Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 400–404
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Almonds and postprandial glycemia—a dose-response study

Andrea R. Josse[a,c], Cyril W.C. Kendall[a,c], Livia S.A. Augustin[a,c], Peter R. Ellis[e], David J.A. Jenkins[a,b,c,d,*]

[a]Clinical Nutrition and Risk Factor Modification Center, St Michael's Hospital, Toronto, Ontario, Canada M5C 2T2
[b]Division of Endocrinology and Metabolism, Department of Medicine, St Michael's Hospital, Toronto, Ontario, Canada M5C 2T2
[c]Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada M5S 3E2
[d]Department of Medicine, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada M5G 2C4
[e]Biopolymers Group, School of Biomedical and Health Sciences, Kings College London, SE1 9NH London, United Kingdom

Received 31 July 2006; accepted 13 October 2006

Abstract

Almonds, together with other nuts, reduce serum cholesterol levels and may reduce the risk of coronary heart disease. There is much current interest in the relation of coronary heart disease to postprandial events. We have therefore assessed the effects of varying amounts of almonds on the postprandial blood glucose response to a carbohydrate meal. Our aim was to assess the effect of adding almonds to a bread meal. Nine healthy volunteers (2 women, 7 men; mean age, 27.8 years; mean body mass index, 22.9 kg/m^2) were randomly fed with 3 test meals and 2 white bread control meals on separate days. Subjects were fed the meals after a 10- to 12-hour overnight fast. Each meal contained 50 g of available carbohydrate from white bread eaten alone or with 30, 60, or 90 g (~1, 2, or 3 oz) of almonds. Capillary finger-prick blood samples for glucose analysis were obtained at 0, 15, 30, 45, 60, 90, and 120 minutes. Glycemic responses were assessed by calculating the incremental area under the 2-hour blood glucose curve. The addition of almonds to white bread resulted in a progressive reduction in the glycemic index of the composite meal in a dose-dependent manner for the 30-g (105.8 ± 23.3), 60-g (63.0 ± 9.0), and 90-g (45.2 ± 5.8) doses of almonds ($r = -0.524$, n = 36, $P = .001$). We conclude that, in addition to lowering serum cholesterol levels, almonds may also reduce the glycemic impact of carbohydrate foods with which they are eaten.

1. Introduction

Research during the last decade has demonstrated that nuts, in relation to their effects on plasma lipids, have beneficial effects on coronary heart disease (CHD) risk reduction. Five of the largest population-based cohort studies in nutritional epidemiology, namely, the Nurses Health Study [1], the Adventist Health Study [2-4], the Cholesterol and Recurrent Events Study [5], the Iowa Women's Health Study [6], and the Physicians Health Study [7], have shown that nut consumption reduces the risk of CHD. A recent meta-analysis incorporating these studies indicated that nut consumption of greater than 5 times per week was associated with an 18% to 51% reduction in CHD risk in all subjects and a 25% to 39% reduction in cohorts including the very old [8] and those with established coronary disease [9].

Postprandial events including postprandial glycemia have attracted attention as indicators of risk for CHD. Postprandial hyperglycemia has been associated with increased risk of CHD as seen in several epidemiological studies [10-16], and 2-hour postprandial glycemia has now been recognized as an independent CHD risk factor [17-20]. It therefore appeared important to determine the effect of almonds on postprandial glycemia as a further possible mechanism, in addition to cholesterol reduction [21-23], as to why nut consumption has been associated with a reduced risk of CHD.

2. Methods

2.1. Subjects

Nine healthy individuals, 7 males and 2 females, with a mean age (±SD) of 27.8 ± 6.9 years (range, 21-39 years) and a mean body mass index (BMI) (±SD) of 22.9 ±

* Corresponding author. Clinical Nutrition and Risk Factor Modification Center, St Michael's Hospital, Toronto, Ontario, Canada M5C 2T2. Tel.: +1 416 978 4752; fax: +1 416 978 5310.
E-mail address: cyril.kendall@utoronto.ca (D.J.A. Jenkins).

0026-0495/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2006.10.024

3.6 kg/m^2 (range, 20.3-31.4 kg/m^2) participated in this study. Subjects were recruited from the staff and students of the Clinical Nutrition and Risk Factor Modification Center at St Michael's Hospital (Toronto, Ontario) and the Department of Nutritional Sciences, University of Toronto (Toronto, Ontario). Exclusion criteria included disorders of the gastrointestinal tract, impaired fasting blood glucose levels, diabetes, use of vitamin or mineral supplements, and smoking. No subjects were taking medications known to influence glucose metabolism. Ethics committee approval was obtained from St Michael's Hospital and the University of Toronto. Informed consent was obtained from each study participant, and the subjects were provided with remuneration.

2.2. Study protocol

Subjects came to the Clinical Nutrition and Risk Factor Modification Center between 7:30 and 8:30 AM on 5 separate occasions. Each testing session was separated by at least a 1-day washout period. Subjects were asked to fast for 10 to 12 hours from the night before the study session (no food or beverages except water). They were also asked to consume the same type of meal at the same time on the previous evening and maintain the same exercise pattern for the day before the testing. Upon arrival to the clinic, the subjects were weighed, and they gave a baseline finger-prick blood sample using either Microlet (Bayer, Toronto, Ontario) or Monoject (Ascencia, Bayer) lancet devices. Subsequent capillary blood samples (~0.2 mL) were taken into Sarstedt blood collection tubes (Sarstedt Inc, Montreal, Quebec) prepared with 50 μL of anticoagulant (0.37 mg sodium fluoride and 0.30 mg potassium oxalate) at 15, 30, 45, 60, 90, and 120 minutes after the subjects started consuming the test meal. Subjects were asked to consume their meals within 10 minutes and to drink 250 mL of water. They were asked to fill out a subjective symptom questionnaire. Before each study session, the participants were asked to rate, in writing, their current level of well-being as excellent, good, fair, or poor; document everything they consumed from 5:00 PM onwards the night before; record the hours of sleep obtained the night before; and record any medications taken.

2.3. Meals

Four meals were consumed in this study. Each meal contained approximately 50 g of available carbohydrate from white bread. The meals consisted of white bread alone, the control meal (0 g almonds; Wonder Bread, Interstate Bakeries, Kansas City, MO), which was consumed twice to increase precision and decrease the variability of the individual glycemic index (GI) measurements [24]; 30 g (~1 oz) of raw, unblanched almonds plus white bread; 60 g (~2 oz) of almonds plus white bread; and 90 g (~3 oz) of almonds plus white bread. Table 1 shows the macronutrient and energy contents of the 4 test meals. The 3 almond meals were given to subjects in random order, straddled by the 2 control meals.

Table 1
Macronutrient and energy content of the test meals

Test meal	kJ (kcal)	Available carbohydrate (g)	Protein (g)	Fat (g)
White bread + 0 g almonds	1075 (257)	49.0	8.4	3.1
White bread + 30 g almonds	1782 (426)	50.4	14.8	18.4
White bread + 60 g almonds	2489 (595)	51.8	21.1	33.7
White bread + 90 g almonds	3192 (763)	53.2	27.3	49.0

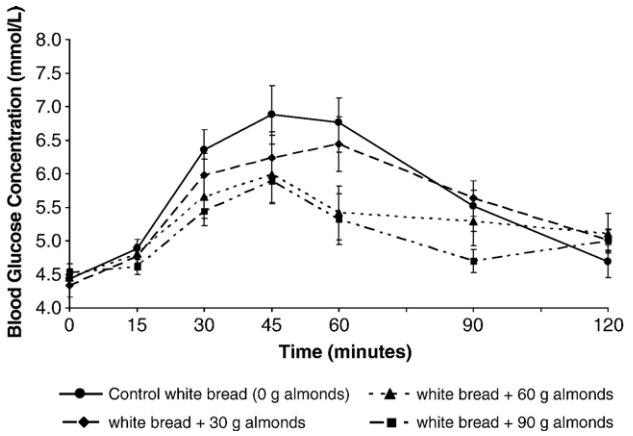

Fig. 1. Two-hour blood glucose response curves with SE bars on each time point for the 3 almond meals and the control meal. The control meal had the highest glucose response, followed by the 30-g, the 60-g, and then the 90-g almond meals.

2.4. Glucose analysis

Capillary blood samples were stored at -20°C until analysis. Analysis was carried out using the YSI STAT Plus Glucose/Lactate analyzer (model 2300, Yellow Springs Instruments, Yellow Springs, OH).

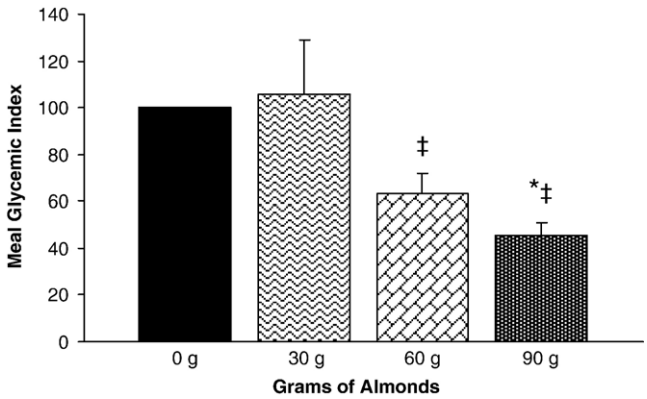

Fig. 2. Bar graph and SE bars showing the GIs for the 3 almond meals for 9 subjects. The white bread control meal (0 g almonds) had a GI of 100. The GIs for the 30-, 60-, and 90-g almond meals were 106, 63, and 45, respectively. The GI of the 90-g almond meal was significantly lower than the GIs of the white bread control meal ($P < .01$) and of the 30-g almond meal ($P < .01$). The GI of the 60-g almond meal was significantly lower than the GI of the 30-g almond meal ($P < .02$). *Significant from control meal. ‡Significant from 30-g almond meal.

2.5. Statistical analysis

Results are expressed as mean ± SEM. Incremental blood glucose area (IAUC) was calculated using the trapezoidal rule to assess the reduction in glycemic response. The meal GI was calculated for the incremental 2-hour blood glucose response with white bread as the standard [25]. Peak heights were the maximum incremental rises in blood glucose levels. Analysis of covariance was carried out on the IAUC data controlling for baseline glucose levels and BMI. Significant pairwise comparisons of the least square means of IAUC, GI, and peak height were identified by Tukey post hoc analysis.

3. Results

3.1. Subjects

Weights remained constant throughout the study for the 0-, 30-, 60-, and 90-g almond doses. The respective body weights were 66.3 ± 4.7 kg, 66.3 ± 4.5 kg, 66.7 ± 4.7 kg, and 66.5 ± 4.7 kg. No subject consumed almonds as part of the evening meal the night before each testing session.

3.2. Glucose analysis

Fasting blood glucose measures were very similar before all test meals were taken, with a mean value of 4.43 ± 0.09 mmol/L. Fig. 1 shows the effects of the almond meals on blood glucose levels over time. Fig. 2 shows the mixed meal GIs. The GIs of the 30-, 60-, and 90-g almond meals were 105.9 ± 23.3, 63.0 ± 9.0, and 45.2 ± 5.8, respectively, with a dose-response correlation of $r = -0.52$ (n = 36, $P = .001$). The 90-g almond meal resulted in a significantly lower GI compared with the white bread control meal ($P = .009$), whereas the GIs of both the 60- and 90-g almond meals were significantly lower than that of the 30-g almond meal ($P = .017$ and $P = .001$, respectively). No other differences were significant. Fig. 3 shows the incremental glucose peak heights. The incremental glucose peak heights (mmol/L) of the 0-, 30-, 60-, and 90-g almond meals were 2.8 ± 0.3, 2.2 ± 0.3, 2.0 ± 0.4, and 1.6 ± 0.2, respectively. The 90-g almond meal had a significantly lower glucose peak height compared with the white bread control meal ($P = .043$).

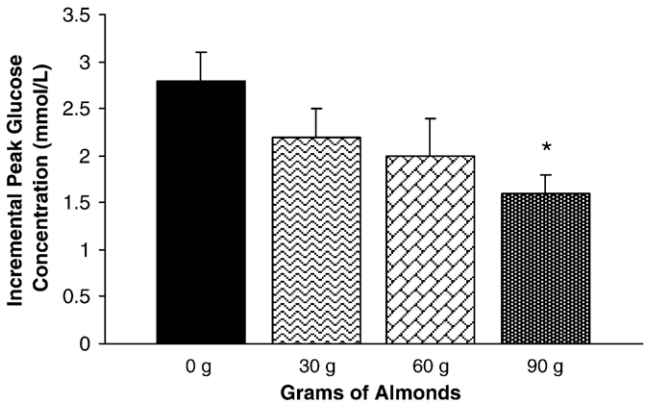

Fig. 3. Bar graph and SE bars showing the mean peak glucose concentration for the 3 almond meals and the white bread control meal (0 g almonds). The 90-g almond meal showed a significant reduction in peak height (*$P = .043$) compared with the control meal. The 30- and 60-g almond meals were not significantly different from the control meal ($P = .687$ and $P = .415$, respectively).

4. Discussion

This study assessed the postprandial effects of different doses of almonds on the attenuation of the blood glucose response of 50 g of available carbohydrate from white bread. Almonds blunted the postprandial glycemic response of white bread in healthy individuals. As the dose of almonds consumed was increased, the meal GI was decreased in a dose-dependent manner.

Almonds contain fat and protein and are therefore a source of additional energy for the bread meal. More than 30 years ago, Hunt and Stubbs [26] observed that there was equal slowing in the gastric emptying of isoenergetic amounts of fat, protein, and carbohydrate, and indicated that added energy and not the type of macronutrient was what determined gastric emptying. Calbet and MacLean [27] also observed that 600 mL of a glucose solution (0.42 kJ/mL [0.1 kcal/mL]) emptied the quickest, and a milk solution (2.93 kJ/mL [0.7 kcal/mL]) emptied the slowest. The energy density of the test drinks was linearly related to the half-time of gastric emptying ($r = 0.96$, $P < .05$). In 2004, Westphal et al [28] reported a positive correlation between increased energy and gastric-emptying time after feeding on meals that differed in macronutrient and energy content. Thus, as the dose of almonds is increased, the rate of gastric emptying would tend to decrease, reducing the glycemic response.

In addition to fat and protein, unblanched, raw almonds are rich sources of phytates and phenolics, both of which have been shown to reduce amylolytic digestion in vitro and to be associated with reduced postprandial glycemia in vivo [29,30]. Based on in vitro studies, the inhibitory action of phytate was considered to result from the binding of calcium (Ca^{2+}) required as a cofactor for amylase enzyme activity [29]. Phenolics are considered to bind directly to the enzyme, thus inhibiting activity [31,32].

Almonds also contain approximately 3.3 g of insoluble dietary fiber per ounce. A high intake of dietary fiber (of the more soluble type), greater than the level recommended by the American Diabetes Association, has been shown to improve glycemic control, decrease hyperinsulinemia, and lower plasma lipid concentrations in patients with type 2 diabetes mellitus [33]. However, the fiber's effect on glycemia is unlikely to be large, but it may play a role in cell wall integrity and almond digestibility [34]. Therefore, in our study, it is possible that part of the reduced glycemic effect was also mediated by the antinutrients (polyphenols and phytic acid) from the almond skin.

Low-GI diets have been implicated in the prevention of chronic diseases including cardiovascular disease, diabetes, and cancer [35-38]. Low-GI diets have been shown to decrease levels of low-density lipoprotein cholesterol [39], C-reactive protein [40], and hemoglobin A_{1c} in people with diabetes [41]. They have also been shown to be associated with higher levels of high-density lipoprotein cholesterol [42,43]. Decreasing dietary GI is a possible strategy to slow glucose absorption and reduce risk factors for chronic disease in the same way that α-glucosidase inhibitors, such as acarbose [44], have been used to decrease postprandial glycemia. Large epidemiological and intervention studies on type 2 diabetes mellitus have shown serum glucose levels after a 2-hour glucose challenge to be a powerful predictor of stroke, CHD risk, and microvascular complications [10-15,18,45]. Furthermore, a meta-analysis of healthy individuals reported that people with the highest 2-hour postchallenge glucose response had a 27% greater risk of stroke, myocardial infarction, and CHD compared with people with the lowest glucose response [46].

Very few intervention studies have been done to assess almond consumption, as part of a healthy diet, and glucose control. Lovejoy et al [47] reported no significant decreases in fasting and 2-hour glucose and insulin responses or significant reductions in levels of hemoglobin A_{1c} after subjects consumed 100 g/d of almonds for 4 weeks. However, the study was of relatively short duration to see any changes in glycosylated proteins, and the subjects showed a small increase in body weight. Nevertheless, significant decreases in levels of low-density lipoprotein cholesterol were observed.

This study demonstrated that increasing energy, in the form of almonds, was beneficial from the standpoint of glycemia; however, in the context of a diet, care must be taken not to increase energy to more than what is required. Fat and protein from nuts can be substituted for saturated fat– and cholesterol-rich protein to depress the glycemic response of a meal.

In conclusion, the ability of almonds to reduce postprandial glycemia, as seen in this study, suggests a further possible mechanism, in addition to the cholesterol-lowering effect, by which almond consumption may reduce CHD risk. The effect may be due to many factors such as the high monounsaturated fat, vegetable protein, phytate, and phenolic content of almonds. Some of these components may also be responsible for the cholesterol-lowering effect of almonds.

References

[1] Hu FB, Stampfer MJ, Manson JE, Rimm EB, Colditz GA, Rosner BA, et al. Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study. BMJ 1998; 317:1341-5.

[2] Fraser GE, Sabate J, Beeson WL, Strahan TM. A possible protective effect of nut consumption on risk of coronary heart disease. The Adventist Health Study. Arch Intern Med 1992;152:1416-24.

[3] Fraser GE, Lindsted KD, Beeson WL. Effect of risk factor values on lifetime risk of and age at first coronary event. The Adventist Health Study. Am J Epidemiol 1995;142:746-58.

[4] Fraser GE, Sumbureru D, Pribis P, Neil RL, Frankson MA. Association among health habits, risk factors, and all-cause mortality in a black California population. Epidemiology 1997;8:168-74.

[5] Brown LRB, Willett C, Sacks F. Nut consumption and risk of recurrent coronary heart disease. FASEB J 1999;13 (Abstract #3063): A538.

[6] Ellsworth JL, Kushi LH, Folsom AR. Frequent nut intake and risk of death from coronary heart disease and all causes in postmenopausal women: the Iowa Women's Health Study. Nutr Metab Cardiovasc Dis 2001;11:372-7.

[7] Albert CM, Gaziano JM, Willett WC, Manson JE. Nut consumption and decreased risk of sudden cardiac death in the Physicians' Health Study. Arch Intern Med 2002;162:1382-7.

[8] Fraser GE, Shavlik DJ. Risk factors for all-cause and coronary heart disease mortality in the oldest-old. The Adventist Health Study. Arch Intern Med 1997;157:2249-58.

[9] Kris-Etherton PM, Zhao G, Binkoski AE, Coval SM, Etherton TD. The effects of nuts on coronary heart disease risk. Nutr Rev 2001;59: 103-11.

[10] de Vegt F, Dekker JM, Ruhe HG, Stehouwer CD, Nijpels G, Bouter LM, et al. Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. Diabetologia 1999;42:926-31.

[11] Donahue RP, Abbott RD, Reed DM, Yano K. Postchallenge glucose concentration and coronary heart disease in men of Japanese ancestry. Honolulu Heart Program. Diabetes 1987; 36:689-92.

[12] Lowe LP, Liu K, Greenland P, Metzger BE, Dyer AR, Stamler J. Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men. The Chicago Heart Association Detection Project in Industry Study. Diabetes Care 1997;20:163-9.

[13] DECODE. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: collaborative analysis of diagnostic criteria in Europe. Lancet 1999;354:617-21.

[14] Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 1999;22:233-40.

[15] Balkau B, Shipley M, Jarrett RJ, Pyorala K, Pyorala M, Forhan A, et al. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. Diabetes Care 1998;21:360-7.

[16] Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. Diabetologia 1996;39:1577-83.

[17] Dickinson S, Brand-Miller J. Glycemic index, postprandial glycemia and cardiovascular disease. Curr Opin Lipidol 2005;16:69-75.

[18] Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-12.

[19] Hanefeld M, Temelkova-Kurktschiev T. Control of post-prandial hyperglycemia—an essential part of good diabetes treatment and prevention of cardiovascular complications. Nutr Metab Cardiovasc Dis 2002;12:98-107.

[20] Ceriello A. Postprandial hyperglycemia and diabetes complications: is it time to treat? Diabetes 2005;54:1-7.

[21] Spiller GA, Jenkins DA, Bosello O, Gates JE, Cragen LN, Bruce B. Nuts and plasma lipids: an almond-based diet lowers LDL-C while preserving HDL-C. J Am Coll Nutr 1998;17:285-90.

[22] Spiller GA, Jenkins DJ, Cragen LN, Gates JE, Bosello O, Berra K, et al. Effect of a diet high in monounsaturated fat from almonds on plasma cholesterol and lipoproteins. J Am Coll Nutr 1992;11:126-30.
[23] Jenkins DJ, Kendall CW, Marchie A, Parker TL, Connelly PW, Qian W, et al. Dose response of almonds on coronary heart disease risk factors: blood lipids, oxidized low-density lipoproteins, lipoprotein(a), homocysteine, and pulmonary nitric oxide: a randomized, controlled, crossover trial. Circulation 2002;106:1327-32.
[24] Brouns F, Bjorck IE, Frayn KN, Gibbs AL, Lang V, Slama G, et al. Glycaemic index methodology. Nutr Res Rev 2005;18:145-71.
[25] Wolever TM. The glycemic index. World Rev Nutr Diet 1990;62: 120-85.
[26] Hunt JN, Stubbs DF. The volume and energy content of meals as determinants of gastric emptying. J Physiol 1975;245:209-25.
[27] Calbet JA, MacLean DA. Role of caloric content on gastric emptying in humans. J Physiol 1997;498(Pt 2):553-9.
[28] Westphal S, Kastner S, Taneva E, Leodolter A, Dierkes J, Luley C. Postprandial lipid and carbohydrate responses after the ingestion of a casein-enriched mixed meal. Am J Clin Nutr 2004;80:284-90.
[29] Yoon JH, Thompson LU, Jenkins DJ. The effect of phytic acid on in vitro rate of starch digestibility and blood glucose response. Am J Clin Nutr 1983;38:835-42.
[30] Thompson LU, Button CL, Jenkins DJ. Phytic acid and calcium affect the in vitro rate of navy bean starch digestion and blood glucose response in humans. Am J Clin Nutr 1987;46:467-73.
[31] Thompson LU, Yoon JH, Jenkins DJ, Wolever TM, Jenkins AL. Relationship between polyphenol intake and blood glucose response of normal and diabetic individuals. Am J Clin Nutr 1984;39:745-51.
[32] Thompson LU, Yoon JH. Starch digestibility as affected by polyphenols and phytic acid. J Food Sci 1984;49:1228-9.
[33] Chandalia M, Garg A, Lutjohann D, von Bergmann K, Grundy SM, Brinkley LJ. Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. N Engl J Med 2000;342:1392-8.
[34] Ellis PR, Kendall CW, Ren Y, Parker C, Pacy JF, Waldron KW, et al. Role of cell walls in the bioaccessibility of lipids in almond seeds. Am J Clin Nutr 2004;80:604-13.
[35] Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. Am J Clin Nutr 2000;71:1455-61.
[36] Salmeron J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, et al. Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes Care 1997;20:545-50.
[37] Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non–insulin-dependent diabetes mellitus in women. JAMA 1997;277:472-7.
[38] Franceschi S, Dal Maso L, Augustin L, Negri E, Parpinel M, Boyle P, et al. Dietary glycemic load and colorectal cancer risk. Ann Oncol 2001;12:173-8.
[39] Jarvi AE, Karlstrom BE, Granfeldt YE, Bjorck IE, Asp NG, Vessby BO. Improved glycemic control and lipid profile and normalized fibrinolytic activity on a low–glycemic index diet in type 2 diabetic patients. Diabetes Care 1999;22:10-8.
[40] Wolever TMS, Chiasson JL, Josse RG, Leiter LA, Maheux P, Rabasa-Lhoret R, et al. Effect of modifying source or amount of carbohydrate glucose and lipid control in type 2 diabetes. Can Diabetes Assoc J 2004;28:294 [Abstract].
[41] Brand-Miller J, Hayne S, Petocz P, Colagiuri S. Low–glycemic index diets in the management of diabetes: a meta-analysis of randomized controlled trials. Diabetes Care 2003;26:2261-7.
[42] Frost G, Leeds AA, Dore CJ, Madeiros S, Brading S, Dornhorst A. Glycaemic index as a determinant of serum HDL-cholesterol concentration. Lancet 1999;353:1045-8.
[43] Ford ES, Liu S. Glycemic index and serum high-density lipoprotein cholesterol concentration among US adults. Arch Intern Med 2001; 161:572-6.
[44] Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA 2003;290:486-94.
[45] Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care 2000;23(Suppl 2):B21-9.
[46] Levitan EB, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Arch Intern Med 2004;164:2147-55.
[47] Lovejoy JC, Most MM, Lefevre M, Greenway FL, Rood JC. Effect of diets enriched in almonds on insulin action and serum lipids in adults with normal glucose tolerance or type 2 diabetes. Am J Clin Nutr 2002;76:1000-6.