Nuts as a Replacement for Carbohydrates in the Diabetic Diet

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OBJECTIVE—Fat intake, especially monounsaturated fatty acid (MUFA), has been liberalized in diabetic diets to preserve HDL cholesterol and improve glycemic control, yet the exact sources have not been clearly defined. Therefore, we assessed the effect of mixed nut consumption as a source of vegetable fat on serum lipids and HbA1c in type 2 diabetes.

RESEARCH DESIGN AND METHODS—A total of 117 type 2 diabetic subjects were randomized to one of three treatments for 3 months. Supplements were provided at 475 kcal per day (75 g/day, mufa-containing supplements, 47 g/day, mufa-containing peanuts, or 19 g/day, mufa-containing nuts, half portions of both). The primary outcome measures were changes in HbA1c between treatments.

RESULTS—The relative increase in MUFAs was 8.7% energy on the full-nut dose compared with mufa-containing peanuts, due to the combined impact of the full-nut dose (3.8% absolute increase) and the mufa-containing peanuts (4.9% absolute increase) compared with mufa-containing nuts. The LDL cholesterol reduction after half-nut dose was intermediate and not significantly different from the full-nut dose or mufa-containing peanuts. Apolipoprotein (apo) B and the apoB:apoA1 ratio behaved similarly. The LDL cholesterol reduction after half-nut dose was intermediate and not significantly different from the full-nut dose or mufa-containing peanuts. Apolipoprotein (apo) B and the apoB:apoA1 ratio behaved similarly. The LDL cholesterol reduction after half-nut dose was intermediate and not significantly different from the full-nut dose or mufa-containing peanuts. Apolipoprotein (apo) B and the apoB:apoA1 ratio behaved similarly.

CONCLUSIONS—Two ounces of nuts daily as a replacement for carbohydrate foods improved both glycemic control and serum lipids in type 2 diabetes.

RESEARCH DESIGN AND METHODS—Subjects were recruited by a newspaper advertisement and from previous studies. A total of 117 subjects were eligible and randomized (Supplementary Fig. 1). Recruitment took place from April 2007 to September 2008, with the last follow-up visit on 18 December 2008. Eligible participants were men or postmenopausal women with type 2 diabetes who were taking antidiabetic agents other than acarbose, with medications stable for the previous 3 months and who had HbA1c values at screening between 6.5 and 8.0% (Table 1). No participants had clinically significant cardiovascular, renal, or liver disease (alanine aminotransferase more than three times the upper limit of normal) or a history of cancer. Subjects were accepted after surgery or myocardial infarction if they had an event-free 6-month period before the study. One subject had changed medications within 3 months before the start of the study. Nevertheless, all randomized subjects were retained for the intention-to-treat analyses.

Protocol
The study was a 3-month randomized parallel study with two supplements and three treatments consisting of the following: a full portion of mixed nuts, a half portion of both nuts and mufa-containing peanuts, or a full portion of mufa-containing peanuts. After stratification by sex and HbA1c (<=7.1%), randomization was carried out using subject identification by a statistician who was geographically separate from the center.
Table 1—Baseline characteristics of study participants

| Number (%) of participants | Nuts | Half dose | Muffins | P       |
|----------------------------|------|----------|---------|---------|
| n                          | 40   | 38       | 30      |         |
| Age (years)*               | 63 (9) | 62 (9)  | 61 (10) | 0.61†  |
| Sex                        |       |          |         |         |
| Male                       | 26 (65) | 26 (68) | 26 (67) | 0.97‡  |
| Female                     | 14 (35) | 12 (32) | 13 (33) |         |
| Race/ethnicity             |       |          |         |         |
| European                   | 23 (58) | 25 (66) | 18 (46) | 0.83‡  |
| Indian                     | 10 (25) | 8 (21)  | 13 (33) |         |
| Far Eastern                | 4 (10)  | 3 (8)    | 3 (8)   |         |
| African                    | 3 (8)   | 2 (5)    | 3 (8)   |         |
| Hispanic                   | 0 (0)   | 0 (0)    | 1 (3)   |         |
| Native American            | 0 (0)   | 0 (0)    | 1 (3)   |         |
| Weight (kg)*               | 80 (15) | 86 (16) | 83 (15) | 0.20†  |
| BMI (kg/m²)*               | 29 (5)  | 30 (5)   | 29 (4)  | 0.37†  |
| Current smokers            | 2 (5)   | 4 (11)   | 3 (8)   | 0.57‡  |
| HbA1c (%)                  |       |          |         |         |
| <7.0                       | 20 (50) | 20 (53) | 22 (56) | 0.84‡  |
| ≥7.0                       | 20 (50) | 18 (47) | 17 (44) |         |
| Duration of diabetes (years)*| 7 (6) | 8 (6)    | 8 (6)   | 0.57‡  |
| Medication use             |       |          |         |         |
| Hypoglycemic medications   | 40 (100) | 38 (100) | 39 (100) | 1.00‡  |
| Thiazolidinedione          | 12 (30) | 11 (29)  | 11 (28) | 1.00‡  |
| Biguanide                  | 35 (88) | 36 (95) | 35 (90) | 0.62‡  |
| Sulfonylurea               | 14 (35) | 13 (34) | 17 (44) | 0.64‡  |
| Meglitinides (nonsulfonylurea)| 2 (5) | 3 (8)    | 2 (5)   | 0.79‡  |
| α-Glucosidase inhibitors   | 0 (0)   | 0 (0)    | 0 (0)   | 1.00   |
| Dipetidyl peptide-4 inhibitor | 0 (0) | 0 (0)    | 1 (3)   | 0.66‡  |
| Cholesterol-lowering medications | 25 (58) | 31 (82) | 30 (77)b | 0.046b |
| Blood pressure medications | 25 (58) | 29 (76) | 28 (72) | 0.12‡  |

Data are n (%) or *mean (SD). †P value is for overall F test for between-groups differences using the generalized linear model ANOVA. ‡P values for Fisher exact test where appropriate calculated separately for distribution of each medication, since participants were from multiple nationalities or on multiple medications. A difference in superscript letters signifies a significant difference in percentage changes using the Q statistic.

Dietary interventions
Participants were counseled to substitute the supplement calories where possible for the carbohydrate foods in their original diets. General dietary advice conforming to the National Cholesterol Education Program Adult Treatment Panel III guidelines to reduce saturated fat and cholesterol intakes (Supplementary Table 1). Of the participants, 43% were obese (50/117, BMI >30 kg/m²) and wished to lose weight. They were informed that this was not a weight-loss study but were given advice on portion size and fat intake to help them meet their weight-reduction objectives. Compliance was assessed from the mean of the five 7-day diet records per treatment (weeks 2, 4, 8, 10, and 12).

Supplements
The nuts supplied consisted of a mixture of unsalted and mostly raw almonds, pistachios, walnuts, pecans, hazelnuts, peanuts, cashews, and macadamias. The muffin was developed to be a healthy whole-wheat product, sweetened with apple concentrate, with no sugar added. The muffin had similar protein content to the nuts, by the inclusion of egg white and skim milk powder. The calories from MUFAs in the muffins were the same by design as the carbohydrate calories in the muffin (Supplementary Table 2).

Energy requirements
Energy requirements were calculated for each participant as referenced previously (3), using the Harris-Benedict equation, with allowance for physical activity. Those participants with energy requirements of
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>2,400 calories received supplements of 630 kcal (100 g nuts [n = 0]); four muffins [n = 1]; or 50 g nuts and two muffins [n = 1]); individuals whose requirements were 1,600–2,400 kcal received supplements of 475 kcal (75 g nuts [n = 38]; 37.5 g nuts plus one and a half muffins [n = 36]; or three muffins [n = 36]); and individuals whose requirements were <1,600 kcal received supplements of 315 kcal (50 g nuts [n = 2]; 25 g nuts and one muffin [n = 1]; or two muffins [n = 2]) (Supplementary Table 2).

Biochemical analyses

HbA1c was analyzed within 2 days of collection on whole blood collected in EDTA Vacutainer tubes and measured by a designated high-performance liquid chromatography (HPLC) method (Tosoh G7 Automated HPLC Analyzer; Tosoh Bioscience, Grove City, OH) (CV 1.7%). Blood glucose was measured in the hospital routine analytical laboratory by a glucose oxidase method. Serum samples stored at -70°C were analyzed for lipids, and apolipoproteins (apo) and oxidative products were analyzed at the end of the study. LDL cholesterol was calculated by the method of Friedwald et al. (3). C-reactive protein (CRP) was measured by end point nephelometry. Oxidized products were measured on participants who completed the study. Oxidized LDL was measured chemically as conjugated dienes and thiobarbituric acid–reactive substances in the LDL fraction (11,12), and oxidized serum proteins were measured as protein thiols (13).

Diets were analyzed in 115 participants with baseline data using a computer program based on the data from the U.S. Department of Agriculture (3) and international glycemic index tables (14), with additional measurements made on local foods.

Power calculations

The initial power calculation was based on an assumption of a 20% dropout and an effect size of 0.8% HbA1c units with an SD of effect of 1.235% (α = 0.05, 1-β = 0.8), for which 30 subjects per group were required. This calculation was revised after publication of a low glycemic index trial. The effect size of the change in HbA1c was adjusted to 0.45% HbA1c units, similar to a modest effect of acarbose with an SD of effect of 0.60% HbA1c units (15). These values were also in line with the HbA1c data of the completer and intention-to-treat groups, respectively, from the recent low glycemic index study. For the comparison of nuts with muffins, 40 subjects would be required per group (α = 0.05, 1-β = 0.8). No prior adjustment was made for the multiple comparisons necessary for assessment of a dose response. To establish significance for the three comparisons using the Bonferroni correction, P < 0.0175 was required. The power was, therefore, designed to assess the primary outcome of the difference in change in HbA1c between full-nut dose versus muffins.

Statistical analyses

Results are expressed as means ± SD or 95% CIs. The significance of treatment differences was assessed by the CONTRAST statement in SAS version 9.2 (16), which allows comparisons of repeated measures over time based on a t test statistic with equal weighting for each value. In this study, the three values for the last month (end of weeks 8, 10, and 12) were expressed individually as changes from the mean baseline (mean of weeks –1 and 0). The model also used baseline as a covariate. The primary analysis was an intention-to-treat analysis, including all randomized subjects (n = 117) with the baseline observation carried forward for subjects who did not have at least one value in the last month (i.e., end of weeks 8, 10, and 12) (n = 14). Subjects who were randomized but did not start (n = 1) had their screening value used as baseline, and this value was carried forward (Supplementary Fig. 1). Unadjusted significance levels are given in the text, tables, and figures. Using the Bonferroni correction, for three-way comparisons, these differences were significant when the P value was <0.0175. Where only start and end values were available (diet, markers of oxidative stress, and body weight), significance was assessed by the least square means procedure in SAS with a Tukey adjustment for multiplicity of comparisons. Pearson correlations were used to examine the relation of nut intake to changes in HbA1c, lipids, and apolipoproteins. Nut consumption was defined as the difference in total tree nut, peanut, and nut butter intake in grams per day between the pretreatment and end of treatment week assessed from the 7-day diet records. The dose-response analyses on nut and MUFA intakes (% energy) and change in study outcome were performed by regression analyses pooling the responses across the three treatment groups.

RESULTS—Of the participants, 39 of 40 (97.5%) completed the full-nut dose (i.e., provided a blood sample in the final month), compared with 32 of 38 (84%) of those taking the half-nut dose and 32 of 39 (82%) on muffins. In the half-nut dose group, one subject dropped out after randomization but was unaware of his treatment allocation, and one participant was withdrawn because of two consecutive HbA1c levels >8.5%. In the muffin group, one participant developed allergic symptoms. In the full-nut dose group, one participant developed a nut allergy. These subjects’ data were retained for the intention-to-treat analyses.

No treatment differences were seen at baseline in diet, blood pressure, or anthropometric measurements (Tables 1 and 2 and Supplementary Table 1). During the study, MUFA intake, expressed as percent of total energy, increased significantly after full-nut dose consumption (Supplementary Tables 1 and 2) compared with muffins (8.7%, 95% CI 7.1–10.4, P < 0.001). There was good compliance with all treatments (90.6–97.3).

Glycemic control and body weight

In the intention-to-treatment analysis, oral hypoglycemic medication dosages increased in one participant in the half-nut dose group, with reductions for two participants. Three participants (one in each group) had their Avandia switched to Actos after media alerts.

The mean HbA1c fell –0.21% absolute HbA1c units (95% CI −0.30 to −0.11, P < 0.001) on the full-nut supplement; –0.07% absolute HbA1c units (−0.19 to 0.05, P = 0.270) on the half-nut dose supplement; and –0.05% absolute HbA1c units (−0.16 to 0.06, P = 0.355) on the muffin supplement (Fig. 1). The reduction in HbA1c on full-nut dose was significantly different from the half-nut dose (P = 0.004) and muffins dose (P = 0.001) (Fig. 1). The significance of the difference between full-nut dose and muffins in HbA1c remained after adjustment for duration of diabetes or body weight using an ANCOVA model (P = 0.023 and P = 0.004, respectively). No significant changes from baseline were seen in blood glucose or body weight, and there were no significant differences in responses between treatments (Table 2 and Supplementary Tables 1 and 3). Nut intake related negatively to change in HbA1c (r = −0.20, n = 115, P = 0.033). Through regression analysis, the full-dose (of 100 g/day) nut intake corresponded
Table 2—Mean (95% CI) value ± standard deviation for plasma lipids and apolipoproteins.

| Lipid Fraction | Full-nut Dose | Half-nut Dose | Difference | P Value |
|----------------|--------------|--------------|------------|---------|
| HDL cholesterol (mmol/L) | 0.9 (0.8–1.1) | 0.7 (0.6–0.8) | 0.2 (0.1–0.3) | 0.001 |
| LDL cholesterol (mmol/L) | 3.7 (3.5–3.9) | 3.5 (3.4–3.7) | 0.2 (0.1–0.3) | 0.001 |
| Triglycerides (mmol/L) | 1.5 (1.4–1.6) | 1.4 (1.3–1.5) | 0.1 (0.0–0.2) | 0.001 |

**CONCLUSIONS**—Increased mixed-nut consumption (cornstarch as a source of unprocessed carbohydrates and polynsaturated fat) may replace daily starch consumption favorably affected both glucose and serum parameters. Oxidized LDL, cholesterol, and blood pressure.

No significant differences were seen between treatments for LDL (Table 3) or measures of oxidative damage (data not shown). Blood pressure measurements were not significant with or without adjustment for blood pressure medication use.

Through a regression analysis, the changes in lipids were related to a reduction in apoB (−0.24 mmol/L; Table 2) and a reduction in apoA1 (−0.22 mmol/L; Table 3). All three differences were significantly raised with the full-nut dose compared with the half-nut dose (full-nut dose: −0.24 mmol/L, 95% CI −0.22 to −0.26; half-nut dose: −0.22 mmol/L, 95% CI −0.20 to −0.24; p < 0.001).

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Figure 1—Mean HbA1c measurements in participants with type 2 diabetes consuming full-nut dose, half-nut dose, or muffins.

The reduction in HbA1c was achieved despite baseline HbA1c concentrations, which on entry were close to the target of <7.0% in participants who were already treated with one or more (average 1.5) antihyperglycemic medications. Furthermore, a reduction in LDL cholesterol was achieved even though the majority of subjects (84/117, or 72%) were already taking statins and had low mean baseline LDL cholesterol concentrations of 2.03 mmol/L (95% CI 1.90–2.16).

The full-nut dose reduced HbA1c by two-thirds of the reduction recognized as clinically meaningful by the U.S. Food and Drug Administration (>0.3% absolute HbA1c units) in the development of antihyperglycemic drugs (23). In addition, the number of participants who achieved an HbA1c concentration of >7% (19 prestudy participants, down to 13 poststudy participants) was significantly greater on the nut treatment than on the muffin treatment (20 prestudy participants, remaining at 20 poststudy participants, Mantel-Haenszel test, P = 0.040). Based on data from the UK Prospective Diabetes Study and the ADVANCE study (24), the HbA1c reduction for the full-nut dose would translate into a predicted 7–8% reduction in microvascular complications.

Methodological weaknesses included use of a 7-day diet history with the errors and inaccurateness associated with self-reported data, lack of binding for participants and dietitians, and the attempt to demonstrate a dose response to nuts when the primary objective of establishing whether nuts improved glycemic control had not first been demonstrated. In addition, in the current study, nut consumption was substantial (37.5 g for the full-nut dose and 75 g/2,000 kcal) for the full-nut dose. However, the baseline nut intake was 12 g/day, and the compliance levels were high (i.e., 95.7 and 97.3% for the full-nut and half-nut groups, respectively). Therefore, we believe that, with the appropriate advice, nut intake at these levels can be achieved and maintained. Furthermore, the resulting relative increase in MUFA intake was modest at 8.7% of total calories for the full-nut dose.

The strengths of the study include its novelty as one of the first studies to assess nuts in type 2 diabetes coupled with measurement of HbA1c and blood lipids at three time points in the last month to increase the validity of the assessment of blood lipids and glycemic control. The study length was adequate to see an HbA1c effect. There was good compliance with the supplement and a dropout rate of 12%, which was lower than that seen in many other longer-term diet trials (25). Finally, there is a requirement for pharmacological interventions aimed at improving glycemic control to demonstrate that they have no negative impact on CHD (23). In this respect, nut consumption not only improved glycemic control but also lipid risk factors for CHD.

We have no explanation for the lack of antioxidant effects of nuts seen with previous studies but may relate to antioxidants in wheat bran and apple concentrate used in the muffins.

We conclude that mixed, unsalted, raw, or dry-roasted nuts have benefits for both blood glucose control and blood lipids and may be used to increase vegetable oil and protein intake in the diets of type 2 diabetic patients as part of a strategy to improve diabetes control without weight gain.

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