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Effect of almonds on insulin secretion and insulin resistance in nondiabetic hyperlipidemic subjects: a randomized controlled crossover trial

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Abstract

Nuts appear to have a marked effect in cohort studies in reducing the risk of coronary heart disease (CHD), but their demonstrated ability to lower cholesterol can only explain a proportion of the reduction in risk. Our aim was to assess whether improvement in carbohydrate metabolism provides a further explanation for the effect of nuts in reducing CHD. The effects of whole almonds, taken as snacks, were compared with the effects of low saturated fat (<5% energy) whole-wheat muffins (control) in the therapeutic diets of hyperlipidemic subjects. In a randomized crossover study, 27 hyperlipidemic men and women consumed 3 isoenergetic (mean, 423 kcal/d) supplements each for 1 month. Supplements provided 22.2% of energy and consisted of full-dose almonds (73 ± 3 g/d), half-dose almonds plus half-dose muffins, and full-dose muffins. Subjects were assessed at weeks 0, 2, and 4 and fasting blood samples were obtained. Twenty-four-hour urinary output was collected at the end of week 4 on each treatment. Mean body weights differed by less than 300 g between treatments. No differences were seen in baseline or treatment values for fasting glucose, insulin, C-peptide, or insulin resistance as measured by homeostasis model assessment of insulin resistance. However, 24-hour urinary C-peptide output as a marker of 24-hour insulin secretion was significantly reduced on the half-and full-dose almonds by comparison to the control after adjustment for urinary creatinine output ($P = .002$ and $P = .004$, respectively). We conclude that reductions in 24-hour insulin secretion appear to be a further metabolic advantage of nuts that in the longer term may help to explain the association of nut consumption with reduced CHD risk.

1. Introduction

Studies have shown that a variety of nuts reduce serum cholesterol [1-7] and this property has been used to explain their marked effect in reducing coronary heart disease (CHD) in cohort studies [8-14]. As a result of these data, the Food and Drug Administration has permitted a CHD risk reduction qualified health claim for nuts and nut products that contain 42 g of nuts per serving [15]. Furthermore, the potential value ascribed to monounsaturated fat, such as olive oil in the Mediterranean diet, has done much to influence thinking about fat in general, such that monounsaturated fats are regarded as "good" fats [16-18]. Many nuts, including almonds, are some of the richest sources of monounsaturated fats and have been shown to reduce low-density lipoprotein cholesterol (LDL-C) and the ratio of total to high-density lipoprotein cholesterol (TC/HDL-C) [1,4-7,19,20]. The high fat content of nuts is therefore no longer a reason why nuts should not be part of the diet for those at risk for CHD.

Nevertheless, nuts have only a relatively small effect (approximately 5%) on cholesterol reduction [2,3,21]. It is difficult to see how reductions of this magnitude could explain the 30% reduction in CHD risk seen in cohort studies [8-14] and which, in statin trials, would correspond to a 30%

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reduction in LDL-C [22-25]. We believe that additional mechanisms must be sought to explain the protection from CHD seen with nut consumption.

Insulin resistance, raised fasting and postprandial insulin levels, impaired carbohydrate tolerance, and, ultimately, diabetes have all been related to increased CHD risk [26-28]. Improvement in any of these aspects of carbohydrate metabolism with nuts would provide a further reason, in addition to cholesterol lowering, why nut consumption would benefit CHD risk.

We have therefore assessed the effect of almonds on markers of carbohydrate metabolism in a previously reported almond dose-response study in which reductions in LDL-C were seen [1].

2. Methods

The study methods have already been described in detail [1].

2.1. Study protocol

Three 1-month diet phases taken in a randomized crossover design with each phase separated by a minimum 2-week washout period were completed by 27 subjects. The 3 phases consisted of a muffin phase (control) and 2 almond phases, 1 full-dose almond and the other half-dose almond plus half-dose muffin. During all study phases, subjects followed their own self-selected low-fat therapeutic diets to which they included the supplement. Subjects were counseled on strategies to facilitate weight maintenance including holding exercise constant throughout the study.

After overnight fasts (12-14 hours), blood samples and body weight and blood pressure measurements were obtained at the start and at weeks 2 and 4 of each 4-week diet phase. A 24-hour urine sample was also collected at the end of week 4. Seven-day weighed diet records were obtained before and at week 4 of each phase. All subjects were instructed to weigh all foods consumed during the weeks when diets were recorded. A self-taring electronic food scale was provided for this purpose.

The study was approved by the Ethics Committees of the University of Toronto and St Michael's Hospital (clinical trials registration number NCT00507520). All subjects gave informed consent.

2.2. Subjects

Healthy hyperlipidemic men and postmenopausal women were recruited by newspaper advertisement and from patients attending the Risk Factor Modification Center, St Michael's Hospital. Of the 43 subjects who started the study, 16 withdrew during or after completing 1 to 2 study phases. Twenty-seven subjects completed all 3 phases: 15 men and 12 postmenopausal women; (mean ± SD) age, 64 ± 9 years (range, 48-86 years); body mass index (BMI), 25.7 ± 3.0 kg/m^2 (range, 20.5-31.5 kg/m^2); baseline LDL-C, 4.32+0.63 mmol/L (range, 2.77-5.32 mmol/L) (Table 1). The 16 subjects who withdrew from the study had characteristics similar to those who completed: 9 men, 7 postmenopausal women; age, 62 ± 8 years (range, 51-74 years); BMI, 25.6 ± 4.0 kg/m^2 (range, 21.3-37.1 kg/m^2); baseline LDL-C, 4.24 ± 0.92 mmol/L (range, 3.19-6.40 mmol/L). All subjects had elevated LDL-C levels on initial assessment at recruitment (>4.1 mmol/L) and triglyceride concentrations less than 4.0 mmol/L. None had clinical or biochemical evidence of diabetes and liver or renal disease. Of the 27 who completed the study, 3 men and 5 women were taking the following medications: a hypolipidemic agent (statin) (n = 2); β-blocking agents (n = 3); angiotensin-converting enzyme inhibitors (n = 3), angiotensin II type I receptor blockers (n = 1), thiazide diuretics (n = 2), levothyroxine (n = 2), and hormone replacement therapy (n = 2) (Table 1). Medication dosages were held constant throughout the study. Subjects were asked to maintain their habitual level of physical activity throughout the study.

2.3. Diets

Before commencing the study, all subjects were following therapeutic National Cholesterol Education Program (NCEP) step 2 diets (<7% energy from saturated fat and <200 mg/d dietary cholesterol). During the study, subjects took all 3 supplements: whole raw unblanched almonds (73 ± 3 g/d), muffins (147 ± 6 g/d), and half portions of almonds (37 ± 2 g/d) plus muffins (75 ± 3 g/d) as described previously [1]. The level of supplement intake was based on subjects' estimated daily energy requirement [29]. The muffins were made from whole-wheat flour with corn oil sufficient to provide the same amount of saturated fatty acid, polyunsaturated fatty acid, and fiber as the almonds, although the monounsaturated fatty acid in the almonds was replaced by the starch in the muffins. Skim milk powder and egg whites provided a similar level of protein, although the muffin protein was 46% of animal origin. Subjects were instructed on reducing total food intake by approximately 20%, which was the calorie value of the supplements, and

Table 1
Baseline subject characteristics

	Values
Subject variable	
n (M/F)	27 (15/12)
Age, mean ± SD (y)	64 ± 9
BMI, mean ± SD (kg/m^2)	25.7 ± 3.0
LDL-C, mean ± SD (mmol/L)	4.32 ± 0.63
Medications (n)	
Statin	2
Angiotensin-converting enzyme inhibitor	3
Thiazide diuretics	2
β-Blocker	3
Angiotensin II receptor blocker	1
Hormone replacement therapy	2
Levothyroxine	2

Table 2
Subject macronutrient intakes calculated from 7-day food records on the control, half-almond, and full-almond treatments in 27 subjects who took all 3 treatments

Treatment	Energy (kcal)	Protein (%)	Vegetable PRO (%)	Fat (%)	SFA (%)	MUFA (%)	PUFA (%)	Available CHO (%)	Total dietary fiber (g/1000 kcal)	Dietary cholesterol (mg/1000 kcal)	Alcohol (%)
Control	1900 ± 89	17.5 ± 0.5	7.2 ± 0.3	26.3 ± 1.0	7.0 ± 0.4	9.0 ± 0.5	8.0 ± 0.3	54.5 ± 1.1	16.3 ± 1.1	89.7 ± 7.3	1.8 ± 0.5
Half-almond	1951 ± 94	17.6 ± 0.5	7.8 ± 0.3	32.1 ± 1.0	7.5 ± 0.4	14.5 ± 0.5	8.0 ± 0.3	48.4 ± 1.1	16.5 ± 0.9	96.8 ± 6.2	1.9 ± 0.5
Full-almond	2034 ± 98	17.4 ± 0.4	8.7 ± 0.3	36.0 ± 1.0	7.2 ± 0.4	18.9 ± 0.6	8.2 ± 0.2	44.8 ± 1.2	16.4 ± 0.9	79.3 ± 5.3	1.8 ± 0.6

SFA indicates saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; CHO, carbohydrate.

to do so especially by reduction in starchy food intake (breads, bagels, nonstudy muffins, and breakfast cereals). This adjustment allowed supplements to be taken as snacks without increasing total energy intake. The background diet was kept constant across all 3 phases to allow direct comparison between the supplements. Table 2 shows subjects' mean dietary intake as assessed from 7-day food records on all 3 phases. To minimize changes in body weight and diet composition, detailed dietary counseling was undertaken before and at weeks 1 and 2 of each phase. During the study, subjects were asked not to consume any additional nuts or nut products or alter consumption of dietary fiber or vegetable protein foods. Compliance was assessed from 7-day diet records, a supplement checklist on which subjects recorded supplements consumed, and return of uneaten supplements, which were weighed and recorded.

2.4. Analyses

Serum stored at −70°C was used for determination of glucose, insulin, and C-peptide at the Banting and Best Diabetes Laboratory (Mount Sinai Hospital, Toronto, Ontario, Canada). Glucose was determined by an enzymatic method using hexokinase on a Roche Integra Analyzer (F. Hoffman-La Roche, Basel, Switzerland), insulin by an electrochemiluminescence immunoassay ("ELICA") on a Roche Elecsys 2010 analyzer (F. Hoffman-La Roche), and C-peptide in serum and urine by a solid-phase, competitive chemiluminescent enzyme immunoassay using an IMMULITE 2000 Analyzer (Siemens Medical Solutions Diagnostics, Tarrytown, NY). Insulin resistance was estimated by homeostasis model assessment of insulin resistance (HOMA-IR) using the formula [glucose (mmol/L) × insulin (pmol/L)]/135 [30]. Urinary creatinine level was determined in the routine clinical laboratory at St Michael's Hospital in Toronto (Synchron LX 20, Beckman Coulter Canada, Mississauga, Ontario, Canada).

Study supplements were analyzed using Association of Official Analytical Chemists methods for fat, protein, and fiber with available carbohydrate calculated by difference [31]. The fatty acid composition was determined by gas chromatography. Dietary macronutrient intakes (Table 1) were assessed on the 7-day diet records, using a computer program based on US Department of Agriculture data. The percentage figures for soluble and insoluble fiber were derived from published data [31].

2.5. Statistical analysis

The data on the 27 subjects who completed the study were analyzed using SAS statistical software (SAS Institute, Cary,

Table 3
Results of blood insulin, glucose, C-peptide, and HOMA-IR at weeks 0 and 4, and urinary C-peptide corrected and uncorrected for creatinine at week 4 (unadjusted mean ± SEM) in 27 subjects who took all 3 treatments

Variable	Week	Control	Half-almond	Full-almond
Serum				
Insulin (pmol/L)	0	41.2 ± 0.8	40.0 ± 0.7	40.4 ± 0.7
	4	38.4 ± 0.5	39.2 ± 0.7	37.6 ± 0.6
Glucose (mmol/L)	0	4.86 ± 0.02	4.87 ± 0.03	4.84 ± 0.03
	4	4.77 ± 0.02	4.88 ± 0.02	4.91 ± 0.02
C-peptide (pmol/L)	0	517 ± 12	409 ± 8	512 ± 11
	4	517 ± 7	510 ± 8	539 ± 8
Insulin resistance (HOMA-IR)	0	1.53 ± 0.04	1.48 ± 0.03	1.49 ± 0.03
	4	1.39 ± 0.02	1.46 ± 0.03	1.39 ± 0.02
Urine				
Volume (mL/d)	4	1909 ± 197	1734 ± 160	1884 ± 197
24-h creatinine output (mmol/d)	4	7.1 ± 0.5	8.9 ± 0.7**	8.6 ± 0.7*
24-h C-peptide output (pmol/d)	4	25736 ± 2863	20952 ± 2699	21150 ± 2343
Creatinine-corrected 24-h C-peptide output (pmol/mmol)	4	3801 ± 76	2491 ± 60**	2578 ± 60**

* $P < .05$ from the control value.
** $P < .01$ from the control value.

NC, 2004). Mixed models were constructed (SAS Proc Mixed) to assess the effect of diet on serum and urinary measures at week 4. Models also included subject as a random factor, sex, diet sequence, and interactions between sex and diet and sex and sequence. For serum outcomes, measures at baseline were also included in the model as a covariate. Diet sequence and interaction were removed from the final models if they were not significant. When diet was significant, post hoc contrasts were used to compare outcomes among the 3 diets (SAS/STAT version 9.1, 2004).

3. Results

Compliance was good with more than 97% of the supplements prescribed being consumed during the 3 phases. There were no significant treatment differences in body weight.

There were no differences in baseline values in fasting blood glucose, insulin, serum C-peptide, or insulin resistance (HOMA-IR) between the control and half- and full-dose almonds (Table 3). After 4 weeks, there were also no treatment differences in fasting blood glucose, insulin, serum C-peptide, or insulin resistance. However, 24-hour urinary C-peptide output corrected for creatinine output was significantly lower on both the half- and full-dose almonds by comparison with the control ($P = .002$ and $P = .004$, respectively) and 24-hour creatinine output was also significantly higher ($P = .007$ and $P = .023$, respectively) (Table 3). No significant differences were seen using the unadjusted 24-hour urinary C-peptide outputs (Table 3).

4. Discussion

The present study demonstrated that inclusion of almonds in the diet such that monounsaturated fatty acids in almonds replaced starch in muffins resulted in a reduced 24-hour insulin secretion as indicated by a lower urinary C-peptide output. Nuts and nut products including peanut butter are now considered to have cardioprotective properties [15]. The primary mechanism proposed has been their ability to lower serum cholesterol, but this is modest by comparison with the often large benefits for CHD risk reduction demonstrated in cohort studies [8-14]. In this respect, in addition to disordered lipid and lipoprotein metabolism, deranged carbohydrate metabolism is also increasingly recognized as associated with cardiovascular disease, and lifestyle interventions that improve glucose metabolism often benefit carbohydrate metabolism [32-35]. However, this relatively short-term study with no weight loss provided no evidence for lower fasting insulin or glucose levels or for improvement in insulin resistance. Nevertheless, there was a significant reduction with almonds in 24-hour insulin secretion assessed as urinary C-peptide output, an effect that may have implications for both diabetes and cardiovascular disease.

One of the reasons to suggest that almonds might have influenced insulin resistance and carbohydrate metabolism is their previously reported effect in depressing the glucose response when added to a bread meal [36,37]. Not only have almonds been shown to achieve this effect in a dose-dependent fashion [37], but the effect also seems to be greater than would be predicted by the simple addition of fat and protein. Furthermore, the almond depression of the postprandial blood glucose response was accompanied by evidence of less oxidative damage to serum proteins [36], possibly as a result of a reduction in free radical generation, all features that might relate to reduced CHD risk [38,39]. Because these are postprandial events, it is likely that the assessment of fasting blood samples in the present study would not have picked up significant glucose and insulin effects. However, the treatment effect seen with 24-hour urinary C-peptide as a marker of insulin secretion captured the alterations in postprandial glucose and insulin responses to meals taken over the day. Over time, the reduction in insulin demand may have decreased the age-related increase in insulin resistance. However, the present study was of relatively short duration and thus the effect on insulin resistance was not seen.

Cohort studies have demonstrated that decreased glycemic load has been associated with less cardiovascular disease [40,41] and with a lower incidence of diabetes [42,43]. Glycemic load may be reduced by reducing the glycemic index of the diet while keeping the carbohydrate content constant or by reducing the total available carbohydrate while keeping the glycemic index of the diet constant. Almonds eaten with a meal appear to reduce the glycemic response for a given amount of carbohydrate. In addition, by substituting for carbohydrate calories in the diet, they will reduce the glycemic load. In the present study, although the almonds were often taken as a snack and no specific instructions were given to take them with the carbohydrate portion of the meal, it is likely that eaten throughout the day, almonds will have reduced insulin secretion, both by displacement of carbohydrate and by their documented effects in reducing postprandial glycemia when eaten with carbohydrate foods [36,37].

In this respect, studies exchanging carbohydrate for monounsaturated fat in type 2 diabetes mellitus have demonstrated a benefit in postprandial glucose and insulin responses, together with reductions in serum triglycerides and very low-density lipoprotein cholesterol [44]. No change in triglycerides was seen in the present study; however, benefits were observed in LDL-C, TC/HDL-C, and a reduction in oxidized LDL-C [1]. The only studies to assess the effect of nuts in diabetes have shown no consistent benefits [45,46]. The first study on almonds was of 4-week duration and possibly too short to show an effect on hemoglobin A_{1c}, although lipid benefits were observed [45]. A second study involving walnuts in subjects with type 2 diabetes mellitus of 6 months' duration also showed no effect on hemoglobin A_{1c}, but did report favorable lipid

modifications (increased HDL-C and decreased LDL-C) despite no change in body weight [46]. Again, these studies did not aim to mix the nuts with the carbohydrate portion of the meals to maximize the effect.

It is possible that the reduced creatinine-adjusted C-peptide output may have been due to increased creatinine output. The increased creatinine output in turn could be the result of increased meat intake, increased rate of muscle protein turnover, or raised creatinine clearance. Animal protein was, if anything, lower on the almond treatment phases and there is no reason to suspect a significant increase in muscle protein turnover. To account for the results, altered creatinine clearance would be of interest but serum creatinine concentrations were not measured, and there are no reports of plant protein–rich foods increasing renal clearance.

We conclude that almonds appear to reduce 24-hour insulin secretion as judged by lower urinary C-peptide output. Acutely, almonds also influence postprandial glucose tolerance and, in the longer term, reduce serum lipids and markers of oxidative damage. Together, these effects could provide an explanation for the significant cardioprotective effect of nuts. Further studies are required where nuts are given as an integral part of the meal. Specifically, nuts should be mixed with the carbohydrate foods to determine whether they can be used for long-term modification of postprandial events and thus favorably influence additional markers of CHD risk reduction.

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