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Almonds Decrease Postprandial Glycemia, Insulinemia, and Oxidative Damage in Healthy Individuals[1]

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Abstract

Strategies that decrease postprandial glucose excursions, including digestive enzyme inhibition, and low glycemic index diets result in lower diabetes incidence and coronary heart disease (CHD) risk, possibly through lower postprandial oxidative damage to lipids and proteins. We therefore assessed the effect of decreasing postprandial glucose excursions on measures of oxidative damage. Fifteen healthy subjects ate 2 bread control meals and 3 test meals: almonds and bread; parboiled rice; and instant mashed potatoes, balanced in carbohydrate, fat, and protein, using butter and cheese. We obtained blood samples at baseline and for 4 h postprandially. Glycemic indices for the rice (38 ± 6) and almond meals (55 ± 7) were less than for the potato meal (94 ± 11) ($P < 0.003$), as were the postprandial areas under the insulin concentration time curve ($P < 0.001$). No postmeal treatment differences were seen in total antioxidant capacity. However, the serum protein thiol concentration increased following the almond meal (15 ± 14 mmol/L), indicating less oxidative protein damage, and decreased after the control bread, rice, and potato meals (−10 ± 8 mmol/L), when data from these 3 meals were pooled ($P = 0.021$). The change in protein thiols was also negatively related to the postprandial incremental peak glucose ($r = -0.29$, $n = 60$ observations, $P = 0.026$) and peak insulin responses ($r = -0.26$, $n = 60$ observations, $P = 0.046$). Therefore, lowering postprandial glucose excursions may decrease the risk of oxidative damage to proteins. Almonds are likely to lower this risk by decreasing the glycemic excursion and by providing antioxidants. These actions may relate to mechanisms by which nuts are associated with a decreased risk of CHD. J. Nutr. 136: 2987–2992, 2006.

Introduction

Postprandial events have attracted much attention for the potentially important role they may play in cardiovascular disease risk (1–3) and diabetic complications (4,5). Data indicate that decreasing postprandial glycemia by the α-glucosidase inhibitor, acarbose, may lower the risk of coronary heart disease (CHD)[8], hypertension, and the development of diabetes in high risk individuals (6,7). Operating through similar mechanisms of slowing carbohydrate absorption, low glycemic index diets are also recommended for the treatment of diabetes and CHD (2,8–10). The mechanism by which lower postprandial glycemia is hypothesized to operate is by decreasing the generation of damaging reactive oxygen species (ROS) (11) produced in the mitochondria in response to glucose surges (12,13). In the absence of adequate antioxidant activity, ROS may damage lipids (14), proteins (15), and DNA and increase resistance in insulin sensitive tissues (16). Recently, studies have demonstrated that it is the magnitude of the glycemic excursion in diabetes, not the ambient glucose level as reflected in the hemoglobin A1c, which determines the degree of oxidative damage as indicated by isoprostane production (17).

A number of cohort studies have shown a negative association between nut consumption and risk of heart disease (18–25), and analysis of almonds and their seed coats demonstrated high levels of antioxidants (26–28). Nuts, by virtue of their fat and protein content, may also depress postprandial glycemia and hence ROS production. We have therefore examined the effect on postprandial oxidative damage to serum proteins of adding almonds to a carbohydrate-rich meal.

Methods

Subjects. Fifteen healthy individuals, 7 men and 8 women (mean ± SD) with an age of 26.3 ± 8.6 y (range, 19–52 y) and a mean BMI of 23.4 ±

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[8] Abbreviations used: CHD, coronary heart disease; IAUC, incremental area under the curve; ROS, reactive oxygen species; TAC, total antioxidant capacity.

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3.4 kg/m^2 (range, 17.4–29.5 kg/m^2), participated in this study. Healthy subjects were recruited from staff and students at the University of Toronto, and from subjects taking part in studies at Glycemic Index Laboratories (Toronto). Exclusion criteria included smoking, vitamin or mineral supplementation, impaired fasting blood glucose, diabetes, liver or kidney disease, or disorders of the gastrointestinal tract. Subjects were asked to avoid consuming any foods containing lycopene for 1 wk prior to study commencement and for the duration of the study and to avoid any water-soluble antioxidant-rich foods for 24 h prior to their study session. A list of foods to avoid was provided for the subjects. These foods included: tomatoes, tomato products, watermelon, papaya, apricots, berries, tea (black, green, and herbal), coffee, chocolate, melon, kiwi, citrus fruit, and fruit juices. Before each study session, subjects were asked to complete a 3-d food record, outlining in detail all foods consumed. Compliance was assessed from the food record. Informed consent was obtained from the subjects. This study was approved by the Ethics committees of the University of Toronto and St. Michael's Hospital.

Study protocol. All subjects completed 5 study sessions, each lasting 4 h, with a minimum 1 wk washout between tests. Subjects consumed the control meal on 2 occasions, and the almond, parboiled rice, and mashed potato meals only once. On the test days, subjects were asked to attend the clinic between 0800 and 0900 after a 12-h overnight fast. They were also asked to eat the same meal the evening prior to each study day and to maintain the same level of physical activity the day prior to and the morning of the study. Body wt was taken and height was measured. Venous blood was drawn from a forearm catheter kept patent with saline and capillary blood samples for glucose analysis were obtained at the same time points with an extra capillary sample at 15 min. Following the baseline sample, a test meal was provided, which subjects were asked to consume within 10 min. Subjects assessed their satiety following each blood-draw by use of a bipolar semantic 7-point visual analogue scale (with −3 representing extremely hungry, 0 neutral, and +3 extremely satiated).

Meals. There were 4 different test meals consumed in random order, each containing 50 g of available carbohydrate (**Table 1**). The control meal was white bread (Wonder Bread, Interstate Bakeries), which was consumed on 2 occasions. Test meals consisted of 60 g raw, unblanched almonds (California Almonds) with white bread; parboiled rice (Uncle Bens Converted, Mars); and instant mashed potatoes (McCain, McCain Foods). The last 2 meals were balanced for fat, protein, and total energy with the almond meal by the addition of fat (unsalted butter; Gay Lea, Gay Lea Foods) and protein (medium cheddar cheese; Black Diamond, Parmalat).

Analyses. Capillary blood samples were collected in Sarstead tubes at 0, 15, 30, 45, 60, 90, 120, and 240 min and were immediately placed in a −20°C freezer until analysis. Blood glucose was analyzed by YSI STAT Plus Glucose/Lactate Analyzer (model 2300 YSI STAT Plus Glucose analyzer; Yellow Springs Instruments).

TABLE 1 Macronutrient and energy content of the 3 test meals and the white bread control meal

Test meal	Energy	Available carbohydrate	Protein	Fat
	kJ	*g*		
97 g White bread alone	1079.4	49.0	8.4	3.1
Almond meal: 60 g almonds + 97 g bread	2499	51.8	21.1	33.7
Parboiled rice meal: 68 g cheese and 14 g butter + 60 g parboiled rice	2473.2	49.2	21.1	34.2
Mashed potato meal: 62 g cheese and 16 g butter + 68 g mashed potatoes	2499	51.3	21.3	33.8

All venous blood samples were collected in serum red-top BD Vacutainer blood tubes with no additives (Oakville). Upon collection, blood tubes were wrapped in tin foil to minimize light penetration and remained at room temperature for 1 h to clot before being spun in a Beckman GPR centrifuge at 1008 × *g*; 15 min. After centrifugation, serum was aliquoted into light-sensitive amber Eppendorf tubes and stored at −70°C.

Venous blood was collected at 0, 30, 45, 60, 90, 120, and 240 min for insulin measurements. Serum insulin was analyzed in the St. Michael's Hospital Core Laboratory using a chemiluminescent ultrasensitive insulin immunoassay (CV 3.1–5.6%) (Access Immunoassay System; Beckman Coulter).

Venous blood was collected at 0, 90, 120, and 240 min for measuring total antioxidant capacity (TAC) and protein thiols. TAC was determined by the ferric reducing-antioxidant power assay (29,30). The CV of samples analyzed in triplicate was 3.8%. Protein oxidation was measured using the 5,5′-dithio-bis(2-nitrobenzoic acid) assay (31) to assess the loss of reduced thiol (−SH) groups as a measure of protein oxidation. Reduced glutathione standards from 100 to 1000 μmol/L were used. The CV of serum samples analyzed in triplicate was 2.2%.

Statistical analyses. Values in the text are expressed as mean ± SEM and differences were considered significant at $P < 0.05$. Blood glucose and insulin areas were calculated as the incremental area under the curve (IAUC) using the trapezoidal rule. Peak heights were maximal incremental rises in glucose and insulin. The glycemic indices of the 4 test meals were calculated using the bread meal as the reference food (32). The mean of the 90-, 120-, and 240-min protein thiol and TAC values expressed as postprandial change from baseline was used to assess the difference between treatments. The differences between treatments were assessed by least-squares means with a Tukey adjustment for multiple comparisons in SAS (SAS version 8.2) with treatment, treatment by sex interaction, sex and a random term representing the subject identity nested within sex as main effects, and baseline as covariate. The difference in protein thiol concentrations between almonds and the other test meals combined was assessed using the CONTRAST statement in SAS (version 8.2). The values of each individual for mean glucose and insulin IAUC and glucose and insulin peak heights were related to the mean postprandial change in protein thiols, providing in each instance 15 separate Pearson correlation coefficients. The Wilcoxon's Signed Rank test was used to test the prevalence and rank of positive or negative correlation coefficients among the 15 subjects using Pearson's product-moment correlations (SAS version 8.2). Slopes and intercepts were derived by simple linear regression of percent change in protein thiol concentration on incremental peak height to plot each subject's linear response. Student's *t* test was used to test the strength of slopes in the linear regressions.

Results

Meal eating time and satiety. The mean time taken to eat the 4 meals was <11 min. The mean eating times for the 4 test meals were: almonds and bread, 10:46 min (range: 7:00–13:00 min); mashed potatoes, 9:39 min (range: 5:06–13:40 min); parboiled rice, 9:39 min (range: 5:34–17:00 min); and control white bread, 9:03 min (range: 5:17–10:45 min). The almond meal eating time differed from that of the control bread meal ($P = 0.006$). No other eating time differences were significant. Furthermore, there was no relation between time taken to consume a meal and the glucose and insulin postprandial response areas. The satiety incremental response area for the almond meal was greater than that of the control white bread meal for 2 h ($P = 0.047$) and for 4 h ($P = 0.011$) (**Fig. 1***C*). There were no other significant differences in 2 h or 4 h satiety response areas.

Glucose. Blood glucose concentrations over the 4 h testing period for each meal are shown in Figure 1*A*. The glycemic indices of the almond (55 ± 7) and rice meals (38 ± 6) were lower than that of the instant mashed potato meal (94 ± 11)

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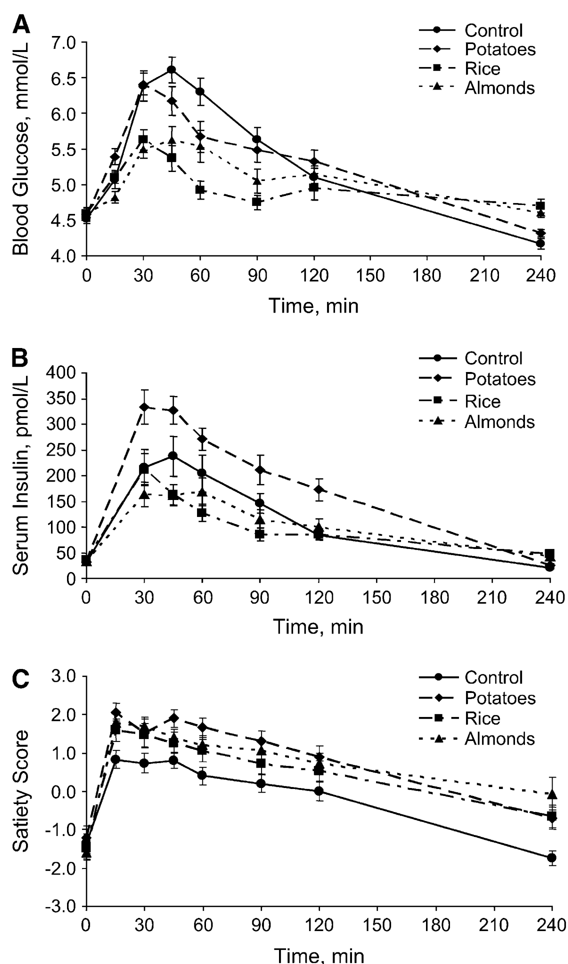

Figure 1 Postprandial capillary blood glucose (*A*), serum insulin concentrations (*B*), and satiety responses (*C*) in healthy subjects for 4 h after consumption of the 3 test meals and the control white bread meal. Values are means ± SEM, $n = 15$.

($P \leq 0.003$). The almond and rice meal glycemic index values did not differ ($P = 0.25$). Similarly, the postprandial glucose peak heights for the almond (5.9 ± 0.2 mmol/L) and rice (5.8 ± 0.1 mmol/L) meals were less than the peak height for the potato meal (6.6 ± 0.2 mmol/L) and the control white bread (6.9 ± 0.2 mmol/L) ($P < 0.001$).

Insulin. Serum insulin concentrations over the 4-h testing period for each meal are shown in Figure 1*B*. The insulin responses for the mixed meals generally reflected the glucose responses (Fig. 1*A*). The insulin indices of the almond (91 ± 19) and rice meals (73 ± 9) were lower than the potato meal (171 ± 19) ($P < 0.001$). The insulin peak height for the almond (224 ± 24 pmol/L) and rice (239 ± 28 pmol/L) meals were both lower than for the potato meal (388 ± 30 pmol/L) ($P < 0.001$) and the control white bread (321 ± 36 pmol/L) ($P \leq 0.042$).

Oxidative damage. Protein thiol concentration, as a marker of protein oxidative damage and serum postprandial TAC, did not differ during or among the individual treatments as assessed by the response curves over the 4 h (data not shown).

The change in the serum protein thiol concentration in response to the almond meal (15 ± 14 mmol/L) was greater ($P = 0.021$) than that following the control bread, potato, and rice meals when the data from these 3 treatments were combined (−10 ± 8 mmol/L). This suggests less postprandial protein damage after consuming almonds. The almond meal did not differ from the combined meals for TAC (data not shown).

Relation to glucose and insulin responses. Using the postprandial data from all 4 treatments (control white bread, almonds and bread, rice, and potatoes) resulting in 60 observations (15 subjects × 4 treatments), the 2-h postprandial incremental glucose and insulin areas were negatively related by Pearson correlation to the change in protein thiols ($r = -0.26$, $P = 0.048$ and $r = -0.25$, $P = 0.053$, respectively). Similar associations were found for the incremental peak glucose and peak insulin values with change in protein thiols ($r = -0.29$, $P = 0.026$ and $r = -0.26$, $P = 0.046$, respectively). The correlation coefficients were also assessed for each subject individually ($n = 15$) using the data from their 4 treatments. The majority of correlation coefficients were negative, indicating the greater the glucose and insulin responses, the greater the postprandial protein oxidative damage. The 2-h postprandial incremental glucose and insulin areas related negatively to the change in protein thiols for 13/15 subjects (for all subjects, $n = 15$; $P = 0.001$) and 12/15 subjects (for all subjects, $n = 15$; $P = 0.008$), respectively (**Table 2**). The peak glucose and insulin concentrations also related negatively to the change in protein thiols for 12/15 subjects (for all subjects, $n = 15$; $P = 0.007$) and 11/15 subjects (for all subjects, $n = 15$; $P = 0.03$), respectively (Table 2). **Figure 2** shows the percent change from baseline in mean postprandial protein thiol concentration vs. incremental peak blood glucose concentration for the 15 subjects after the 4 meals. The lines were derived from linear regression. A negative mean gradient was observed (slope = −4.8; $n = 15$; $P = 0.014$), indicating that the higher the postprandial incremental peak blood glucose concentration, the greater the damage to protein thiols (Fig. 2). Peak insulin concentrations tended to be negatively related to the mean postprandial protein thiol concentrations (slope = −0.03; $n = 15$; $P = 0.057$) (curves not shown). TAC was not related significantly to the glucose or insulin responses.

TABLE 2 Pearson correlation coefficients for the postprandial changes in protein thiols vs. incremental glucose and insulin response areas and peak heights for each subject using data from all 4 treatments

Subjects	2 h Glucose IAUC, *mmol × min/L*	2 h Insulin IAUC, *pmmol × min/L*	Glucose peak height, *mmol/L*	Insulin peak height, *pmol/L*
1	−0.61	−0.93	0.03	0.32
2	−0.11	0.59	−0.29	0.87
3	0.03	−0.06	0.01	−0.09
4	−0.46	−0.54	−0.65	−0.65
5	−0.66	−0.66	−0.25	−0.84
6	−0.65	−0.94	−0.79	−0.96
7	−0.65	−0.61	−0.87	−0.83
8	−0.16	−0.95	−0.62	−0.94
9	0.29	0.34	0.64	0.42
10	−0.46	0.26	−0.01	0.21
11	−0.26	−0.51	−0.39	−0.43
12	−0.30	−0.79	−0.46	−0.86
13	−0.72	−1.00	−0.88	−0.93
14	−0.09	−0.11	−0.59	−0.48
15	−0.59	−0.37	−0.72	−0.39
Mean	−0.36	−0.42	−0.39	−0.37
P-value[1]	0.001	0.008	0.007	0.030

[1] The *P*-value indicates whether mean associations in a column are negative.

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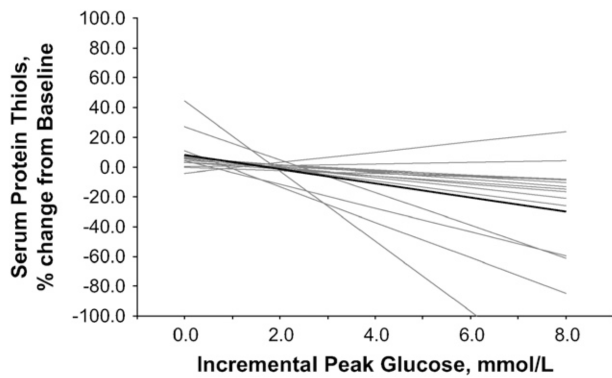

Figure 2 Percent change from baseline in mean postprandial serum protein thiol concentration vs. incremental peak blood glucose concentration for the 15 healthy subjects after consumption of the 4 meals. A negative mean gradient is shown by the thick black line (slope = −4.8; $n = 15$; $P = 0.014$). The higher the incremental peak blood glucose concentration, the greater the damage to protein thiols.

Discussion

The data indicate that almonds decrease the glycemic and insulinemic responses to bread. The oxidative damage to proteins related to the magnitude of the postprandial glucose and insulin areas and peak heights, with higher postprandial responses increasing the risk of protein damage. Protein oxidative damage follows increased mitochondrial generation of ROS, possibly driven by raised intracellular glucose concentrations (5,13,15). ROS are linked to vascular endothelial damage, with implications for microvascular and macrovascular disease (5,13).

One way in which ROS damage proteins is by oxidizing sulfhydryl groups. Disulfide bonds are created in thiol containing molecules: cysteine, methionine and glutathione, both in intracellular and plasma proteins. Therefore, a reduction in protein thiol concentrations can be used as a marker of oxidative stress (33). Protein thiols were proposed as the most expendable source of plasma antioxidants and are preferentially consumed in the presence of free radicals (34). Studies have shown that thiols are decreased in clinical states associated with increased oxidative stress, including autoimmune diseases (35), diabetes (36), and uremia (37). Their levels were inversely correlated with disease activity in systemic lupus erythematosus (35) and were improved in diabetes after administration of an antioxidant supplement (36). Autoimmune diseases (38) and diabetes (5) are both associated with an increased risk of CHD.

Postprandial glycemia did not relate to TAC. This lack of effect on TAC has been reported in other studies where eicosapentanoic acid and docosahexanoic acid were fed to healthy subjects, despite evidence of oxidative damage ex vivo to LDL cholesterol (39). The protein thiol test may be more useful in the present situation, because the results reflect protein damage rather than antioxidant potential. This difference may be particularly relevant in view of the fact that protein thiols are preferentially consumed in situations of increased oxidative stress (34). Protein thiols are not captured by the TAC test used (40).

For over a quarter of a century, there has been an interest in postprandial lipid metabolism and the risk for cardiovascular disease (1,41). More recently, studies indicate that 2-h postprandial glycemia is a risk factor for CHD (5), a concept supported by many large cohort studies, including the Hoorn Study (42), the Honolulu Heart Study (1-h postchallenge) (43), the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe Study (44), and the 20-y follow up of 3 European cohorts: the Whitehall Study, the Paris Protective Study, and the Helsinki Policemen Study (45). Furthermore, reports show that acarbose, the α-glucosidase inhibitor that specifically lowers postprandial hyperglycemia, also lowers the risk of CHD in individuals at high risk for type 2 diabetes (7).

In normal and diabetic subjects, postprandial hyperglycemia was associated with increased production of nitrotyrosine, as another indicator of oxidative stress (46). The importance of postprandial glycemia in generating ROS in diabetes was demonstrated by the association of the urinary marker of oxidative stress, 8-isoprostaglandin F2α, with the mean amplitude of glycemic excursions rather than with the mean 24-h glucose concentration or even hemoglobin A1c (17). As a determinant of postprandial glycemia, the association of meal glycemic index with the level of oxidative damage may therefore have important implications.

Nut consumption in the Seventh Day Adventist Study, the Nurses' Health Study, the Physicians Health Study, the Health Professionals Study, and the Iowa Women's Health Study were all associated with a protective effect of nuts on CHD (24). This study opens the possibility that, in addition to cholesterol lowering (47–52), lower postprandial glycemia, insulinemia, and oxidative stress following nut consumption may also contribute to the decreased risk of CHD.

Recent reports suggest that the effect of antioxidants given as supplements in decreasing CHD risk is largely negative (53–56), despite acute effects in improving postprandial brachial artery vasodilatation (57–60). However, it is possible that the antioxidant supplementation in these studies did not achieve the intended protection from oxidative damage. There are no intervention studies where lipid and protein markers of oxidative damage were measured in addition to the primary cardiovascular endpoint. Where long-term studies of antioxidant supplementation were undertaken and markers of oxidative damage measured, the results have been inconsistent (61,62).

Little is known of the antioxidant activity of nuts apart from their content of monounsaturated fatty acids and phenolics. But even so, data on the phenolic content of different nuts are limited. However, detailed studies on almonds have shown that almond skins contain ~30 different antioxidant compounds, including catechin, epicatechin, isorhamnetin, quercetin, and kampferol (28), all of which may contribute to their antioxidant activity. Also, the type of sweet almond seed used in this study contains only trace amounts of cyanogenic compounds that may influence antioxidant enzyme expression. In contrast, the mean cyanide content of bitter almonds is ~250 mg/100 g (63). The TAC of almonds, assessed by Oxygen Radical Absorbance Capacity, places almonds 5th out of 10 different types of nuts (44.5 μmol trolox equivalents [TE]/g) (64), and this may well have provided sufficient endogenous antioxidant activity to be responsible for much of the effect in preserving protein thiols. Lack of antioxidant data on the meal components of the other meals precludes a direct comparison.

The composition of the meals may also have influenced the glycemic and insulinemic responses. The higher protein content of the mashed potato and cheese meal may be responsible for the high postprandial insulin and lower blood glucose compared with the control white bread. The saturated fat from the cheese and butter in both the mashed potato and parboiled rice meals might also account for the differences in glycemia by comparison with meals containing polyunsaturated fatty acids (65). However, the major fatty acid in almonds is monounsaturated fatty acid, and that fat appears to be more similar to saturated

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fat (65,66) and therefore does not explain the lower insulin and glucose concentrations seen after ingesting almonds with bread compared with the other meals.

We conclude that the combination of lower glucose, insulin, and less postprandial protein oxidative damage suggests that there may be additional mechanisms, besides cholesterol lowering (47–52), by which nuts may be associated with a decreased risk of CHD (24). In the case of almonds, it may be that both the attenuated glycemic response together with their known antioxidant content (26–28) may have resulted in the antioxidant advantage of the almond meal. This finding is consistent with the decrease in oxidized LDL reported after addition of almonds to the diet (50).

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