

Effect of Almond Supplementation on Glycemia and Cardiovascular Risk Factors in Asian Indians in North India with Type 2 Diabetes Mellitus: A 24–Week Study

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Abstract

Background: Type 2 diabetes (T2D) statistics have reached menacing proportions in India. Appropriate dietary intervention, as part of healthy lifestyle, is imperative to curb further spread of this disease.

Objectives: This pre–post intervention study was conducted in New Delhi, India, to investigate the effects of daily consumption of almonds for 24 weeks in T2D subjects, specifically on measures of glycemia and cardiovascular disease (CVD) risk factors.

Methods and Study Design: In this study, the 24-week intervention period was preceded by a control diet and exercise run-in period of 3 weeks. Raw almonds (20% of energy intake) were provided to the patients for consumption along with diet and physical activity counseling. Patients were assessed for anthropometry, blood pressure, measures of glycemia (fasting blood glucose, glycosylated hemoglobin), lipids [total cholesterol (TC), triglycerides, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, lipoprotein(a)], surrogate marker of atherosclerosis (Pulse wave velocity), and marker of inflammation (high sensitivity C-reactive protein [hs-CRP]) at baseline and after the intervention period.

Results: Statistically significant improvement in mean values for various parameters post intervention was as follows: waist circumference ($P < 0.03$), waist-to-height ratio ($P < 0.005$), TC ($P < 0.002$), serum triglycerides ($P < 0.004$), low-density lipoprotein cholesterol ($P < 0.01$), glycosylated hemoglobin ($P < 0.04$), and hs-CRP ($P < 0.01$). A trend toward improvement in pulse wave velocity ($P < 0.06$) was also observed.

Conclusion: The study findings illustrate that incorporation of almonds in a well-balanced healthy diet leads to multiple beneficial effects on glycemic and CVDs risk factors in Asian Indian patients with T2D.

Keywords: type 2 diabetes, Asian Indians, almonds, cardiovascular disease, glycemia

Introduction

DESPITE EARLY KNOWLEDGE of the symptoms of diabetes, as evident from their reference in medical texts originating in India as far back as 2000–2500 BC,¹ the spread of this menacing disease has reached epic proportions today. Ironically, India is now considered the diabetes capital of the world.²

The International Diabetes Federation (IDF) 2015 estimate of 69.2 million people with type 2 diabetes (T2D) in India is predicted to double before the year 2040.³ Although IDF has reported the current prevalence of T2D in Indian adults at about 8.5%,³ recent research in India provides far more disturbing statistics. A study carried out across 11 Indian states to ascertain the prevalence of T2D in middle-class urban

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Indians found an age-adjusted known or diagnosed prevalence of 16%,⁴ with more than 25% of diabetics undiagnosed.

A 10-year follow-up to the Chennai Urban Rural Epidemiology Study (CURES) found 26% of subjects with normal glucose tolerance converting to prediabetes, and another 20% converting to diabetes, with an overall dysglycemia conversion rate of 45% and no sex-wise differences observed.⁵ The incidence rate of diabetes in the same study was 79 per 1000 person-years, one of the highest reported in a large ethnic group and twice the rate for Caucasians (35–40 per 1000 person years).⁵ Not only is the disease spreading at an alarming rate, but it also seems to be cutting across all social, demographic, and age groups in India.

Initially recognized as a disease of affluent migrants,⁶ T2D seems to be extending its strong foothold across all Indian population types. A recent cross-sectional analysis of representative samples of subjects from a South-Asia study and another for South Asians living in America showed a higher age-adjusted diabetes prevalence among Indians in India (38%) than among Indians residing in the United States (24%).⁷ Another recent study in Maharashtra, India, to assess the risk factors for T2D among three different social and demographic class groups—affluent medical students, rural subjects, and subjects from urban slums—demonstrated that the rural subjects, although the least sedentary and significantly more active than the medical students, were most centrally obese and at a higher risk for T2D compared with the two other groups.⁸

Symptoms of the disease are not just widespread but are also occurring at a younger age. A cross-sectional study of Indian adolescents in rural Wardha (central India) found 14% of subjects with impaired fasting blood glucose (FBG) values.⁹

In addition, the burden of dysglycemia is known to translate into additional disease burdens, such as hypertension,¹⁰ cardiovascular disease (CVD),¹¹ metabolic syndrome,⁹ non-alcoholic fatty liver disease,¹² diabetic nephropathy,¹³ diabetic retinopathy, liquefaction and syneresis of the vitreous¹⁴ peripheral neuropathy leading to foot ulceration and even amputation,¹⁵ potential increased predisposition to hepatitis C infection,¹⁶ and co-morbid depression.^{17,18} The cost of dealing with diabetes and its complications translates into a colossal economic burden for the country and its people.¹⁹

Several factors are known to play a role in dictating the onset of prediabetes and the progression to T2D among Indians. However, the primary factor postulated for higher and earlier incidence in Indians versus other ethnicities has come to be known as the “South Asian” or the “Asian Indian” phenotype, which is characterized by higher waist circumference, higher levels of total and visceral fat, hyperinsulinemia, insulin resistance, and, thus, a great predisposition to diabetes compared with some other ethnicities with comparable body mass index (BMI).⁵ With a genetic predisposition to insulin resistance and T2D, it is imperative that Indians adopt lifestyle modifications to help delay prediabetes onset and to manage the disease better. Nutrition is an important aspect of a healthy lifestyle. A recent review of the nutrient intake of Asian Indian and South Asian diets reveals a low intake of monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), and fiber and high intake of saturated fats, trans-fatty acids, and carbohydrates.²⁰

The required change in Indian dietary patterns should be inclusion of nutritious foods that are already part of Indian culture and can easily be accommodated into the everyday

diet. Almonds fit the requirements of a food item that is not only culturally trusted and accepted for its nutritional value,²¹ but has also been clinically proven to impart the health benefits necessary to help manage dysglycemia and its disease manifestations, which are known to impact cardiometabolic health.^{22–25} Results from these and other successful clinical studies of almond intervention provide sufficient data and confidence to test the effects of almond consumption on health outcomes in Indian subjects, despite their unique “Asian Indian” phenotype. This study was therefore conducted to investigate the effects of daily consumption of almonds for 24 weeks in T2D subjects, specifically on measure of glycemia and CVD risk factors.

Materials and Methods

Study population

Patients with T2D were recruited through physician referral at the outpatient department of the Fortis C-DOC Center of Excellence for Diabetes, Metabolic Diseases and Endocrinology, Delhi. In accordance with the inclusion criteria, the study staff recruited patients in the age range of 25–70 years, on stable doses of metformin for a period of 3 months, with glycosylated hemoglobin (HbA1c) levels <9%, and low-density lipoprotein cholesterol (LDL-c) levels ≥ 100 mg/dL. The study excluded subjects on insulin therapy, pioglitazone, insulin secretagogues, beta blockers or steroids, or those suffering from diabetes for more than 10 years. Subjects with high uric acid levels (≥ 8 mg/dL) and accelerated hypertension (stage 2 hypertension according to the Joint National Committee guidelines),²⁶ uncontrolled hypothyroidism, acute infection, any debilitating disease, renal failure, or appreciable weight loss (>10%) in the previous 6 months were also excluded from the study. Patients were screened for any known food allergies, lipid-altering medications, or extraneous factors that are known to affect glycemic or lipid parameters.

Ethics committee statement

An independent review committee, “Ethics Committee for Human Research,” approved the study protocol with the statement—*The Ethics Committee hereby gives an approval to conduct the study at Fortis Flt. Lt. Rajan Dhall Hospital, Vasant Kunj, New Delhi.* Written informed consent form, approved by the ethics committee, was obtained from all the study participants.

The study was registered at clinicaltrials.gov with registration number NCT02027740.

Study design

A free-living pre–post intervention study design was used to assess the effect of almond supplementation over a period of 24 weeks after a run-in control period of 3 weeks. The study was designed as a pre–post intervention to ensure that all subjects received almond treatment. During the run-in period ($n=63$), all subjects consumed standard diets formulated according to the dietary guidelines for Asian Indians, appropriate to the diabetes status of the individual. The diet composition of the control diet was as follows: carbohydrates, 60%; protein, 15%; and fat, 25%. Subjects were advised 45 min of walking at least 5 days in a week and

TABLE 1. CHANGES IN OUTCOME VARIABLES AFTER RUN-IN PERIOD

Variable	Screening Mean \pm SD	After 3 weeks Mean \pm SD	Difference (95% CI)	P-value
Total cholesterol (mg/dL)	201.4 \pm 31.4	202.3 \pm 31.4	0.9 (–6.8, 8.6)	0.802
Serum triglycerides (mg/dL)	182.5 \pm 87.5	195.3 \pm 112.1	12.8 (–9.1, 34.8)	0.212
Low-density lipoprotein (mg/dL)	133.9 \pm 19.7	131.1 \pm 21.4	–2.8 (–8.3, 2.6)	0.330
High-density lipoprotein (mg/dL)	41.7 \pm 9.3	42.1 \pm 8.9	0.4 (–1.1, 1.9)	0.635
Very low-density lipoprotein (mg/dL)	38.9 \pm 22.2	36.7 \pm 18.2	2.3 (–2.3, 6.9)	0.342
Fasting blood glucose (mg/dL)	133.9 \pm 31.3	131.9 \pm 29.2	–1.9 (–7.8, 3.8)	0.511
Glycosylated hemoglobin (%)	7.9 \pm 1.7	7.7 \pm 1.2	–0.2 (–0.5, 0.1)	0.128

SD, standard deviation.

were asked to maintain the same level of physical activity throughout the study period. The subjects enrolled for the study were patients with T2D, already attending the outpatient department frequently for treatment. These patients were previously given standardized diet and exercise counseling repeatedly and were following such advice before recruitment in the study.

Diet and compliance

After the run-in period, during the treatment phase, subjects received the almond diet and were advised on how to substitute 20% of total energy intake with whole raw almonds (unblanched kernels, with brown skin intact). In the almond diet, almonds were substituted for some visible fat (cooking oil and butter) and a portion of carbohydrates. The dietary composition of the almond diet was as follows: carbohydrates, 55%; protein, 17%; and fat, 28%. Instructions were provided verbally and in writing according to the subject's local language.

Compliance to the study protocol was ensured through compliance questionnaires, biweekly telephone calls with subjects, and cross-checks with spouses or family members residing with the subjects. In addition, subjects were asked to return empty almond packets on their hospital visits. Spouses and family members were also given a supply of almonds for daily consumption to help ensure subject compliance. Subject compliance to the protocol was found to be nearly 85%.

Assessments

Each subject's right arm was used for blood pressure measurement. According to standard protocol, the subject was required to be in a relaxed sitting position.²⁶ Assessments for anthropometric, glycemia [FBG and glycosylated hemoglobin (HbA1c)], and lipid parameters [total cholesterol (TC), serum triglycerides (TG), LDL-C, high-density lipoprotein cholesterol (HDL-C), and very low-density lipoprotein cholesterol (VLDL-C)] were carried out as described previously.²⁷ BMI and waist-to-height ratio (WtHR) were calculated. HbA1c, lipoprotein(a) [Lp(a)], and high sensitivity C-reactive protein (hs-CRP) levels were measured as described previously.^{28–30} Arterial stiffness indices were assessed noninvasively by measuring carotid–femoral pulse wave velocity with a SphygmoCor cuff (Atcor Medica, Australia). Assessments listed above were conducted on the first day of enrollment, the last day of the run-in period, and the last day of the almond intervention period.

Statistical methodology

Data were recorded on predesigned case report forms and managed on Excel spreadsheets. Quantitative variables were summarized as mean \pm standard deviation or median (range) as per their distribution (normal/non-normal). A paired *t*-test was used to compare pre- to post intervention differences in mean values. The Wilcoxon signed-rank test was used to compare pre intervention (*after the run-in period*) to post-intervention differences in median values. STATA 11.0 statistical software was used for data analyses.

All the parameters were compared at the beginning and at the end of run-in period. There was no significant difference between before and after the run-in period in all the considered biochemical and anthropometric parameters (Table 1).

Results

Study population

Study staff screened 190 subjects and enrolled 63 of these subjects on the basis of inclusion/exclusion criteria mentioned above (Fig. 1). Five of the enrolled subjects dropped out of the study during the run-in period: three due to relocation and two due to personal reasons not related to the study. A total of 58 subjects completed the run-in period. Another three subjects withdrew before the treatment phase for personal reasons. A total of 55 subjects began the almond intervention, and a total of 50 subjects completed the study (Fig. 1), with two out of five dropouts lost to follow-up and the remaining three lost to poor compliance. Of the 50 completers, there were 27 males and 23 females, with an overall mean age of 45.8 \pm 9.3 year and a mean body weight of 73.6 \pm 12.1 kg, waist circumference of 99.4 \pm 9.2 cm, and BMI of 28.7 \pm 4.5 kg/m² (Table 2).

Anthropometry and blood pressure

There was no significant change in body weight and BMI, but significant decreases in mean values of waist circumference ($P=0.03$) and WtHR ($P=0.05$) were observed after almond intervention compared with the control diet given in the run-in period (Table 2). Blood pressure measurements did not change significantly post intervention compared with the control diet.

Measures of glycemia

FBG levels did not show a significant change over the course of the study (Table 2). Statistically significant improvement was seen in levels of HbA1c ($P=0.04$) after almond intervention compared with the control diet (Table 2).

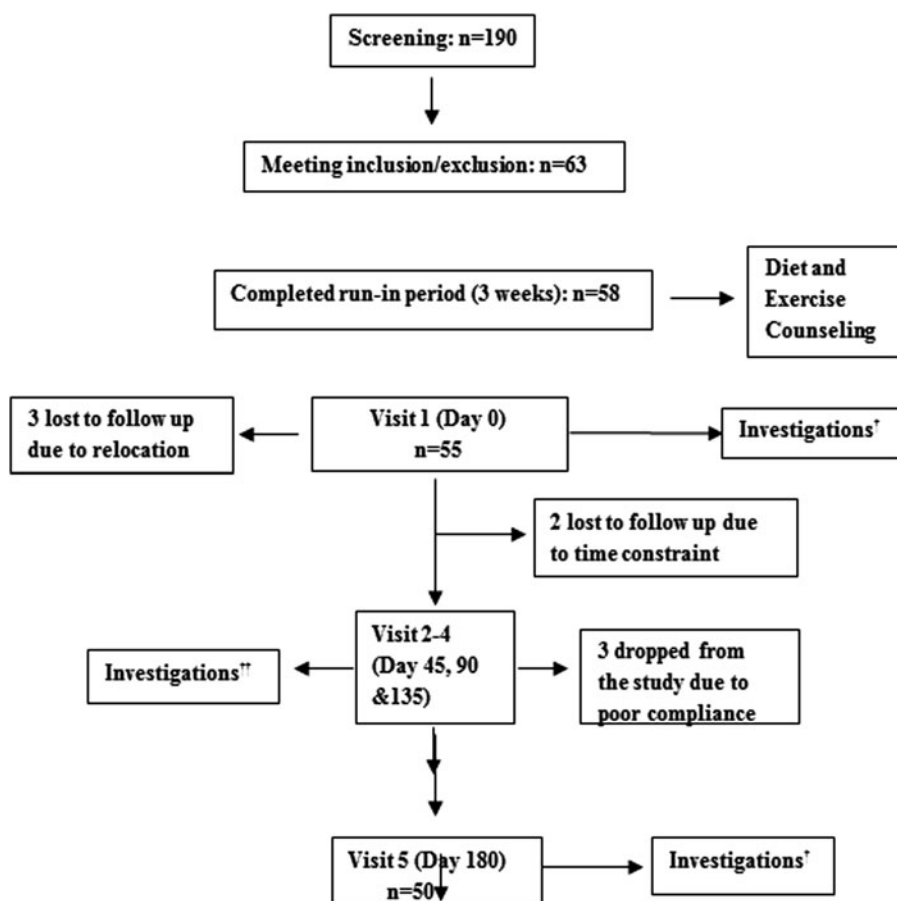


FIG. 1. †Investigation: anthropometry, blood pressure, fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), total cholesterol (TC), serum triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), lipoprotein(a) (LP(a)), high sensitivity C-reactive protein (hs-CRP), pulse wave velocity, diet, and physical activity assessments. ††Investigations: anthropometry, blood pressure, FBG, lipids (TC, TG, HDL-C, LDL-C).

Lipid parameters

Statistically significant improvements in levels of TC ($P=0.002$), TG ($P=0.004$), LDL-C ($P=0.01$), VLDL-C ($P=0.007$), and hs-CRP ($P=0.01$) were observed post-intervention (Table 2). HDL-C did not change and Lp(a) demonstrated a trend toward reduction, although the decrease failed to attain statistical significance (Table 2). Pulse wave velocity also demonstrated an improvement post-intervention, however, the change was not statistically significant ($P>0.06$).

Discussion

This study demonstrated that daily almond consumption at 20% of total energy intake for 24 weeks helped improve anthropometric, glycemic, and lipid parameters significantly in Asian Indian subjects with T2D.

An intake of whole almonds adds protein, total dietary fiber, MUFAs, PUFAs, vitamin E, and potassium³¹ to the diet and has been shown by others to improve the quality of diet without increasing energy intake.^{23,32} There is evidence from other almond supplementation studies collectively that almonds may have a greater impact on multiple cardiometabolic health parameters in the same subjects.^{25,33} These multiple health benefits were observed in the current study as well. Waist circumference and WHtR decreased significantly after almond supplementation (Table 2) and may well explain the benefits on glycemia and lipid parameters observed in the subjects.

In addition to improved anthropometric measures, this study demonstrated a statistically significant decrease in HbA1c levels in subjects after almond supplementation compared with their levels on the control diet. HbA1c has been validated for the diabetic Asian Indian population.³⁴ The HbA1c results from this study are comparable, maybe even better, to those obtained in other nut intervention studies (Table 3).

High HbA1c has been found to be associated with greater waist circumference and higher serum triglycerides.³⁵ Subjects in the current study demonstrated a concurrent and significant decrease in HbA1c, waist circumference, and serum triglycerides (Table 2), thereby providing strong evidence in support of this association. It has also been clinically proven and scientifically accepted that any reduction in levels of HbA1c significantly decreases the risk of diabetic complications.³⁶ Although the incidence of diabetic complications was not recorded in this study due to its limited duration, the benefits of daily almond intake have been shown by others to reduce risks of complications.³³

The benefits of almonds on postprandial glucose regulation have been clearly and consistently demonstrated in many studies.^{22,23,41,42} However, results from studies looking at benefits resulting from chronic consumption have been mixed. Although Li et al.²⁵ demonstrated a statistically significant reduction in fasting glucose in 58-year-old Taiwanese subjects with T2D on a 60 g daily dose of almonds for 4 weeks, the current study failed to demonstrate a statistically significant difference on fasting glucose levels.

TABLE 2. CHANGES IN OUTCOME VARIABLES PRE- AND POST INTERVENTION

Outcome variable	All enrolled (n=63) [#]			All compliant (n=50)				
	Pre intervention mean±SD	Post intervention mean±SD	Difference (95% CI)	P value	Pre intervention mean±SD	Post intervention mean±SD	Difference (95% CI)	P value
Weight (Kg) ^a	74.9±12.4	74.1±11.9	-0.8 (-1.7, 0.1)	0.071	73.6±12.4	72.9±12.2	-0.7 (-1.7, 0.4)	0.192
BMI (Kg/m ²) ^a	28.9±4.4	28.6±4.5	-0.3 (-0.6, 0.06)	0.022	28.7±4.4	28.5±4.7	-0.3 (-0.6, 0.03)	0.071
Waist circumference (cm) ^a	100.1±9.4	98.7±10.4	-1.3 (-2.5, -0.09)	0.04	99.4±9.2	97.8±10.4	-1.6 (-3.2, -0.1)	0.031*
Waist-height ratio ^a	0.62±0.07	0.61±0.08	-0.007 (-0.02, 0.001)	0.05	0.62±0.07	0.61±0.08	-0.009 (-0.02, 0.002)	0.05*
Total cholesterol (mg/dL) ^a	202.3±31.4	191.2±25.1	-11.1 (-17.7, -4.4)	0.001	201.3±32.1	187.4±22.7	-13.9 (-22.3, -5.7)	0.002*
S. Triglycerides (mg/dL) ^b	195.3 (59, 499)	175.4 (72, 499)	—	0.002	170.5 (59, 499)	149.5 (72, 499)	—	0.004*
LDL-C (mg/dL) ^a	131.1±21.4	124.6±18.9	-6.5 (-11.7, -1.3)	0.021	129.7±22.5	121.5±18.5	-8.2 (-14.7, -1.7)	0.011*
HDL-C (mg/dL) ^a	42.1±8.9	41.3±9.7	-0.7 (-2.1, 0.6)	0.301	41.6±8.9	40.7±9.8	-0.9 (-2.7, 0.8)	0.301
VLDL-C (mg/dL) ^b	34.4 (11.8, 99.8)	29.8 (14.4, 99.8)	—	0.005	34.1 (11.8, 103)	28.5 (14.4, 99.8)	—	0.005*
Lipoprotein (a) ^b (mg/dL)	21.4 (9.4, 122)	19.8 (9.4, 111)	—	0.201	21.8 (9.38, 122)	19.8 (9.38, 111)	—	0.310
FBG (mg/dL) ^a	131.9±29.2	129.2±31.8	-2.8 (-9.4, 3.9)	0.403	133.5±31.4	129.9±34.7	-3.5 (-11.9, 4.9)	0.411
HbA1C (%) ^a	7.7±1.2	7.4±1.1	-0.3 (-0.5, -0.01)	0.040	7.7±1.2	7.3±1.1	-0.3 (-0.6, -0.01)	0.041*
hs-CRP (mg/L) ^b	2.9 (0.4, 34.9)	2.6 (0.2, 13.6)	—	0.011	3.3 (0.3, 4.9)	2.6 (0.2, 13.6)	—	0.011*
U. microalbumin (mg/L) ^b	9.4 (1.3, 83.4)	9.0±(1.3, 157)	—	0.403	9.39 (1.3, 83.2)	8.75 (1.3, 157)	—	0.221
SBP (mmHg) ^a	122.7±15.7	121.7±11.6	-0.9 (-4.1, 2.1)	0.501	122.2±15.8	121±10.4	-1.2 (-5.1, 2.7)	0.530
DBP (mmHg) ^a	78.2±6.6	77.6±6.1	-0.8 (-3.1, 1.5)	0.523	78.2±6.6	77.4±5.9	-0.8 (-3.1, 1.5)	0.402
PWV (m/s) ^b	8.1 (4.2, 19)	7.9 (4.5, 17.0)	—	0.033	8.1 (4.2, 19)	7.8 (4.5, 16.6)	—	0.061

^aValues are presented as mean±SD, paired *t*-test.

^bValues are presented as median (range), Wilcoxon sign rank test.

**p*<0.05; statistically significant.

[#]Subjects who were not available post intervention, pre intervention values were carried forward as post intervention values assuming that intervention did not have an effect on them.

—Difference could not be calculated.

S. triglycerides, serum triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1C, glycosylated hemoglobin; hs-CRP, highly sensitive C-reactive protein; U. microalbumin, urine microalbumin; SBP, systolic blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity.

TABLE 3. COMPARISON OF HbA1C VALUE AFTER INTERVENTION WITH TREE NUTS IN SELECTED STUDIES

Study	Subject type; completers (n)	Subject age (year)	Nut treatment: amount (g)	Intervention duration (month)	Baseline HbA1c (%)	End of intervention HbA1c (%)	P value
Tapsell et al. ³⁷	T2D ^a ; 18	54±8.7	Walnuts: 30	6	7.3±1.2	7.1±1.5	0.023
Jenkins et al. ³⁸	T2D ^a ; 40	63	Mixed nuts: 50–100	3	7.1±0.2	6.9±0.2	0.001
Cohen et al. ³⁹	T2D ^a ; 6 ^b	66.0±3.3	Almonds: 28	3	7.1±0.2	6.8±0.3	0.045
Gulati et al. ⁴⁰	MetS ^c ; 30	41.6±8.4	Pistachios	6	5.9±0.4	5.7±0.3	0.301

^aT2D refers to type 2 diabetes subject type.

^bPilot study.

^cMetS refers to subjects with metabolic syndrome as per modified International Diabetes Federation definition.

With no difference observed in fasting glucose and in the absence of fasting insulin measures, it is difficult to postulate the potential mechanism of action involved in the other observed benefits.

Similar results for fasting glucose levels have been observed in several mixed-nuts studies with almond intake. Despite reporting a significant improvement in HbA1c, insulin resistance, insulin sensitivity, or insulin levels, these studies have failed to show a change in FBG.^{38,43,44} These results suggest that the preferred mechanism of action of almonds behind long-term glycemic control might be through a pivotal role in insulin management rather than in reduction of glucose absorption or increased clearance.

The relationship between fasting blood lipid levels, particularly levels of LDL-C and TC, and the risk of CHD is well established in the scientific literature.^{45–47} Specifically, for every 1% reduction in LDL-C, there is a corresponding 1%–2% decrease in the risk of CHD.^{45,48} Results from the current study demonstrated a statistically significant decrease in levels of TC, LDL-C, and VLDL-C after almond supplementation in study subjects compared with intake of the control diet. Comparable results have been observed in multiple studies conducted using similar almond intake.^{49–54} As observed in other almond consumption studies, HDL-C did not change significantly after almond consumption when compared with the control diet.^{52,55–57} This might also be indicative of the preferred mechanism of action for almonds, working primarily on the cluster of lower density lipoproteins.

In addition to improved lipid levels, the subjects demonstrated significant improvement in hs-CRP levels. Higher hs-CRP levels in Asian Indian men have been correlated with high fasting insulin levels.⁵⁸ Reduced hs-CRP levels in this study again point to a potential increase in insulin sensitivity. Absence of insulin measures in this study does not confirm this finding, but a substantial decrease in hs-CRP does provide strong evidence in that direction.

The current study had a few obvious limitations, particularly the absence of insulin measures, followed by a shorter duration of the control treatment than the test treatment. However, the latter had minimal impact, as the results obtained in this study are quite comparable to studies with equal control and treatment intervention durations. However, effect of slight difference in macronutrient composition in control and intervention diets cannot be completely excluded. It is understandable that slight difference in the macronutrient composition would occur in any such investigational diet compared to control diets. Furthermore, the

pre–post design of the study using run-in as control period reduces data variability, thereby increasing the credibility of the results obtained. The role of almonds in insulin management clearly remained elusive and needs further exploration.

In terms of its strength, this is the first study ever demonstrating health benefits of almond consumption in free-living Asian Indians with T2D, despite their unique Asian Indian phenotype and their predisposition toward the disease. This study provides scientific proof of the value of almond consumption to a population that already believes in the goodness of almonds.

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Author Contributions

S.G. researched data, conducted the study, wrote the article, A.M. conceived the study idea, supervised the study, wrote the article, reviewed/edited the article, and R.M.P. performed the statistical analysis and reviewed the article.

Author Disclosure Statement

No competing financial interests exist.

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