JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Review

pubs.acs.org/JAFC

Health Benefits of Almonds beyond Cholesterol Reduction

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ABSTRACT: Almonds are rich in monounsaturated fat, fiber, α-tocopherol, minerals such as magnesium and copper, and phytonutrients, albeit being energy-dense. The favorable fat composition and fiber contribute to the hypocholesterolemic benefit of almond consumption. By virtue of their unique nutrient composition, almonds are likely to benefit other modifiable cardiovascular and diabetes risks, such as body weight, glucose homeostasis, inflammation, and oxidative stress. This paper briefly reviews the nutrient composition and hypocholesterolemic benefits; the effects of almond consumption on body weight, glucose regulation, oxidative stress, and inflammation, based on the data of clinical trials, will then be discussed. Although more studies are definitely warranted, the emerging evidence supports that almond consumption beneficially influences chronic degenerative disease risk beyond cholesterol reduction, particularly in populations with metabolic syndrome and type 2 diabetes mellitus.

KEYWORDS: *almonds, anti-inflammation, antioxidation, body weight, cholesterol, glucoregulation*

INTRODUCTION

The topic of this review is the health benefits of almond consumption beyond the improvement in lipoprotein profile. Given their favorable fatty acid composition and high fiber content, the U.S. Food and Drug Administration (FDA) released a health claim recognizing that almonds can help maintain a healthy cholesterol level, particularly in patients with hypercholesterolemia. Besides, almonds contain other putatively beneficial phytonutrients. As almonds may now be recommended by the American Heart Association (AHA) for individuals at risk for cardiovascular disease (CVD), a re-evaluation has been prompted of the possible role of almonds in healthy diets. First, we will present clinical evidence showing that almonds could play a role in body weight (BW) management given that almond consumption might elicit satiety, as well as the fact that the fats in almonds may not be so accessible for absorption. Because of their low carbohydrate (CHO) and high unsaturated fat content, almonds are also regarded as a low glycemic index (GI) food. Given the aforementioned, we will then discuss the evidence on the impact of almonds on glucose homeostasis in healthy individuals or those who are at increased risk for metabolic syndrome and type 2 diabetes mellitus (T2DM). Finally, as almonds contain a variety of nutrients exerting antioxidant and anti-inflammatory actions, that is, α-tocopherol and polyphenols, we will present studies demonstrating how almonds could ameliorate biomarkers of inflammation and oxidative stress.

PRODUCTION

Almond (*Prunus dulcis*) is a species of tree related to peach, plum, and cherry in the subgenus *Amygdalus*. Almond probably originated in the Middle East and spread to other parts of the world.[1,2] California, specifically the Central Valley of the Sacramento and San Joaquin areas, is currently the leading producer of almonds worldwide because the region has the ideal growing conditions for almonds, including mild climate, rich soil, and abundant sunshine. During the past 20 years, perhaps in response to increasing consumer awareness about the healthfulness of almonds, California's almond production has doubled, such that they are now a leading agricultural product.[3] The top 10 almond-producing varieties among the over 30 major varieties are Nonpareil, Monterey, Butte/Padre, Carmel, Butte, Fritz, Padre, Aldrich, Sonora, and Price.[3] During the 2009/2010 crop year, California produced 1.406 billion pounds of almonds on 720 000 bearing acres, which is ∼80% of almonds consumed globally.

In botanical terms, the almond fruit is not a nut, but a drupe, 3.5−6 cm (1−2 in.) long, consisting of a thick leathery gray-green hull (exocarp and mesocarp) and a reticulated hard woody shell (endocarp) with the seed [("nut") endosperm] inside. Almonds are grouped into two types: sweet and bitter. Sweet almonds are grown for their edible nuts and commonly consumed, whereas bitter almonds have been used medicinally in folk medicine in Asia and Europe.[2,4] The bitter taste of the bitter almonds is attributed to amygdalin. Besides the taste difference from the sweet almonds, the bitter almond contains traces of prussic or hydrocyanic acid in its raw state, which can be lethal to animals and humans. The toxicity of the poison is destroyed by heat and processing.[5]

NUTRITION COMPOSITION

Almonds are a nutrient-dense food as defined by the FDA; a standard 28 g serving is an excellent source [i.e., containing >20% of the daily value (DV)] of α-tocopherol (36.4%) and manganese (36.0%). Almonds are also a good source (i.e., containing 10−20% DV) of magnesium (19.5%), copper (16.0%), phosphorus (13.4%), fiber (13.2%, with an

Special Issue: Food Bioactives and the Journal of Agricultural and Food Chemistry

Received: November 2, 2011
Revised: January 31, 2012
Accepted: February 1, 2012
Published: February 1, 2012

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Table 1. Effect of Almonds on Cholesterol in Clinical Interventions

ref	subjects	study design/duration	diet intervention	results[a]
Sabaté et al., 2003[12]	11 F, 14 M, healthy and hypercholesterolemic	crossover, controlled feeding, 4 weeks	68 g almonds vs NCEP Step 1 diet	TC: 4.4% ↓ LDL-C: 7.0% ↓
Jenkins et al., 2003[13]	9 F, 16 M, hyperlipidemic	parallel, controlled feeding, 1 month	16.6 g/1000 kcal almonds vs Portfolio diet	TC: 26.6% ↓ LDL-C: 35% ↓
Spiller et al., 1998[14]	33 F, 12 M, hypercholesterolemic	parallel, 4 weeks	100 g almonds diet vs olive oil diet vs dairy diet	TC: 9% ↓ LDL-C: 12% ↓ HDL-C: no change
Hyson et al., 2002[15]	12 F, 10 M, healthy	crossover, 6 weeks	35 g almond oil and 66 g whole almonds vs baseline diet	TC: 4%, 4% ↓ LDL-C: 6%, 7% ↓ HDL-C: 4%, 7% ↑
Jenkins et al., 2002[16]	12 F, 15 M, hypercholesterolemic	crossover, 4 weeks	28 and 56 g almonds vs LFA baseline diet	LDL-C: 4.7%, 9.9% ↓
Kohls et al., 1987[19]	11 F, 1 M, healthy	crossover, controlled feeding, 5 weeks	1.2 g arginine vs baseline diet	TC and LDL-C: ↓ (P = 0.047 and 0.039)

[a] ↓, decrease; ↑, increase.

insoluble/soluble fiber ratio of 4:1), riboflavin (13.5%), and protein (12.1%).[6] In addition, almond proteins possess good digestibility and are unusually high in arginine.[7] The 164 kcal provided by 28 g of almonds is derived largely from their fat content (49.4% of weight). However, it is important to note that their fatty acid composition is largely of unsaturated fats (13 g of unsaturated fat and only 1 g of saturated fat) with monounsaturated fatty acids (MUFA) being 67%. Almonds also contain an array of phytonutrients including phenolic acids, phytosterols, and polyphenolic compounds such as flavonoids and proanthocyanidins, all of which are included in nutrient databases.[7] A recent review has shown 100 g of almonds contains 2 μg of carotenoids, 261 mg of gallic acid equivalents of total phenolics, 25.01 mg of flavonoids, 184.02 mg of proanthocyanidins, 192.37 mg of phytosterols, 25.01 mg of flavonoids/100 g, and 595.63 μg of lignans.[8] Importantly, the aforementioned profile is affected not only by cultivar but also harvest year and orchard location, processing steps, and storage.[9] Almond polyphenols have been found to be bioaccessible, bioavailable, and subsequently metabolized by phase II conjugating enzymes and gut microflora.[10]

CHOLESTEROL REDUCTION

Almonds and other tree nuts were not originally considered good choices for inclusion in heart-healthy diets because of their high fat content. However, results of numerous clinical studies conducted to date in healthy individuals, as well as in individuals with hypercholesterolemia, have demonstrated that almond consumption has positive effects on lipoprotein profile, primary targets for CVD prevention. The effect of almond consumption on the lipoprotein profile has been extensively reviewed, as well as the putative mechanisms of action.[11] In this review, we have briefly examined such an effect of almonds (Table 1). Sabaté et al.,[12] in a randomized crossover controlled feeding trial, included 68 g of almonds in a National Cholesterol Education Program (NCEP) Step I diet to replace 20% of total calories for 4 weeks and found that total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) concentrations were 4.4 and 7.0% lower, respectively, than in the same diet without almonds in healthy and mildly hypercholesterolemic adults (11 F, 14 M; age, 41 years; BMI, <30 kg/m^2). Similarly, including 16.6 g/1000 kcal almonds with plant sterols, soy protein, and viscous fiber in their vegan Portfolio Dietary Plan for 1 month, Jenkins et al.,[13] in a randomized controlled feeding study, reported reductions of approximately 26.6 and 35% in TC and LDL-C, respectively, in hyperlipidemic patients (9 F, 16 M; age, 60 years; BMI, 26.6 kg/m^2).

Almonds have a high unsaturated to saturated fatty acid ratio, which facilitates a favorable shift in the fatty acid profile of the diet when almonds are substituted for foods that are high in saturated fat.[6] Spiller et al.[14] first reported that consumption of 100 g of almonds daily for 4 weeks in a randomized parallel design study decreased TC (9%) and LDL-C (12%) in 26 free-living hypercholesterolemic patients (33 F, 12 M; age, 53 years; BW, 66 kg) and did not affect high-density lipoprotein-cholesterol (HDL-C). This reduction in LDL-C was greater than that obtained by the corresponding intervention with 48 g/day olive oil, which is also rich in unsaturated fat. Hyson et al.[15] extended this observation in a randomized crossover trial of 22 free-living healthy subjects (12 F, 10 M; age, 43.5 years; BMI, 23.7 kg/m^2) by achieving reductions in TC (4%, 4%) and LDL-C (6%, 7%) and increases in HDL-C (4%, 7%) by replacing half of their fat intake with 66 g of whole almonds (containing 35 g fat) and 35 g of almond oil, respectively for 6 weeks. Jenkins et al.[16] illustrated the robustness of this effect in a randomized crossover study by demonstrating a linear dose–response relationship with the addition of 28 and 56 g of almonds daily to an isocaloric diet for 1 month, lowering LDL-C by 4.7 and 9.9%, separately, and extrapolating that each 7 g/day of almond intake reduces LDL-C by 1%. They further extrapolated these results from 27 free-living hyperlipidemic subjects (12 F, 15 M; age, 64 years; BMI, 25.7 kg/m^2) to suggest that 28 and 56 g/day almonds for 1 month would reduce the 10 year risk of CVD by 7.1 and 9.0%, respectively.

Although almonds are recognized for their unique fatty acid profile, approximately 15% of their energy is protein, making almonds a good protein source.[6,7] Diets that partially replace CHO with protein have been shown to have beneficial effects on LDL-C levels in both normolipidemic and hypercholesterolemic individuals.[17,18] More specifically, as aforementioned, the amino acid arginine is abundant in nuts.[7] Besides arginine being a substrate of nitric oxide (endothelial relaxant), arginine may have a cholesterol-lowering effect. A 5 week crossover, controlled feeding trial of 12 subjects (11 F, 1 M) supplemented with arginine (1.2 g) or placebo resulted in a significant reduction in both serum TC (P < 0.047) and LDL-C (P < 0.039) with the administration of arginine, as compared to the placebo group.[19]

dx.doi.org/10.1021/jf2044795 | J. Agric. Food Chem. 2012, 60, 6694–6702

Table 2. Effect of Almonds on Body Weight in Clinical Interventions

reference	subjects	study design/duration	diet intervention	results
Fraser et al., 2002[26]	38 F, 43 M, healthy	crossover, 6 months	56 g/day almonds vs baseline diet	BW: 0.4 kg ↑ waist/hip ratio: no change
Hollis et al., 2007[22]	24 subjects, healthy	crossover, 10 weeks	2 oz serving of almonds vs baseline diet	food intake: 0.05% ↑ kcal
Cassady et al., 2009[29]	5 F, 8 M, healthy	crossover, controlled feeding, 4 days	chewing 55 g almonds 10, 25, or 40 times vs baseline diet	up to 2 h after consumption: (1) hunger ↓ < baseline (2) gullness ↑ > baseline longer for 40 than 25 chews
Wien et al., 2003[31]	28 F, 37 M, overweight and obese	prospective, 24 weeks	84 g/day almonds vs a CHO-based low-calorie diet	BW: 62% ↓ BMI: 62% ↓ waist circum: 50% ↓ fat mass: 56% ↓
Scott et al., 2003[32]	17, metabolic syndrome and T2DM	parallel, 42 weeks	almond-based, high-fat diet vs AHA diet	nonsignificant ↓ in BW compared to control

Nuts are rich sources of other bioactive nutrients including dietary fiber and phytosterols. Among nuts, almonds have the highest fiber content and are considered a good source of dietary fiber, providing approximately 12% of the daily recommended amount of fiber per serving.[6] The role that insoluble fiber plays in reducing intestinal transit time and the subsequent increase in satiation may be the mechanism by which almonds decrease LDL-C.[20,21] The results of a 23 week crossover study demonstrated that when 24 free-living subjects (age, 24 years; BMI, 25.9 kg/m^2) consumed a 2 oz serving of almonds daily for 10 weeks, they compensated for the energy provided by the almonds and reduced their food intake from other sources that have a less favorable nutrient profile.[22] Phytosterols are a class of compounds that interfere with intestinal cholesterol absorption and thus help lower blood cholesterol. Almonds contain 192.4 mg of phytosterols per 100 g;[8] the NCEP diet for individuals with high blood cholesterol recommends consumption of 2 g of plant sterols daily.[23] According to Segura et al.,[24] phytosterols might justify part of the cholesterol-lowering effect of nut intake beyond that attributable to fatty acid exchange. Collectively, these studies demonstrate a consistent LDL-C lowering effect of almonds.

BODY WEIGHT CONTROL

The rapidly growing prevalence of overweight and obesity and its implication for obesity-related diseases, including cancer, CVD, and T2DM, is due principally to inadequate levels of physical activity and excessive consumption of calories. Thus, energy-dense foods such as nuts would appear contraindicated as part of the solution to this problem. However in this review, we have examined how nut consumption is not associated with a higher BW (Table 2). According to the review conducted by Sabaté et al.,[25] nut consumption is not associated with a higher BMI among free-living individuals. In addition, Fraser et al.[26] reported in a randomized crossover study that including 56 g/day almonds (providing 320 kcal/day) for 6 months in the habitual diet of 81 free-living healthy people (38 F, 43 M; age, 40.4 year; BMI, 24.3−28 kg/m^2) resulted in a nonsignificant mean gain of 0.4 kg and no change in waist/hip ratio. This lack of effect was attributed to the observed displacement of energy from other foods, satiating property of almonds, and probable modest malabsorption of fat from almonds. With regard to the latter factor, a series of experiments by Ellis et al.[27] suggest fats in almonds may be poorly absorbed as their cell walls limit the bioaccessibility of fats to physical and enzymatic actions in the gastrointestinal tract. Consistent with these results, preliminary evidence from Zemaitis and Sabaté[28] indicated an increase in fat excretion in people consuming almonds.

Satiation reflects processes that influence the size of an eating event, and satiety is defined by the processes that influence eating frequency. One of the lesser studied properties of almonds that may contribute to their satiety effect is their physical structure. They are crunchy and must be mechanically reduced to particles small enough for swallowing. During a 23 week crossover design study, 20 free-living women (age, 24 years; BMI, 25.9 kg/m^2) were required to consume almonds for 10 weeks followed by another 10 weeks following their customary diet. Hollis and Mattes[22] found that almond consumption (2 oz/day) did not cause a change in BW predominately due to compensation for the energy contained in the almonds through reduced food intake from other sources. Mattes and his colleagues[29] further explored the effect of mastication of almonds on appetite and appetite hormone response in a randomized crossover controlled feeding study involving 13 healthy adults (5 F, 8 M; age, 24 years; BMI, 23.1 kg/m^2) chewing 55 g of almonds, 10, 25, or 40 times. They found that hunger was acutely suppressed below baseline ($P < 0.05$) and fullness elevated above baseline ($P < 0.05$) longer after 40 chews than after 25 chews. This study underscores the important effects of chewing on various factors that influence weight management, that is, fat absorption, release of gut peptides, and satiety.

According to the large cohort of the Women's Health Initiative, low-fat diets (20% of energy or less) have poor adherence.[30] Thus, alternative approaches with healthful diets including more moderate fat content, that is, 35% of total energy intake and <10% total calories from saturated fats, which improves palatability, may enhance compliance and maintain weight reduction for outpatient treatment of obesity. Wien et al.[31] applied this approach in a randomized prospective 24 week trial using a low-calorie diet (1012 kcal/day) containing 39% of calories from fat in 65 free-living overweight and obese subjects (28 F, 37 M; age, 55 years; BMI, 38 kg/m^2). Their menu plan included 84 g/day almonds and led to reductions in BW, BMI, waist circumference, and fat mass that were 62, 62, 50, and 56% greater, respectively, than a comparable, CHO-based low-calorie diet equivalent in protein, saturated fat, and polyunsaturated fatty acids. Furthermore, insulin responsiveness and circulating insulin and glucose concentrations were slightly improved by the almond diet compared to the low-CHO diet. Similarly, after a 42 week randomized intervention with an almond-based, high-fat diet (44, 22, and 25% calories from fat, MUFA, and protein, respectively) versus a

contemporary AHA diet (30, 15, and 15% calories from fat, MUFA, and protein, respectively) in 17 free-living patients (BMI >25 kg/m^2) with metabolic syndrome and T2DM, Scott et al.[32] found reductions in BW in the former diet. Triglyceride, fasting glucose, and LDL-C were also improved in the almond versus the contemporary AHA diet. Hence, the current data do not indicate that free-living people on self-selected diets including almonds or other nuts frequently have a higher BMI or increased BW. As almonds are a rich source of various nutrients, vitamins, minerals, unsaturated fat, protein, and antioxidants, they could be part of a balanced, healthy diet in BW management.

GLUCOREGULATION

Blood glucose is tightly regulated through catabolic hormones (i.e., glucagon, cortisol, and catecholamines) and anabolic hormones (i.e., insulin), as part of metabolic homeostasis. Impaired glycemic control, manifested with hyperglycemia and insulin resistance, contributes greatly to the development and progression of metabolic-related disorders and diseases, that is, metabolic syndrome, T2DM, and CVD. With the increasing prevalence of overconsumption and physical inactivity associated with the Western lifestyle, the increase in obesity and its associated hyperglycemia and insulin resistance continue to be matters of great health concern. Although there are many approaches to alleviating the risk of diseases related to or evolved from impaired glycemic control, lifestyle modifications (dietary changes, physical activity, and weight loss) appear to be feasible and cost-effective.[33]

The nutrient composition of almonds and other nuts (i.e., high in unsaturated fats and fiber and low in CHO) and emerging clinical evidence provide a strong justification in support that they might decrease the risk of T2DM (Table 3). Josse et al.[34] reported in a GI controlled feeding trial with nine healthy volunteers (age, 27.8 years; BMI, 22.9 kg/m^2) that the addition of almonds to 50 g of available CHO from white bread resulted in a reduction in the GI of the composite meal in a dose-dependent manner for the 30 g (105.8), 60 g (63.0), and 90 g (45.2) doses (r = −0.524, P = 0.001). From the same group, Jenkins et al.[35] in a randomized crossover controlled feeding trial with 15 healthy individuals (age, 26.3 years; BMI, 23.4 kg/m^2) compared the GI values of 60 g of almonds added to white bread, parboiled rice, or instant mashed potatoes. GI values for rice at 38 and almonds plus white bread at 55 were found to be less than for potatoes at 94, even though all meals contained the comparable amounts of protein, fat, and CHO. The postprandial areas under the insulin concentration time curve were different as well. Because the nutrient bioaccessibility of almonds consumed in different physical forms might be different, Mori et al.[36] studied whether the effect of almonds on postprandial glucose response was physical form dependent. In a randomized crossover controlled feeding trial with 14 patients (age, 39.3 years; BMI, 33.0 kg/m^2) with impaired glucose tolerance, 42.5 g of whole almonds, but not comparable amounts of almond butter or defatted almond flour, added to a 75 g available CHO-matched breakfast meal was found to decrease postprandial glucose response compared to a no-almond vehicle. As almond oil exhibits the same degree of blunting effect on postprandial glucose response, the authors suggested that the outcome might be most likely ascribed to the high unsaturated fat composition of almonds. Cohen and Johnston[37] in a controlled feeding trial further examined the effect of 28 g of almonds added to a treatment meal on

Table 3. Effect of Almonds on Glycemic Control in Clinical Interventions

reference	subjects	study design/duration	diet intervention	results
Jenkins et al., 2006[35]	8 F, 7 M, healthy	crossover, controlled feeding, 10 weeks	60 g almonds added to composite meal vs parboiled rice and potatoes	GI values for rice (38) and almonds (55) were 59% and 41% less than for potatoes (94)
Mori et al., 2011[36]	14 subjects, impaired glucose tolerant	crossover, controlled feeding, 10 weeks	42.5 g whole almonds, almond butter or defatted almond flour vs composite meal	whole almonds but not almond butter or defatted almond flour ↓ postprandial glucose response (P < 0.001)
Cohen and Johnson, 2011[37]	3 F, 4 M, diabetes; 11 F, 2 M, no diabetes	parallel, controlled feeding, 12 weeks	28 g almonds vs treatment meal	almonds ↓ postprandial glucose response by 30% in 4 participants with T2DM but did not in 11 participants without T2DM
Lovejoy et al., 2002[39]	17 F, 13 M, T2DM	crossover, 4 weeks	57−113 g/day almonds vs LFA and HFA diet	glycemic status: no change insulin sensitivity: no change HbA1$_c$: no change
Scott et al., 2003[32]	17 subjects, metabolic syndrome and T2DM	parallel, 42 weeks	almond-based, high-fat diet (44% calories from fat) vs AHA diet (30% calories from fat)	modestly better glycemic control (−3.2 vs −2.2 mmol)
Li et al., 2010[40]	11 F, 9 M, T2DM	crossover, 12 weeks	almonds (20% calories) vs NCEP Step 2 diet	fasting blood glucose: 4.1% ↓ insulin: 0.8% ↓HOMA: 9.2% ↓

dx.doi.org/10.1021/jf2044795 | J. Agric. Food Chem. 2012, 60, 6694−6702

postprandial glycemic response as compared to the isocaloric control meal with similar CHO and fat contents. They confirmed that almonds blunted postprandial glucose response by 30% in four participants with T2DM (age, 66 years) but did not influence this parameter in 11 participants without diabetes (age, 53 years). Overall, almonds decrease GI values of coconsumed foods with high GI values and, in turn, help diminish postprandial blood glucose surge and consequent oxidative stress and inflammation.

According to the American Diabetes Association, the primary objective in the management of diabetes should be regulation of blood glucose levels.[38] Almonds are low in available CHO, have a healthy fatty acid profile, and are high in vegetable protein, fiber, and magnesium. Therefore, almonds appear to be a suitable candidate food to be included in a diabetes management plan, although more research is warranted to monitor potential diet and drug interactions. To date, there have been four clinical trials[32,37,39,40] examining the effect of almonds on glycemic control in patients with T2DM with mixed results. Lovejoy et al.[39] found in a randomized crossover trial that incorporating 57−113 g/day almonds (10% calories) to either a low-fat (25% calories from fat) or high-fat (37%) habitual diet in 30 free-living T2DM patients (13 M, 17 F; age, 53.8 years; BMI, 33 kg/m^2) for 4 weeks did not change their glycemic status, insulin sensitivity, and $HbA1_c$. After a 42 week intervention with an almond-based, high-fat diet (44, 22, and 25% calories from fat, MUFA, and protein, respectively) versus a contemporary AHA diet (30, 15, and 15% calories from fat, MUFA, and protein, respectively) in 17 free-living patients (BMI $\geq$ 25 kg/m^2) with metabolic syndrome or T2DM, Scott et al.[32] noted that the former diet was modestly better in glycemic control. Li et al.[40] reported in a randomized, crossover, controlled trial that almonds replacing 20% calories of the NCEP Step 2 diet significantly decreased fasting blood glucose and insulin and homeostatic model assessment (HOMA) in 20 free-living Chinese patients (9 M, 11 F; age 58 years; BMI, 26 kg/m^2) with T2DM as compared to the NCEP Step 2 diet without almonds. Cohen and Johnston[37] reported in a 12 week randomized, parallel designed trial with 13 free-living patients with T2DM (age, 66 years; BMI, 34.6 kg/m^2) that consumption of 28.4 g/day almonds (173 kcal) at a frequency of 5 days/week decreased $HbA1_c$ as compared to cheese control containing 160 kcal energy (almond vs cheese: 4% reduction vs 1% increase, as compared to the corresponding baseline value). The differences in subject ethnicity, study duration, background diet, and almond dosage could somewhat contribute to the inconsistency in the results reported in the four studies. Furthermore, an increase in BW found in the Lovejoy et al. study[39] might have masked the benefit of almond intake on glycemic control. Future studies with robust study design shall be performed taking the above factors into consideration to substantiate the benefits of incorporation of almonds into healthy diets on glycemic control in patients with T2DM and individuals at increased risk of developing the diabetes.

Almonds may help to decrease the incidence of metabolic syndrome, T2DM, and CVD via the mechanism of glucose regulation because postprandial hyperglycemia has been associated with increased risk of CVD.[41] The possible mechanisms of action of almonds on glycemic control remain to be examined. It has been proposed that the high-energy density of almonds might decrease gastric emptying, in turn decreasing the rates of CHO breakdown and glucose absorption. Polyphenolics and phytates present in whole almonds with skins might also contribute by exerting an inhibitory effect on starch digestive enzymes.[42,43]

■ ANTIOXIDATION

A diet rich in fruits, vegetables, and minimally refined grains is associated with lower risk for chronic degenerative diseases. It has been assumed that dietary antioxidants may explain this protective effect as oxidative stress is common in chronic degenerative diseases. As above-mentioned, almonds contain an array of antioxidants, including α-tocopherol and polyphenolics.[8] With different properties, almond antioxidants may work in an additive/synergistic manner to increase antioxidant defense capacity via either radical scavenging action, up-regulation of endogenous antioxidant systems, or both (Table 4). In an in vitro LDL oxidation study, we have demonstrated that almond polyphenols and α-tocopherol could protect LDL against Cu^{2+}-induced oxidation to a degree greater than the sum of each alone, suggesting that individual foods or meals containing all of these nutrients may provide greater than anticipated antioxidant activity.[44,45] The antioxidant effect of almonds is also demonstrated in a handful of clinical trials. Jambazian et al.[46] demonstrated the bioavailability of α-tocopherol from almonds by feeding 16 free-living healthy volunteers (8 F, 8 M; age, 41 year; BMI, 25.2 kg/m^2) 28 or 58 g/day (replacing 10 and 20% total energy intake, respectively) for 4 weeks, with plasma α-tocopherol concentrations being increased by 13.7 and 18.7%, respectively. Jenkins et al.[47] found that the addition of 36.5 or 73 g/day almonds to the habitual diet of 27 free-living hyperlipidemic (12 F, 15 M; age, 64 year; BMI 25.5 kg/m^2) patients for 4 weeks significantly increased the resistance of LDL-C to oxidation and decreased serum MDA and urinary isoprostanes. Similarly, Jalali-Khanabadi et al.[48] demonstrated that the resistance of LDL against in vitro Cu^{2+}-induced oxidation was enhanced by 60 g/day almonds for 4 weeks in 30 free-living healthy Iranian men with mild hyperlipidemia (age, 45 years; BMI, 24.3 kg/m^2). Consistently, our preliminary data showed that adding ~60 g/day almonds to the NCEP Step 2 for 4 weeks decreased circulating oxidized LDL and decreased LDL oxidizability to in vitro Cu^{2+}-induced oxidation in 20 free-living Chinese patients with T2DM.[46] However, Hyson et al.[15] did not find a change in LDL-C oxidizability in 22 free-living normolipidemic subjects fed 66 g/day almonds for 6 weeks.

Some studies have shown the antioxidant effects of almonds are not limited to reduced fatty acid peroxidation. Jenkins et al.[35] reported in a controlled feeding study with 15 healthy young adults that a meal with 60 g of almonds significantly increased postprandial serum protein thiol concentrations as compared with breakfast meals of rice or potato containing comparable amounts of protein, fat, and CHO. Similarly, our preliminary data showed that the incorporation of ~60 g/day almonds to the NCEP Step 2 diet decreased serum protein carbonyl content in free-living Chinese T2DM patients.[49] These data could reflect an antioxidative effect of almond antioxidants on postprandial oxidative damage to proteins. However, it shall be noted that the glucose excursion effect of almond nutrients may decrease glucose-derived radical generation and consequent oxidative damage. Li et al.[50] reported in a crossover, randomized, clinical trial with 60 free-living young male smokers (age 18−25 years; 5−20 cigarettes/day) that 4 weeks of almond consumption at 84 g/day insignificantly decreased lymphocyte DNA strand breaks

Table 4. Effect of Almonds on Oxidative Stress in Clinical Interventions

ref	subjects	study design/duration	diet intervention	results
Jambazian et al., 2005[46]	8 F, 8 M, healthy	crossover, controlled, 4 weeks	28 or 58 g/day almonds vs baseline diet	plasma α-tocopherol concentrations: 13.7 and 18.7% ↑
Jenkins et al., 2008[47]	12 F, 15 M, hyperlipidemic	crossover, 3 months	36.5 or 73 g/day almonds vs baseline diet	for 73 g/day almonds, serum MDA: 19% ↓ urinary isoprostanes: 15% ↓
Jalali-Khanabadi et al., 2010[48]	30 M, healthy	parallel, 4 weeks	60 g/day almonds vs baseline diet	LDL oxidizability: 30% ↓ (prolonged lag time)
Chen et al., 2011[49]	20 subjects, T2DM	crossover, 4 weeks	~60 g/day almonds vs NCEP Step 2 diet	circulating oxidized LDL-C: ↓ serum protein carbonyls content: ↓
Hyson et al., 2002[15]	12 F, 10 M, healthy	crossover, 6 weeks	66 g whole almonds and 35 g almond oil vs baseline diet	LDL oxidizability: no change
Jenkins et al., 2006[35]	8 F, 7 M, healthy	crossover, controlled feeding, 10 weeks	60 g almonds added to composite meal vs parboiled rice and potatoes	increased postprandial serum protein thiol concentrations (15 mmol/L) were 50% greater than rice and potatoes (10 mmol/L)
Li et al., 2007[50]	60 subjects, smokers	crossover, 4 weeks	84 g/day almonds vs baseline diet	lymphocyte DNA strand breaks: ↓ urinary 8-hydroxy-deoxyguanosine: ↓ activities of serum superoxide dismutase: ↑ activities of glutathione peroxidase: ↑

and urinary 8-hydroxydeoxyguanosine as compared to isocaloric pork (120 g/day). They also demonstrated that adding almonds led to increased activities of serum superoxide dismutase and glutathione peroxidase.

Clinical evidence mostly supports that almond nutrients could increase antioxidant defense and protect susceptible macromolecules against oxidation locally and systematically in individuals with enhanced oxidative stress. Whereas challenges in demonstrating antioxidant efficacy of foods or nutrients in healthy individuals is well appreciated, it will be worthwhile to examine the antioxidant activity of almond nutrients in healthy people subjected to an acute bout of enhanced oxidative stress, that is, exhaustive exercise. The contribution of almond antioxidants in this regard remains unknown. Nevertheless, it is clear that the antioxidant effect of almonds can be a consequence of the cooperative action of all antioxidant nutrients in almonds. On the other hand, the reductions in biomarkers of oxidative stress can simply reflect the improvements in pathological conditions that can cause production of oxidants. For example, Jenkins et al.,[47] after feeding 73 g/day of almonds to free-living hyperlipidemic subjects, attributed the reduction in biomarkers of oxidative stress to their phenolic antioxidant content as no increase in serum vitamin E was obtained with the intervention, despite its proven bioavailability.[46] Finally, the improvements in hyperlipidemia and hyperglycemia may contribute to a decrease in oxidative stress.

■ ANTI-INFLAMMATION

Inflammation plays a critical role in the risk for and progression of CVD and T2DM such that biomarkers such as C-reactive protein (CRP) and interleukin-6 (IL-6) are independent predictors of their pathology.[51−53] An anti-inflammatory action by almonds and other nuts is consistent with the observation that each of these biomarkers is inversely associated with an increased frequency of nut and seed consumption[54] (Table 5). In a randomized, controlled, crossover clinical trial, Rajaram et al.[55] examined the effect of different doses of almonds on selected biomarkers of inflammation. Among free-living healthy adults (14 F, 11 M; age, 40 years; BMI, <30 kg/m^2), incorporating almonds into the diet at 10 and 20% of calories (34 and 68 g/2000 kcal, respectively) for 4 weeks lowered CRP compared to a nut-free control diet, although no dose−response relationship was observed. E-selectin, a cell adhesion molecule activated by cytokines during inflammation, was also significantly lower, but only with the higher almond dose. In the randomized crossover trial of the Portfolio Dietary Plan by Jenkins et al.,[56] 34 free-living hyperlipidemic subjects (14 F, 20 M; age, 55.4−62.7 years; BMI, 27.3 kg/m^2) completed three 1 month interventions on a very low saturated fat control diet, the same diet with 20 mg of lovastatin, and a portfolio diet high in plant sterols (1.0 g/1000 kcal), soy protein (21.4 g/1000 kcal), viscous fibers (9.8 g/1000 kcal), and almonds (14 g/1000 kcal). Percent reduction in CRP on the portfolio diet was comparable to that achieved with lovastatin plus NCEP Step 2 diet, 23.8−28.2 and 16.3−33.3%, respectively, as well as a calculated risk of coronary heart disease at 25.8 and 24.9%, respectively.

The Mediterranean diet rich in foods high in monounsaturated fat has been shown to have beneficial effects on inflammatory biomarkers and endothelial function. In the PREDIMED study of 772 free-living asymptomatic adults (age, 68 years; BMI, 37−50 kg/m^2),[57] a Mediterranean diet including mixed nuts (30 g/day of walnuts, hazelnuts, and almonds)

dx.doi.org/10.1021/jf2044795 | J. Agric. Food Chem. 2012, 60, 6694−6702

Table 5. Effect of Almonds on Inflammation in Clinical Interventions

reference	subjects	study design/duration	diet intervention	results
Rajaram et al., 2010[55]	14 F, 11 M, healthy	crossover, 4 weeks	almonds 10 and 20% of calories vs baseline diet	CRP: 6.3% ↓ E-selection: 7.8% ↓
Jenkins et al., 2005[56]	14 F, 20 M, hyperlipidemic	crossover, 3 months	14 g/1000 kcal almonds vs Portfolio diet vs 20 mg lovastatin	CRP ↓ on the portfolio diet comparable to lovastatin plys NCEP Step 2: 23.8−28.2% ↓ vs 16.3−33.3% ↓
Estruch et al., 2006[57]	433 F, 339 M, high cardiovascular risk	parallel, 3 months	Mediterranean diet, mixed nuts (30 g/day walnuts, hazelnuts, and almonds) vs low-fat diet	circulating IL-6: 1.3 ng/mL ↓ ICAM-1: 97 ng/mL ↓ VCAM-1: 167 ng/mL ↓ CRP: no change
Salas-Salvadó et al., 2007[58]	433 F, 339 M, high cardiovascular risk	parallel, 3 months	Mediterranean diet, mixed nuts (30 g/day walnuts, hazelnuts, and almonds)	lowest concentrations of ICAM-1 in the highest quintile of nuts vs lowest quintile of nuts (17% > ↓)
Mena et al., 2009[59]	106 subjects (43% women), high cardiovascular risk	parallel, 3 months	Mediterranean diet, mixed nuts (30 g/day walnuts, hazelnuts, and almonds)	with supplemental mixed nuts (>3/weeks) IL-6: 20% ↓ ICAM-1: 10% ↓ VCAM-1: no change CRP: no Change

reduced levels of circulating IL-6 ($P < 0.018$), intracellular adhesion molecule-1 (ICAM-1) ($P < 0.003$), and vascular cell adhesion molecular-1 (VCAM-1) ($P < 0.003$) from baseline after 3 months, but not CRP compared with a low-fat diet. Salas-Salvadó et al.[58] extended this observation in a substudy by achieving lower concentrations of ICAM-1 in the highest quintile of nut consumption ($P < 0.003$). Similarly, in another substudy of 106 older participants (age, 68 years), Mena et al.[59] illustrated a reduction in IL-6 and ICAM-1 from baseline after 3 months on a Mediterranean diet with supplemental mixed nuts (>3 servings/week) ($P < 0.05$), but not VCAM-1 and CRP, compared with a low-fat diet. In conclusion, these studies suggest the capacity of almonds and other nuts to modulate inflammation, particularly among individuals with enhanced inflammatory status. More studies are warranted to elucidate the mechanism of actions for these reductions in inflammatory biomarkers.

In conclusion, the available data demonstrate that almond consumption among controlled and free-living individuals at greater risk for chronic disease may favorably influence well-being above that of lipoprotein management. The nutrient composition of almonds and other nuts (i.e., high in unsaturated fats, fiber, and phytonutrients and low in carbohydrates) and emerging clinical evidence provide a strong justification in support of their being an appropriate food to incorporate into a healthy diet for individuals with increased risk for CVD and patients with metabolic syndrome and T2DM. Although almonds are an energy-dense food, their consumption has not been shown to be associated with a higher BMI, probably attributed to the observed displacement of energy from other foods, satiating property of almonds, and modest malabsorption of almond fat. The coconsumption of almonds may decrease to some extent postprandial glucose response to a meal. Clinical evidence also supports almond nutrients could increase antioxidant defense and protect susceptible macromolecules against oxidation locally and systematically in individuals with enhanced oxidative stress. Finally, almonds as well as mixed nuts as part of the Mediterranean diet have been shown to have beneficial effects on inflammatory biomarkers and endothelial function, particularly among individuals with enhanced inflammatory status. More research is needed, especially clinical evidence, to better identify the possible mechanisms of action underlying the health benefits of almond consumption. Furthermore, given that the majority of the studies discussed in this review focused on individuals at increased risk for future chronic health problems, future long-term studies are warranted to examine the health benefits of nuts incorporated into diets of free-living healthy people because a short-term study is underpowered to reveal subtle changes in studied markers in relatively healthy subjects.

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Funding

Supported by U.S. Department of Agriculture (USDA)/Agricultural Research Service Cooperative Agreement 58-1950-7-707 and a grant from the Almond Board of California. The contents of this publication do not necessarily reflect the views or policies of the USDA nor does mention of trade

names, commercial products, or organizations imply endorsement by the U.S. government.

Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS USED

AHA, American Heart Association; BW, body weight; BMI, body mass index; CRP, C-reactive protein; CHO, carbohydrate; CVD, cardiovascular disease; DV, daily value; F, female; GI, glycemic index; HDL-C, high-density lipoprotein; IL-6, interleukin-6; ICAM-1, intracellular adhesion molecule-1; LDL-C, low-density lipoprotein cholesterol; M, male; MUFA, monounsaturated fatty acids; NCEP, National Cholesterol Education Program; TC, total cholesterol; T2DM, type 2 diabetes mellitus; VCAM-1, vascular cell adhesion molecular-1.

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