Biorad Labs, CA, USA). Serum C-peptide levels (fasting) were determined quantitatively by solid phase direct sandwich enzyme-linked immunosorbent assay (ELISA) using commercial kits (SIGMA, St Louis, USA). For glucagon analysis, blood samples were collected in EDTA vacutainers treated with aprotinin (Trasylol 10,000 KIE/ml; Bayer Health care AG 51368), which was added to give a final concentration of 200 KIE per ml of peripheral blood. Plasma glucagon levels were measured by Elisa using commercially available kits (Glucagon kit, Sincere biotech, China). Serum proinsulin levels were assessed by Elisa (DRG, Germany). High-sensitivity C-reactive protein (hs-CRP) was assessed using Immunoturbidimetry (Roche, Germany). Tumor necrosis factor-alpha (TNF-α) was assessed using ELISA (Diaclone, France). The inter-assay and intra-assay coefficients of the estimation kit were as per the manufacturer's instructions.

3. Statistical methodology

3.1. Sample size calculation

Based on previous studies [23], the following assumptions have been made in deciding the sample size: Mean GTT level post-test meal (m 1) = 118, mean GTT level post-standard meal (m 2) = 138, the standard deviation of GTT value for test meal ($\sigma 1$) = 25, the standard deviation of GTT value for a standard meal ($\sigma 2$) = 30, confidence level = 95%, power = 80%. For detecting the difference of about 20 points between 2 diets as significant, a sample size of 30 in each meal was taken.

In this parallel arm study design, we had two independent samples, and therefore the two-sample, t– test was used for testing the difference in the change in parameters in the test meal *vs.* the change in parameters in standard meal.

Randomization: Random numbers were generated by the statistician, not involved in the trial Stata 15.0 statistical software (College Station, Texas, USA). The study Investigator enrolled the participants and assigned participants to the different study arms of interventions. The trial was stopped after the last follow-up of the last participant enrolled in the study. For every participant, the allocated random number was placed in an opaque envelope. Only the sequence number was mentioned on the cover of the envelope. The envelope was opened at the time of enrolment for every participant.

3.2. Statistical analysis

Quantitative variables were assessed for approximate normal distribution and were summarised as mean values and standard deviations. Student's t-test was used to compare the difference in mean values between the two arms. Variables following non-

normal distribution were summarised by medians, 25th, and 75th percentiles, and the Wilcoxon rank-sum test was used to compare differences in the distribution between the two arms. ANCOVA was used to compute mean values at day 90 post-intervention adjusting for age, family type, and baseline values of outcome parameters. We used 'intention-to-treat' and 'per-protocol' analysis for analysing data. In the 'intention-to-treat' analysis, for missing values, we used the 'last observation carried forward' method for imputing the values, and the 'per-protocol' analysis was used for analysing the data of participants who completed the study. Stata 24.0 statistical software (College Station, Texas, USA) was used for data analysis. In this study, P < 0.05 has been considered statistically significant.

4. Result

Sixty participants completed the study (thirty participants in each arm). Gender-wise distribution of the data was: the control arm, twelve males and twenty-two females; and the treatment arm, sixteen males and sixteen females. There were no statistical differences in the socio–demographic parameters between the two arms except for body weight (Table 4). As per the 'intention-to-treat' analysis, overall additional mean reduction compared with the control arm in the parameters (after adjusting for age, gender, body weight, and baseline values of the respective parameters) 90 days were as follows: body weight, −3.1 (95% CI -4.0, −2.2; p < 0.001); WC (cm), −3.0 (95% CI -3.8, −2.3; p<,0.001), hip circumference (cm), −3.3 (95% CI -4.3, −2.3, p < 0.001); BMI (kg/m^2) −1.2 (95% CI -1.6,-0.9, p < 0.001); subscapular skinfolds (mm), −3.0 (95% CI -3.8, −2.2, p < 0.001), suprailiac skinfolds (mm), −2.3 (95% CI -3.0, −1.7, p < 0·001), the sum of skinfolds (truncal and peripheral) (mm) −5.2 (95% CI -7.2, −3.2, p < 0.001), and handgrip strength (Kg), +1.1(95% CI 0.5, 1.7, p < 0·001) (Table 5). In blood parameters overall additional mean reduction in the treatment arm as compared to the control arm was as follows: FBG (mg/dL), −6.1(95% CI -8.6, −3.7, p < 0·001); blood glucose after ingestion of 75 g of oral glucose (mg/dL) −25.8 (95% CI -33.4, −18.3, p < 0·001); HbA1c (%), −0.4 (95% CI -0.5, −0.3, p < 0·001); serum insulin after ingestion of 75 g of oral glucose (mU/L), (p < 0·001); HOMA-IR, (p < 0·001); fasting proinsulin (pmol/L), −1.2 (95% CI -1.6, −0.7, p < 0·001); total cholesterol (mg/dL), −14.0 (95% CI -19.5, −8.5, p < 0·001); very low-density lipoprotein cholesterol (mg/dL), −5.1(95% CI -6.8, −3.3, p < 0·001); and low-density lipoprotein cholesterol (mg/dL), −11.8 (−17.3, −6.2, p < 0·001). However, we did not see any statistically significant trend with respect to mid upper arm circumference, biceps and triceps skinfolds, fasting serum insulin, fasting C-peptide, fasting plasma glucagon, hs-CRP, TNF-α, HOMA-βCF, DI, serum triglycerides and high-density lipoprotein cholesterol (Table 6).

The SMBG data (blood glucose values, fasting, 2 h post lunch and 2 h post dinner) revealed that the FBG normalized in 10 participants (33.3%) in the treatment arm *vs.* 4 (13.3%) participants in the control arm; 2 h post-OGTT (2 h POGTT) blood glucose normalized in 23 participants (76.7%) in the treatment *vs.* 7 participants (23.3%) in the control arm (p < 0.001). HbA1c normalized in 9 (30%) participants in the treatment arms and 1 subject (3.3%) in the control arm (P < 0.008). We also observed a change to a complete normoglycemic state (FBG<100 mg/dL and 2 h POGTT glucose <140 mg/dL) in 7/30 (23.3%) participants in the treatment arm, which is comparable to postprandial glucose regulator drug, Acarbose (25%) (Fig. 3). We also observed significantly greater satiety as compared to those in the control arm (Supplementary Fig. 1). In the treatment arm 24/30 (75%) of the participants reported a feeling of fullness 2 h after ingestion of main meals post intervention as compared to 8/30 (25%) of the participants in the control arm.

5. Discussion

In this study, we show for the first time that a premeal almond load of 20 g, 30 min before three main meals leads to a significant reduction in FBG, 2 h POGTTBG, HbA1c, 2 h POGTT serum insulin, fasting proinsulin, HOMA-IR, lipids, bodyweight, and truncal subcutaneous fat in Asian Indians with prediabetes. Most importantly, the intervention also led to a reversal to normal glucose regulation from the state of prediabetes. These findings are of practical and clinical significance keeping in mind the dysmetabolic state of Asian Indians, and their greater tendency to convert to diabetes from the prediabetes stage.

Reversal of prediabetes is a holy grail of medicine. Many large-scale epidemiological trials have focused on different approaches for a reversal from prediabetes to normoglycemic condition. In the

Table 4
Baseline characteristics.

Variable		Treatment (n = 32)	Control (n = 34)	*P* value
		n (%)	n (%)	
Gender	Male	16 (50)	12 (35.3)	0.459
	Female	16 (50)	22 (64.7)	
Age (years)	Mean ± SD	41.3 ± 7.1	42.6 ± 9.1	0.527
Family type	Joint[a]	12 (37.5)	9 (26.5)	0.100
	Nuclear	18 (56.2)	17 (50.0)	
	Extended[b]	2 (6.3)	8 (23.5)	
Monthly income (Indian National Rupees)	<50,000	18 (56.3)	17 (50)	0.258
	>50,000	14 (43.8)	17 (50)	
Tobacco use	Not at all	27 (84.4)	33 (97.1)	0.103
	Sometimes	1 (3.1)	1 (2.9)	
	Regularly	4 (12.5)	0 (0)	
Alcohol use	Not at all	27 (84.4)	32 (94.1)	0.339
	Sometimes	4 (12.5)	1 (2.9)	
	Regularly	1 (3.1)	1 (2.9)	
BMI (kg/m^2)	Mean ± SD	31.6 ± 4.1	30.5 ± 4.2	0.296
Weight (kg)	Mean ± SD	81.5 ± 12.6	75.6 ± 10.9	0.044
Resting pulse (bpm)	Mean ± SD	77.9 ± 6.3	76.6 ± 7.6	0.483
Systolic blood pressure (mmHg)	Mean ± SD	120.9 ± 7.8	122.4 ± 8.5	0.486
Diastolic blood pressure (mmHg)	Mean ± SD	79.3 ± 5.6	82.1 ± 6.5	0.064

[a] Coparceners staying together.
[b] Parents staying together with married children.

Table 5
Comparison of anthropometric parameters pre- and post-intervention between the treatment and control arms.

Variable		Intention-to-treat			Per protocol		
		Treatment (n = 32)	Control (n = 34)	Effect Size[a] (95%CI); *p*-value	Treatment (n = 30)	Control (n = 30)	Effect Size[a] (95%CI); *p*-value
Anthropometry							
Body weight (kg)	Baseline	81.5 ± 12.6	75.6 ± 10.9	−3.1(-4.0, −2.2)	82.2 ± 12.8	75.5 ± 11.3	−3.2(-4.1, −2.3)
	Post intervention	77.6 ± 12.5	74.8 ± 11.3	<0·001	77.9 ± 12.8	74.5 ± 11.7	<0·001
WC (cm)	Baseline	101.7 ± 11.0	98.1 ± 9.1	−3.0(-3.8, −2.3)	101.7 ± 11.2	98.3 ± 9.5	−3.2(-3.9, −2.4)
	Post intervention	98.9 ± 10.6	97.2 ± 9.2	<0·001	98.8 ± 10.8	97.3 ± 9.7	<0·001
HC (cm)	Baseline	102.7 ± 8.6	103.2 ± 9.3	−3.3(-4.3, −2.3)	102.8 ± 8.7	103.8 ± 9.3	−3.5(-4.5, −2.5)
	Post intervention	99.8 ± 8.8	102.3 ± 9.1	<0·001	99.7 ± 9.0	102.7 ± 9.2	<0·001
MUAC (cm)	Baseline	30.3 ± 2.6	28.7 ± 2.4	0.01(-0.3, 0.3)	30.3 ± 2.6	28.5 ± 2.5	0.01 (−0.3,0.3)
	Post intervention	29.9 ± 2.6	28.1 ± 2.4	0.966	29.9 ± 2.6	28.1 ± 2.4	0.966
Body fat (%)	Baseline	36.7 ± 8.3	40.6 ± 6.9	−1.7(-2.3, −1.1)	36.5 ± 8.2	40.8 ± 7.2	−1.7(-1.1, −2,3)
	Post intervention	34.3 ± 7.9	40.2 ± 7.4	<0·001	34.3 ± 7.9	40.2 ± 7.4	<0.001
BMI) (kg/m^2)	Baseline	31.6 ± 4.2	30.5 ± 4.2	−1.2(-1.6, −0.9),	31.8 ± 4.2	30.6 ± 4.4	−1.3(-1.7, −0.9)
	Post intervention	30.1 ± 4.1	30.2 ± 4.4	<0·001	30.1 ± 4.2	30.2 ± 4.6	<0·001
Skinfolds (mm)							
Biceps	Baseline	23.3 ± 5.4	21.3 ± 5.2	−0.2(-0.4,0.8)	23.4 ± 5.6	21.0 ± 5.2	0.2(-0.4, 0.8)
	Post intervention	22.3 ± 5.4	19.8. ± 5.4	0.571	22.3 ± 5.4	19.8 ± 5.4	0.571
Triceps	Baseline	31.1 ± 5.8	30.4 ± 5.9	−0.1(-0.6, −0.8)	31.0 ± 6.0	30.7 ± 5.5	0.1(0.6, 0.8)
	Post intervention	29.9 ± 6.3	29.5 ± 5.6	0.770	29.9 ± 6.3	29.5 ± 5.6	0.770
Subscapular	Baseline	36.4 ± 7.0	38.0 ± 7.7	−3.0(-3.8, −2.2)	36.2 ± 7.1	38.1 ± 8.1	−3.1(-3.9, −2.3)
	Post intervention	34.4 ± 7.1	37.2 ± 7.7	<0·001	34.1 ± 7.1	37.2 ± 8.2	<0·001
Suprailiac	Baseline	35.7 ± 9.2	39.9 ± 11.6	−2.3(-3.0, −1.7)	36.0 ± 9.4	40.4 ± 12.0	−2.4(-3.1, −1.8)
	Post intervention	33.7 ± 8.9	39.1 ± 11.6	<0·001	33.8 ± 9.2	39.5 ± 12.0	<0·001
Sum of skinfolds	Baseline	126.5 ± 16.7	129.5 ± 20.3	−5.2 (−7.2, −3.2)	126.6 ± 17.2	130.3 ± 21.1	1.0 (0.9, 1.1)
	Post intervention	117.3 ± 17.3	126.3 ± 21.3	<0·001	117.3 ± 17.3	126.3 ± 21.3	<0·001
Handgrip strength (kg)	Baseline	25.8 ± 8.8	21.7 ± 6.5	1.1(0.5, 1.7)	25.4 ± 8.8	21.5 ± 6.6	1.2(0.6, 1.8)
	Post intervention	27.1 ± 9.3	21.8 ± 6.7	<0·001	26.9 ± 9.4	21.6 ± 6.8	<0·001

WC; waist circumference, HC; hip circumference, MUAC; mid upper arm circumference, BMI; body mass index.
*Adjusted for baseline, age, gender, and body weight.
[a] Values are expressed as Mean ± SD or Median (Min, Max).

"Study to Prevent NIDDM (STOP-NIDDM) Trial" 1429 individuals with IGT were randomized to receive a postprandial regulator drug, Acarbose or placebo. Acarbose significantly reduced the incidence of diabetes by 25% over a period of 3 months [33]. In the Diabetes Prevention Program 31% diabetes risk reduction from prediabetes state has been reported with metformin over 2.8 years [34] and in Da Qing study 36% risk reduction has been reported with lifestyle changes in participants with prediabetes [35]. In our study, the percentage remission of prediabetes by blood glucose and by HbA1c over three months period was similar to data from above-mentioned studies (Fig. 3). This effect looks promising but needs long-term data. This strategy should be further researched in non-obese individuals where weight loss as a strategy for the reversal of prediabetes or diabetes may not work.

HbA1c has a closer association with PPHG than FBG [36]. In the present study, the effect of a premeal load of almonds on the HbA1c reduction was statistically significant. We had previously reported a statistically significant improvement in the HbA1c with almond supplementation (as a single snack) compared with the control diet after a 24-week intervention in Asian Indians with T2D [26]. But in another study with the intervention of pistachio nuts in Asian Indians with metabolic syndrome (HbA1C < 6.5), we did not observe any significant effect on HbA1c [37].

Typical Indian breakfast foods are high in carbohydrates [e.g., bread, paratha (shallow-fried flatbread made with whole wheat, and spices), and cereal porridge]. It is known that consuming fat and protein at breakfast lowers PPHG and increases satiety [38] Pedersen et al. [39] showed that a low-carbohydrate breakfast significantly reduced mean and peak glucose levels up to 5 h after a meal. However, the impact of carbohydrate restriction at breakfast on 24 h postprandial hyperglycemia and glycemic variability was not reported. Studies have shown that the contribution of PPHG overall glycemic control decreases as HbA1c increases [40]. Therefore, controlling PPHG may be most important to prevent diabetes complications in patients with T2D who are fairly well controlled [i.e., those close to achieving glycemic targets of 7%] [40] but who are still at significant risk of developing cardiovascular disease. In the present study, we observed a statistically significant reduction in fasting glucose, 2 h POGTTBG and insulin, and HOMA-IR. Importantly this was achieved without restricting the carbohydrates in meals.

Several postprandial glucose-regulating drugs have been used in the treatment of T2D. These include α-glucosidase inhibitors, glinides, and some insulins. Intervention with α-glucosidase inhibitor, Acarbose (a prototype and commonly use postprandial glucose regulator) not only decreased PPHG but also lowers the risk of CVD [41], hypertension, postprandial hypertriglyceridemia, pro-inflammatory cytokines and prevent the development of diabetes in those with prediabetes as stated previously [42,43]. Importantly, Enc et al. [44] showed that intervention with 100 g of Acarbose before a meal augmented glucagon-like peptide (GLP-1) response which may also help in decreasing PPHG. Use of postprandial glucose regulator drugs (Acarbose, Nateglinide, Voglibose, and Repaglinide) leads to a reduction in fasting and postprandial blood glucose ranging from 19.4 to 49.7 mg/dL and 27.9–61 mg/dL, respectively but have minimal effect on body weight and waist circumference (Table 1). On the other hand, almonds taken as a premeal load led to a reduction in glycemia as well as body weight, waist circumference, and truncal skinfolds, along with improvement in other metabolic markers such as lipid profile, and serum insulin. Furthermore, there is no adverse effect reported in this study, whereas postprandial regulator drugs, specifically Acarbose have adverse effects such as stomachaches, abdominal bloating, indigestion etc. in up to 20–30% of cases. In the STOP NIDDM study [33], 31% of the participants discontinued the study in the Acarbose arm *vs* 19% in the placebo arm. It appears that a premeal load of almonds,

Table 6
Comparison of biochemical parameters pre- and post-intervention between the treatment and control arms.

Variable		Intention-to-treat			Per protocol		
		Treatment (n = 32)	Control (n = 34)	Effect Size[a] (95%CI), *p*-value[b]	Treatment (n = 30)	Control (n = 30)	Effect Size[a] (95%CI); *p*-value[b]
Biochemistry							
FBG (mg/dL)	Baseline	100.1 ± 7.1	99.9 ± 7.7	−6.1(-8.6, −3.7)	99.7 ± 7.2	99.6 ± 7.8	−6.3(-9.0, −3.6)
	Post intervention	93.8 ± 7.2	100.0 ± 8.3	<0·001	93.0 ± 6.7	99.7 ± 8.5	<0·001
2 h POGTT BG (mg/dL)	Baseline	159.8 ± 18.9	159.9 ± 18.5	−25.8(-33.4, −18.3) <0·001	158.8 ± 18.8	160.3 ± 19.5	−27.1(-35.1, −19.1) <0·001
	Post intervention	133.0 ± 23.2	159.3 ± 21.4		130.3 ± 20.9	159.5 ± 22.6	
FSI (uU/ml)	Baseline	15.6 (6.4, 75.6)	15.5 (6.1, 32.6)	0.059	15.5 (6.1, 32.6)	17.7 (6.3, 75.6)	0.059
	Post intervention	11.9 (2.9, 64.3)	18.9 (6.2, 34.2)		11.9 (2.9, 64.3)	18.9 (6.3, 34.2)	
2 h POGTT SI (mU/L)	Baseline	90.3 (17.5, 390)	121.9 (28.4, 370.1)	<0·001	85.8 (17.5, 390)	123.7 (28.4, 370.1)	<0·001
	Post intervention	63.8 (12.3, 284.2)	121.6 (30.1, 304.8)		63.8 (12.3, 284.2)	121.6 (30.1, 304.8)	
HbA1c	Baseline	6.2 ± 0.4	6.1 ± 0.5	−0.4(-0.5, −0.3)	6.2 ± 0.4	6.1 ± 0.5	−0.4(-0.6, −0.3)
	Post intervention	5.8 ± 0.5	6.2 ± 0.5	<0·001	5.8 ± 0.5	6.2 ± 0.5	<0·001
Fasting C-peptide (ng/ml)	Baseline	2.4 (0.8, 6.3)	1.9 (0.8, 4.1)	0.559	2.4 (0.7, 6.3)	1.9 (0.8, 4.1)	0.559
	Post intervention	2.4 (0.6, 6.1)	2.2 (0.9, 4.5)		2.4 (0.6, 6.1)	2.2 (0.9, 4.5)	
Pro-Insulin(pmol/L)	Baseline	3.5 ± 1.4	2.9 ± 1.0	−1.2(-1.6, −0.7)	3.5 ± 1.4	2.9 ± 1.0	−1.3(-1.7, −0.8)
	Post intervention	2.4 ± 0.9	3.3 ± 1.1	<0·001	2.3 ± 0.8	3.3 ± 1.2	<0·001
Glucagon(pg/ml)	Baseline	636.2 (95.1, 1341)	718.7 (88.4, 1257)	0.437	636 (95.1, 1341)	718.8 (88.4, 1221)	0.437
	Post intervention	575.5 (97.2, 1247)	616.5 (98.7, 1213)		575.5 (97.2, 1247)	637 (98.7, 1213)	
hs-CRP (mg/L)	Baseline	2.6 (0.4, 16.6)	3.1 (0.2, 11.2)	0.183	2.6 (0.4, 16.6)	3.1 (0.2, 11.2)	0.183
	Post intervention	2.5 (0.3, 16.1)	4.1 (0.5, 13.2)		2.5 (0.2, 16.1)	4.1 (0.5, 13.2)	
TNF-α (pg/ml)	Baseline	6.5 (0.9, 29.1)	6.0 (1.2, 12.8)	0.569	6.6 (1.1, 10.4)	6.0 (1.2, 18.1)	0.569
	Post intervention	4.6 (1.2, 18.1)	6.2 (1.1, 10.4)		4.6 (0.9, 29.1)	6.2 (1.2, 12.8)	
HOMA-IR	Baseline	4.1 (1.6, 19.5)	3.8 (1.5, 9.2)	<0·001	4 (19.5, 1.6)	4.3 (9.2, 1.5)	<0·001
	Post intervention	2.8 (0.6, 15.5)	4.6 (1.5, 8.9)		2.8 (0.6, 15.5)	4.6 (1.5, 8.9)	
HOMA-βCF	Baseline	50.8 (17.8, 257.7)	56.0 (19.4, 111.6)	0.386	50.8 (17.8, 257.7)	62.3 (19.4, 111.6)	0.386
	Post intervention	43.7 (7.8, 233.3)	57.3 (19.4, 121.1)		41.2 (7.8, 233.3)	63.3 (19.9, 121.1)	
DI	Baseline	421.0 (376.0, 444)	423.5 (381.1, 436.3)	0.160	421.0 (376.0, 444.0)	426.1 (381.1, 436.3)	0.160
	Post intervention	83.4 (31.6, 338.8)	60.0 (9.0, 226.9)		85.5 (31.6, 338.8)	60.3 (9.0, 226.9)	
Lipids							
TC (mg/dL)	Baseline	164.5 ± 30.3	165.3 ± 26.4	−14.0(-19.5, −8.5)	163.9 ± 30.7	167.2 ± 26.9	−15.3(-21.3, −9.3)
	Post intervention	150.8 ± 30.4	165.7 ± 26.9	<0·001	149.2 ± 30.3	167.7 ± 27.4	<0·001
TG (mg/dL)	Baseline	110.7 ± 31.6	113.5 ± 34.1	−3.3(-7.5, 0.8) 0.117	110.7 ± 32.6	116.0 ± 35.2	−3.3(-7.5, 0.8) 0.117
	Post intervention	109.2 ± 31.4	117.3 ± 33.2		109.2 ± 31.4	117.3 ± 33.2	
VLDL-C (mg/dL)	Baseline	22.9 ± 7.1	21.9 ± 5.8	−5.1(-6.8, −3.3)	23.1 ± 7.3	22.4 ± 6.0	−5.8(-7.6, −3.9)
	Post intervention	19.3 ± 5.7	23.5 ± 6.6	<0·001	19.2 ± 5.9	24.1 ± 6.7	<0·001
LDL-C (mg/dL)	Baseline	98.9 ± 25.7	99.4 ± 25.9	−11.8(-17.3, −6.2)	98.7 ± 26.4	100.7 ± 27.0	−12.8(-19.0, −6.5)
	Post intervention	92.5 ± 23.0	105.0 ± 95.8	<0·001	91.8 ± 23.5	107.0 ± 26.9	<0·001
HDL-C (mg/dL)	Baseline	44.8 ± 10.2	44.3 ± 7.1	0.1(-0.4, 0.6) 0.735	44.3 ± 10.2	44.5 ± 7.5	0.1(-0.4, 0.7) 0.690
	Post intervention	44.6 ± 9.9	44.0 ± 7.1		44.1 ± 9.9	44.1 ± 7.5	

FBG; fasting blood glucose, 2h POGTT BG; 2h post-OGTT blood glucose, FSI; Fasting serum insulin, 2h POGTT SI; 2h post-OGTT Serum Insulin, C-pep; c-peptide, hbA1c; glycosylated haemoglobin, hs-CRP; high sensitivity c-reactive protein, HOMA-IR; homeostatic model assessment, HOMA-βCF; HOMA beta cell function, DI; disposition index, TNF-α; tumour necrosis factor-alpha, TC; total cholesterol, TG; serum triglycerides, VLDL-C; very low-density lipoprotein cholesterol, LDL-C; low-density lipoprotein cholesterol, HDL-C; high-density lipoprotein cholesterol.
For participants who were not available post-intervention (ITT analysis), the last observation values were carried forward as post-intervention values assuming that the intervention did not have an effect on them.
[a] Values are expressed as Mean ± SD or Median (Min, Max).
[b] Post-intervention values are after adjusting for age, family type and baseline outcome variable.

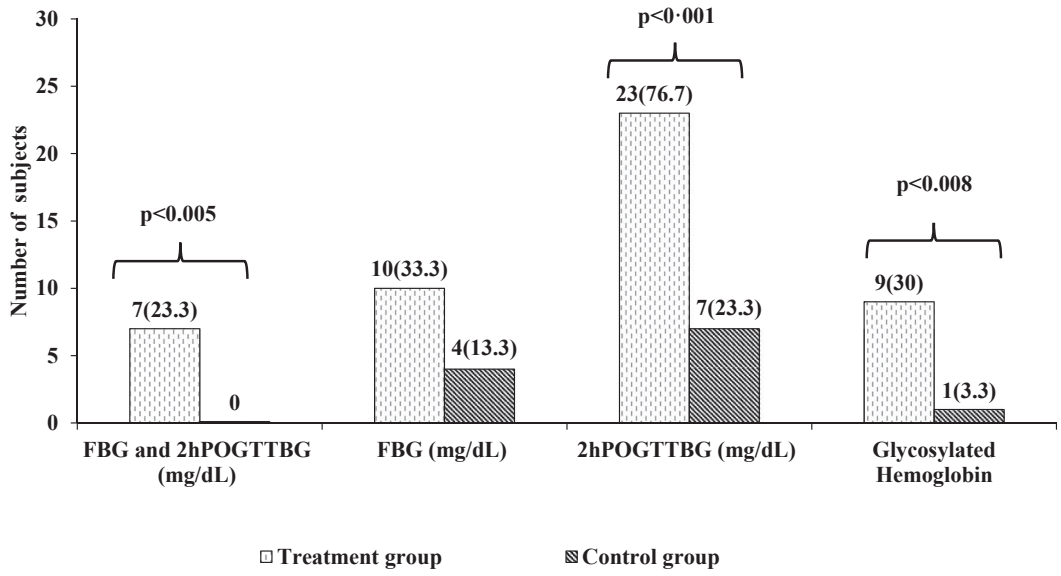

Fig. 3. Number of Participants normalizing in glycaemic parameters after the intervention. The figure in parenthesis shows percentage: n (%). X-axis shows a gradient of normalization of fasting blood glucose and 2 h post-Oral glucose tolerance test. Y axis shows the number of participants. P value shows the significant difference in the control and treatment arms. FBG: Fasting blood glucose; 2hPOGTTBG: 2 h post-oral glucose tolerance test blood glucose. Normal fasting blood glucose levels are defined as: blood glucose< 100 mg/dL. Normal 2hPOGTTBG: blood glucose< 140 mg/dL.

in comparison to conventionally used postprandial regulators, are similar or inferior in reduction of PPHG but better in reduction of weight, WC, and some metabolic parameters and, without any adverse effects Finally, over the short term, there is a promising effect of reversal to normal glucose regulation, similar to Acarbose and metformin.

The exact mechanism for this improvement in parameters of glucose metabolism by a premeal load of almonds is difficult to ascertain. Almonds are a rich source of monounsaturated fatty acids (MUFAs) and soluble fiber both could lead to salutary effects on blood glucose levels through various mechanisms [45,46]. Strategy to minimize PPHG by administering a small load of protein, fat (mainly MUFA], and soluble fiber all of which are present in almonds, which when given before a meal, leads to the release of peptides such as GLP-1, GIP, and cholecystokinin (CCK) which can slow gastric emptying and stimulate insulin secretion [47,48]. Further, the inclusion of almonds increases a feeling of satiety and leads to a strong dietary compensation effect as has been shown in our data. In addition, because of the inefficiency in energy absorption, nut consumption does not promote a greater energy intake than other foods [49]. In a randomized cross-over study, after 12 weeks of incorporating high oleic peanuts into the diet, a less- than-predicted increase in body weight was found, despite a large additional amount of energy being consumed from the peanuts [50]. Similarly, Li et al. [40] and our group [26] also reported no changes in body weight and BMI with the almond diet, however, a statistically significant improvement is seen in body weight and anthropometric parameters in the present study.

Although our study involved participants with prediabetes who had well-controlled, predominantly uncomplicated metabolic states, the improvement in postprandial glycemia was marked and highly consistent. Further evaluation is now required in poorly controlled patients and those taking oral hypoglycaemic agents in order to determine whether the same hypoglycaemic effect is replicated in patients with frank diabetes. Its effect on the reversal of prediabetes must be evaluated in long- term studies, especially in non-obese individuals where weight loss as a strategy may not work.

The limitations of our study are the relatively small sample size and limited period of intervention. Since the study has been conducted only on participants with prediabetes, we cannot extrapolate the same impact of a premeal load of almonds in participants with T2D.

6. Conclusions

Incorporation of 20 g of almonds, 30 min before each major meal over 90 days leads to significant improvement in body weight and related anthropometric parameters, measures of glycemic control, PPHG, lipid parameters, and improved satiety. This strategy has good potential for the reversal of prediabetes to normal glucose regulation.

Authors contribution

SG designed the research, conducted the study, and wrote the paper, AM designed the research, wrote the paper, and had primary responsibility for the final content. RMP, ADU, and HCS performed the statistical analysis. RT and MS contributed to the data collection and conduct of the study. All authors read and approved the final manuscript.

The authors declare that there are no conflicts of interest.

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Disclaimer

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Clinical trial registry number

The study was registered at clinicaltrials.gov (registration no. NCT04769726).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2022.12.028.

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