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Humaira Jamshed
Aga Khan University

Fateh Ali Tipoo Sultan
Aga Khan University, fatehali.tipoo@aku.edu

Romaina Iqbal
Aga Khan University, romaina.iqbal@aku.edu

Anwar Gilani
Aga Khan University, anwar.gilani@aku.edu

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Dietary Almonds Increase Serum HDL Cholesterol in Coronary Artery Disease Patients in a Randomized Controlled Trial[1–3]

Humaira Jamshed,[4] Fateh Ali Tipoo Sultan,[5] Romaina Iqbal,[7] and Anwar Hassan Gilani[6]*

[4]Cardiology Section, Department of Medicine, [5]Department of Community Health Sciences and Medicine, and [6]Natural Product Research Unit, Department of Biological and Biomedical Sciences, Medical College, Aga Khan University, Karachi, Pakistan; and [7]Pakistan Council for Science and Technology, Islamabad, Pakistan

Abstract

Background: More than one-half of coronary artery disease (CAD) patients have low HDL cholesterol despite having well-managed LDL cholesterol. Almond supplementation has not been shown to elevate circulating HDL cholesterol concentrations in clinical trials, perhaps because the baseline HDL cholesterol of trial subjects was not low.

Objective: This clinical trial was designed to test the effect of almond supplementation on low HDL cholesterol in CAD patients.

Methods: A total of 150 CAD patients (50 per group), with serum LDL cholesterol ≤100 mg/dL and HDL cholesterol ≤40 mg/dL in men and ≤50 mg/dL in women, were recruited from the Aga Khan University Hospital. After recording vital signs and completing a dietary and physical activity questionnaire, patients were randomly assigned to 1 of the following 3 groups: the no-intervention group (NI), the Pakistani almonds group (PA), and the American almonds group (AA). The respective almond varieties (10 g/d) were given to patients with instructions to soak them overnight, remove the skin, and eat them before breakfast. Blood samples for lipid profiling, body weight, and blood pressure were collected, and assessment of dietary patterns was done at baseline, week 6, and week 12.

Results: Almonds significantly increased HDL cholesterol. At weeks 6 and 12, HDL cholesterol was 12–14% and 14–16% higher, respectively, in the PA and AA than their respective baselines. In line with previous reports, serum concentrations of total cholesterol, triglycerides, LDL cholesterol, and VLDL cholesterol; total-to-HDL and LDL-to-HDL cholesterol ratios, and the atherogenic index were reduced in both the PA and AA at weeks 6 and 12 compared with baseline ($P < 0.05$). Effects on serum lipids did not differ between the 2 almond groups. Dietary patterns, body weight, and blood pressure did not change in any of the 3 groups during the trial.

Conclusion: A low dose of almonds (10 g/d) consumed before breakfast can increase HDL cholesterol, in addition to improving other markers of abnormal lipid metabolism in CAD patients with low initial HDL cholesterol. This trial was registered at the Australian New Zealand Clinical Trial Registry as ACTRN12614000036617. *J Nutr* 2015;145:2287–92.

Keywords: almond varieties, low-dose, empty stomach, soaked, parallel design, optimal LDL cholesterol

Introduction

Low circulating HDL cholesterol concentrations are prevalent throughout the world, particularly in the Asian population (1), and the insufficiency of therapeutic options signifies the need to explore new avenues to counter the pathologic consequences of low HDL cholesterol (2). Approximately 35–39% of the population of the United States (3) and 33–40% of the population in the United Kingdom (4) have serum HDL cholesterol below normal. In Pakistan, the prevalence of low HDL cholesterol is reported to be as high as 60–80% (5).

Recommendations for management of low HDL cholesterol include both pharmacologic and nonpharmacologic approaches. Tolerability and safety issues of pharmacotherapies limit their use (6). Hepatotoxicity (7) and hyperglycemia (8) caused by niacin, gallstone formation (9) and myopathies (10) by fibrates, and hypertension (11) and elevation of aldosterone and cortisol (12) by torcetrapib (inhibitors of cholesteryl ester transfer protein), among others, are some of the problems calling for alternative measures to address low HDL cholesterol.

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* To whom correspondence should be addressed. E-mail: anwar.gilani@aku.edu.

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Nonpharmacologic strategies are shown to raise HDL cholesterol by 10–15% (13). Such strategies include regular exercise (14), weight reduction (15), cessation of smoking (16), and dietary modifications characterized by intake of fewer saturated fats (17), more unsaturated fats (18), high fiber, and vitamins. Almonds fit this profile because they are rich in monounsaturated fats, fiber, and vitamin E (19).

Along with other nuts, almonds are approved by the FDA because they have the potential to significantly reduce cardiovascular disease risk (20). A meta-analysis of lipid-neutralizing potential concluded that dietary almonds decrease serum cholesterol, with a strong trend to lower LDL cholesterol [P-trend = 0.05), but do not affect HDL cholesterol (21). The almond trials included in this meta-analysis, as well as others reporting serum lipid concentrations, were conducted in participants who were normolipidemic (22–27), prediabetic and/or diabetic (26, 28, 29), obese (30), and/or hyperlipidemic (31–34), without having low HDL cholesterol at baseline. It seems desirable to investigate the HDL cholesterol–raising potential of almonds in a population that has low HDL cholesterol at baseline (35), such as South Asians.

This clinical trial was conducted in coronary artery disease (CAD)[8] patients. Even with well-maintained LDL cholesterol in CAD patients, low HDL cholesterol remains an independent indicator of cardiovascular disease risk (36). Almost one-half of CAD patients at the time of hospitalization have normal LDL cholesterol but low HDL cholesterol (37). The aim of this randomized controlled clinical trial was to test the effect of almonds on HDL cholesterol in CAD patients starting with low HDL cholesterol.

Methods

Participants. Eligibility criteria included CAD patients with optimal LDL cholesterol (≤100 mg/dL) and low HDL cholesterol (men ≤40 mg/dL and women ≤50 mg/dL) (37). Patients were prediagnosed by their respective cardiologists to have CAD based on the following criteria: history of acute myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting; evidence of silent myocardial infarction on the basis of Q waves on an electrocardiogram or elevated troponins >0.1 μg/L; evidence of myocardial ischemia or infarction as shown either by segmental wall motion abnormalities on a stress echo or reversible or fixed perfusion defects on a myocardial perfusion imaging study; or CAD on angiography. Exclusion criteria included patients presenting with acute myocardial infarction in the previous 5 wk, regular nut consumers (>15 g/d; 3 d/wk), and/or patients with a nut allergy. The recruited participants were men (n = 113) and women (n = 37) aged 32–86 y with a mean body weight of 76 ± 12 kg and serum HDL cholesterol of 33 ± 6 mg/dL in men and 36 ± 6 mg/dL in women.

Study design. Ethical approval for this clinical trial (2230-Med-ERC-12) was obtained from the Ethical Review Committee, Aga Khan University, Karachi (ACTRN12614000036617).

A sample size (n = 36 per group) was calculated with the use of previous reports of a 6% HDL cholesterol improvement from almond consumption (30). The power of the study to detect significant improvement in HDL cholesterol was 80%, with a significance level of 5%. Fifty CAD patients in each of 3 groups (total n = 150) were recruited from Cardiology Clinics, Aga Khan University Hospital, Karachi, Pakistan from February to June 2012.

The medical records of patients were checked for eligibility, and recent lipid profiles (within the previous 4 wk) were considered. After obtaining informed consent, patients were randomly assigned (computer-generated block randomization) to 1 of the following 3 groups: the no-intervention group (NI) (control), the Pakistani almonds group (PA), or the American almonds group (AA). Participants in the NI were not given almonds and were instructed not to consume other nuts during their enrollment in the trial. Pakistani and American almonds were dispensed to participants in the PA and AA, respectively, for 6 wk. Patient diaries were also provided to record daily almond consumption. Compliance was monitored through regular phone calls (2 times/wk).

All participants were requested to follow the recommendations of their respective cardiologists, including drug regimens. At baseline, vital signs and prescribed drug regimens were noted. FFQs and lifestyle patterns (physical activity) were also collected. A nonfasting blood sample (5 ml) was drawn for lipid profiling.

The first follow-up visits were at week 6 (±3 d), at which nonfasting blood samples were drawn; blood pressure and body weight, among other variables, were measured; any change in medications was noted; lifestyle (i.e., physical activity patterns) and FFQs were filled out, and patients' diaries were collected. Almonds, along with patients' diaries for the next 6 wk, were dispatched to participants in the PA and AA.

At the final follow-up at week 12 (±3 d), blood samples, vital signs, changes in drug regimens, food consumption, exercise patterns, and patients' diaries were collected. Almonds were provided to the NI only after the completion of the trial (final follow-up at week 12).

Almond intervention. The Pakistani almond variety used in this study was Talwar (sword-shaped), which is grown around the region of Quetta, the capital city of Balochistan province. Locally available imported American almonds (Carmel variety, California Shelled) were obtained from the Utility Store of Defense Housing Society in Karachi. Almonds were dispensed in the form of preweighed packets (10 g/d). Participants were instructed to soak the almonds overnight and eat them after removing the skin, before breakfast (presumably on an empty stomach). Selection of this dose and mode was based on the traditional recommendation, in which 7 almonds are eaten early in the morning.

Biochemical analysis. Serum was separated from the blood samples of nonfasting subjects collected at baseline and the 2 follow-up visits by centrifuging at 2000 × g for 15 min at 4°C. Aliquots of these serum samples were stored at −80° C until further analysis. Concentrations of total cholesterol, TGs, and LDL and HDL cholesterol were measured with the use of a c-111 automated analyzer (Roche Cobas) and commercially available kits (38). VLDL cholesterol concentrations (VLDL cholesterol = TGs/5), the atherogenic index (AI) (AI = non-HDL cholesterol/HDL cholesterol), and total-to-HDL cholesterol and LDL-to-HDL cholesterol ratios were calculated (38).

Statistical analysis. Data were analyzed with the use of SPSS version 17.0 and GraphPad Prism; results are presented as means ± SEMs. Two-factor repeated-measures ANOVA was used to compare means of groups, followed by Bonferroni post hoc tests. For categorical data, a chi-square test was used to compare differences between groups. Trends in HDL cholesterol response to dietary treatments were tested with the use of multivariate linear regression, keeping HDL cholesterol as the fixed factor and nutrients (macro- and micro-) as dependent variables. A P value < 0.05 was considered statistically significant (95% CI).

Results

Follow-up was 75.3%. Reasons for attrition are presented in **Figure 1**, which also shows the flow of patients through the trial. As expected, no adverse effects were reported to be associated with almond consumption. The age, weight, and nutrient profile of patients at baseline is provided in **Supplemental Table 1**.

Drug regimens did not differ between groups and also remained fairly constant over time. Similarly, no major change in the type and intensity of physical activity, as per the questionnaire records, was noted over time for the participants of the 3 groups. Dietary patterns remained fairly constant throughout the trial duration and among the 3 groups.

[8] Abbreviations used: AA, American almonds group; AI, atherogenic index; CAD, coronary artery disease; NI, no-intervention group; PA, Pakistani almonds group.

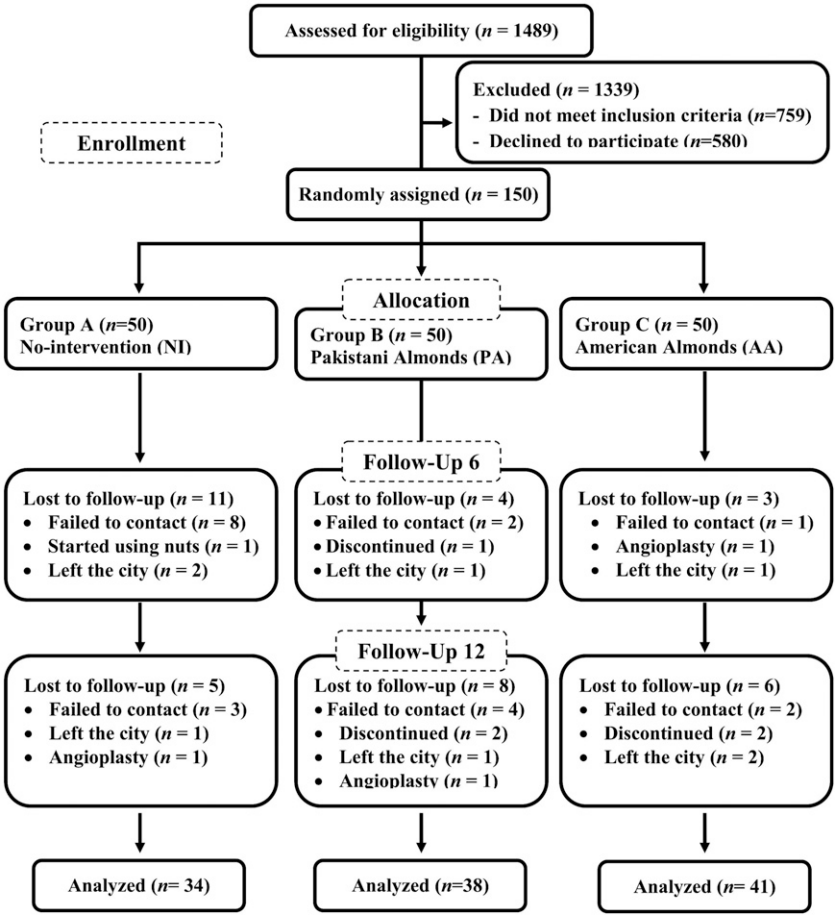

FIGURE 1 The flow of participants enrolled in the clinical trial analyzing the HDL cholesterol–raising effect of almond supplementation, participant random assignment and allocation (to either the no-intervention, American almonds, or Pakistani almonds group), and their follow-up visits.

The almond interventions significantly increased serum HDL cholesterol concentrations. At week 6, there were 16% and 14% increases in the HDL cholesterol concentration in the PA and AA compared with their respective baseline values (**Figure 2**A). At week 12, HDL cholesterol increased 22% and 21% in the PA and AA compared with their respective baseline concentrations (Figure 2B).

The PA and AA had 11% and 9% higher HDL cholesterol concentrations, respectively, than the NI at week 6, and 15% and 13% higher concentrations, respectively, at week 12 (**Table 1**). The effect on HDL cholesterol did not differ between the 2 almond groups.

The almond interventions caused a significant decrease ($P < 0.05$) in serum lipid concentrations (TGs and total, LDL, and VLDL cholesterol), at both week 6 and week 12 (Figure 2) when compared with NI. Similarly, the almond interventions significantly decreased total-to-HDL and LDL-to-HDL cholesterol ratios and the AI at weeks 6 and 12, compared with their respective baseline values (Figure 2), with no difference between the PA and AA. Systolic and diastolic blood pressure and body weight remained fairly constant in the 3 groups over time.

Discussion

To our knowledge, this is the first randomized controlled clinical trial with almonds that showed marked improvement in low serum HDL cholesterol in CAD patients. A meta-analysis showed that almond administration had no effect on HDL cholesterol (21), perhaps because most of the previous trials included healthy (24), hyperlipidemic (31), obese (39), or diabetic (26) individuals whose baseline HDL cholesterol was not particularly low.

Although the serum cholesterol and LDL cholesterol of trial participants were within normal ranges (mostly from use of lipid-lowering therapy), the almond interventions further reduced lipidemia, which is not uncommon (27). TGs, VLDL cholesterol, total-to-HDL and LDL-to-HDL cholesterol ratios, and the AI were lowered by consuming only 10 g/d of either almond variety. This is in line with previous reports, in which a high dose of almond supplementation had a similar response (33).

Almond consumption has been shown to lower serum lipids in a dose-dependent manner, with every 10 g/d corresponding to a 1% LDL cholesterol reduction (21). We observed a relatively higher reduction in serum lipids, which could be explained by the following: *1*) the CAD patients were already on lipid-lowering therapies, which may have synergistic effects on serum lipids; and *2*) the mode of almond consumption varied. Previously, almonds were mostly added to foods such as, e.g., cereals and muffins (24, 31), whereas we recommended that almonds be eaten on an empty stomach (early in the morning, before breakfast). A number of recent studies have also recommended the preferential use of almonds as snacks (40), on an empty stomach (41, 42).

Whereas patients were given 10 g/d almonds in the current study, the lowest amount previously used was 25 g/d, which was powdered and added to meals (33). Ground almonds are shown to have higher bioaccessibility of active contents (43), but the food matrix is known to hinder the gastrointestinal absorption of these contents (44). Participants of this trial used whole almonds, which may be hard to digest (45), but prolonged residence in the gut may have a prebiotic effect (46, 47). Mastication of whole almonds enhances bioavailability (48), promoting satiety (49) and limiting

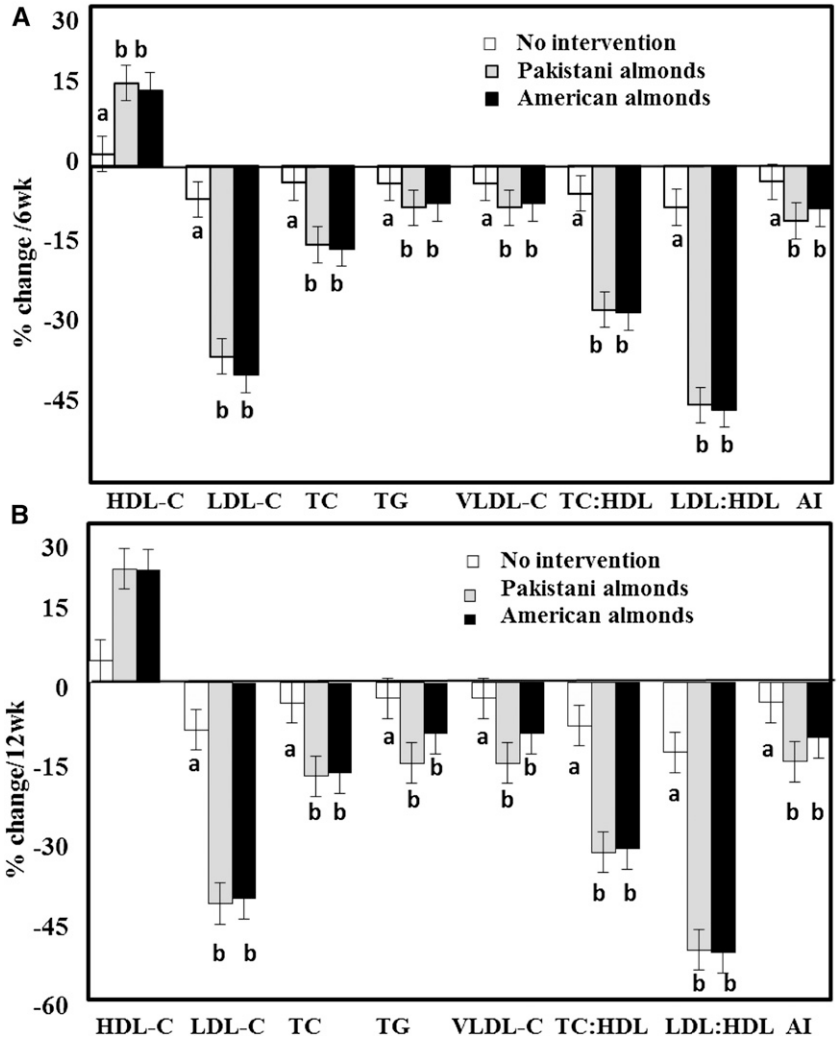

FIGURE 2 Percentage changes in serum lipids, lipoproteins, and ratios from baseline, at week 6 (A) and week 12 (B) in coronary artery disease patients in the NI, PA, or AA. Values are means ± SEMs; n = 34 in the NI, n = 38 in the PA, and n = 41 in the AA. a > b > c, where means without a common letter differ, $P < 0.05$. AA, American almonds group; AI, atherogenic index; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; NI, no-intervention group; PA, Pakistani almond group; TC, total cholesterol; VLDL-C, VLDL cholesterol.

food intake, thereby preventing weight gain (50). This may be the underpinning reason why we observed that the body weight of the participants did not change over time.

Patterns of dietary consumption were not changed over time in the study, although habitual almond consumption is reported to induce favorable dietary modifications, such as an increase in the

TABLE 1 Body weight, blood pressure, and serum lipids of coronary artery disease patients enrolled in the NI, PA, or AA at baseline, week 6, and week 12[1]

	NI			PA			AA		
	Baseline	Week 6	Week 12	Baseline	Week 6	Week 12	Baseline	Week 6	Week 12
Body weight, kg	73.4 ± 0.2^{a,x}	73 ± 0.3^{a,x}	73 ± 0.5^{a,x}	79 ± 0.2^{a,x}	79 ± 0.2^{a,y}	78 ± 0.2^{a,y}	75 ± 0.2^{a,x}	74 ± 0.1^{a,y}	74 ± 0.2^{a,y}
Blood pressure, mm Hg									
Systolic	127 ± 0.4^{a,x}	128 ± 0.5^{a,x}	126 ± 1^{a,x}	126 ± 2^{a,x}	126 ± 2^{a,y}	124 ± 3^{a,y}	128 ± 3^{a,x}	127 ± 2^{a,y}	125 ± 3^{a,y}
Diastolic	70 ± 0.2^{a,x}	71 ± 0.3^{a,x}	70 ± 2^{a,x}	67 ± 1^{a,x}	67 ± 0.5^{a,y}	66 ± 1^{a,y}	68 ± 1^{a,x}	67 ± 0.2^{a,y}	67 ± 1^{a,y}
HDL-C, mg/dL	33.9 ± 6^{c,x}	34.6 ± 6^{b,x}	35.3 ± 6^{b,x}	33 ± 5^{c,x}	38.5 ± 6^{a,y}	40.5 ± 7^{a,y}	33 ± 5^{c,x}	37.6 ± 6^{a,y}	40.0 ± 6^{a,y}
LDL-C, mg/dL	57 ± 10^{a,x}	53.5 ± 9^{b,x}	52.0 ± 9^{b,x}	57 ± 9^{a,x}	36.6 ± 6^{c,y}	33.4 ± 5^{c,y}	626 ± 9^{a,x}	37.2 ± 6^{c,y}	36.4 ± 6^{c,y}
TC, mg/dL	121 ± 21^{a,x}	117 ± 20^{b,x}	116 ± 20^{b,x}	119 ± 19^{a,x}	101 ± 16^{c,y}	98 ± 16^{c,y}	121 ± 19^{a,x}	102 ± 16^{c,y}	100 ± 16^{c,y}
TG, mg/dL	149 ± 26^{a,x}	144 ± 25^{b,x}	145 ± 25^{b,x}	142 ± 23^{a,x}	130 ± 21^{c,y}	120 ± 19^{c,y}	130 ± 20^{a,x}	122 ± 19^{c,y}	118 ± 18^{c,y}
VLDL-C, mg/dL	30 ± 5^{a,x}	29 ± 5^{b,x}	29 ± 5^{b,x}	28 ± 5^{a,x}	26 ± 4^{c,y}	24 ± 4^{c,y}	26 ± 4^{a,x}	24 ± 4^{c,y}	23 ± 4^{c,y}
TC:HDL-C ratio	3.6 ± 0.6^{a,x}	3.4 ± 0.6^{b,x}	3.3 ± 0.6^{b,x}	3.7 ± 0.6^{a,x}	2.7 ± 0.4^{c,y}	2.5 ± 0.4^{c,y}	3.7 ± 0.6^{a,x}	2.7 ± 0.4^{c,y}	2.6 ± 0.4^{c,y}
LDL-C:HDL-C ratio	1.7 ± 0.3^{a,x}	1.56 ± 0.3^{b,x}	1.47 ± 0.2^{b,x}	1.8 ± 0.3^{a,x}	0.97 ± 0.1^{c,y}	0.87 ± 0.1^{c,y}	1.9 ± 0.3^{a,x}	1.05 ± 0.1^{c,y}	0.95 ± 0.1^{c,y}
Atherogenic index[2]	1.9 ± 0.3^{a,x}	1.87 ± 0.3^{b,x}	1.86 ± 0.3^{b,x}	1.9 ± 0.3^{a,x}	1.70 ± 0.3^{c,y}	1.61 ± 0.3^{c,y}	1.8 ± 0.3^{a,x}	1.66 ± 0.3^{c,y}	1.62 ± 0.3^{c,y}

[1] Values are means ± SEMs; NI, n = 50 baseline and n = 34 at weeks 6 and 12; PA, n = 50 at baseline and n = 38 at weeks 6 and 12; AA, n = 50 at baseline and n = 41 at weeks 6 and 12; a > b > c, where labeled means for a group without a common letter differ, $P < 0.05$; x > y, where labeled means in a group at a time without a common letter differ $P < 0.05$. AA, American almonds group; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; NI, no-intervention group; PA, Pakistani almonds group; TC, total cholesterol; VLDL-C, VLDL cholesterol.

[2] Calculated as the ratio of non–HDL-C and HDL-C.

consumption unsaturated fats, fibers, and vitamins, with a decrease in the consumption of saturated fats, sodium, and sugar (27). A probable explanation for this ambiguity could be that, unlike the free-living, presumably healthy subjects from the latter study, CAD patients from the current trial had already modified their dietary patterns according to general recommendations for lipid neutralization. The 12 wk duration and low dose (10 g/d) may also be insufficient for changing dietary intake.

In South Asian tradition, almonds are considered to be a general health tonic; ~7 almonds (10 g) are soaked overnight, peeled in the morning, and eaten before breakfast (51). The participants of this study were instructed to follow the same approach based on the general acceptance of this mode of consumption in our population.

Comparison of almond varieties in this trial was based on efficacy, whereas, in previous studies, varieties were compared on the basis of composition or in vitro antioxidant potential (52, 53). Despite the fact that previous reports showed minor compositional differences between varieties, our results indicate that the medicinal effects are fairly similar.

In conclusion, almond supplementation can markedly improve low HDL cholesterol, in addition to reducing other serum lipids. To our knowledge, this is the first study of almond varieties in CAD patients showing efficacy in a lower dose (10 g/d) of almonds given on an empty stomach. This study presents almonds as a cost-effective complementary treatment strategy for low HDL cholesterol, which requires lifelong management.

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