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Research Studies on Konjac Glucomannan

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Konjac-Mannan (Glucomannan) Improves Glycemia and Other Associated Risk Factors for Coronary Heart Disease in Type 2 Diabetes

A randomized controlled metabolic trial

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OBJECTIVE — To examine whether Konjac-mannan (KJM) fiber improves metabolic control as measured by glycemia, lipidemia, and blood pressure in high-risk type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — A total of 11 hyperlipidemic and hypertensive type 2 diabetic patients treated conventionally by a low-fat diet and drug therapy participated. After an 8-week baseline, all were randomly assigned to take either KJM fiber-enriched test biscuits (0.7 g/412 kJ [100 kcal] of glucomannan) or matched placebo wheat bran fiber biscuits during two 3-week treatment phases separated by a 2-week washout period. The diet in either case was metabolically controlled and conformed to National Cholesterol Education Program Step 2 guidelines, while medications were maintained constant. Efficacy measures included serum fructosamine, lipid profiles, apolipoproteins, blood pressure, body weight, and nutritional analysis.

RESULTS — Compared with placebo, KJM significantly reduced the metabolic control primary end points: serum fructosamine (5.7%, $P = 0.007$, adjusted $\alpha = 0.0167$), total:HDL cholesterol ratio (10%, $P = 0.03$, adjusted $\alpha = 0.05$), and systolic blood pressure (sBP) (6.9%, $P = 0.02$, adjusted $\alpha = 0.025$). Secondary end points, including body weight, total, LDL, and HDL cholesterol, triglycerides, apolipoproteins A-1, B, and their ratio, glucose, insulin, and diastolic blood pressure, were not significant after adjustment by the Bonferroni-Hochberg procedure.

CONCLUSIONS — KJM fiber added to conventional treatment may ameliorate glycemic control, blood lipid profile, and sBP in high-risk diabetic individuals, possibly improving the effectiveness of conventional treatment in type 2 diabetes.

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Abbreviations: apo, apolipoprotein; CHD, coronary heart disease; CVD, cardiovascular disease; dBp, diastolic blood pressure; KJM, Konjac-mannan; NCEP, National Cholesterol Education Program; RIA, radioimmunoassay; sBP, systolic blood pressure; WB, wheat bran.

A table elsewhere in this issue shows conventional and Systeme International (SI) units and conversion factors for many substances.

Hyperglycemia and diabetes are strong and independent risk factors of both all-cause and cardiovascular disease (CVD) mortality (1). These links are more pronounced when the diabetes is associated with other unfavorable risk factors such as hyperlipidemia (2), hypertension (3), or a cluster of metabolic disorders (4). Because people with diabetes have almost twice the risk of dying from CVD (69.6%) compared with people in the general U.S. population (5), the control of high glucose levels and other concomitant coronary heart disease (CHD) risk factors represents the most effective approach to prevention (6). The importance of stronger nutrition-hygienic measures has been stressed repeatedly for the public at large (4,7). When these measures prove inadequate, an aggressive drug therapy is often required to meet the conventional treatment guidelines (7). In the general population, this approach has been shown to be effective in lowering both the prevalence of hypertension (3) and serum cholesterol levels (8), but it has not reduced the incidence of diabetes (9).

Tighter fasting and postprandial glycemic control results in a considerable reduction in CHD and all-cause mortality (1), as well as fewer long-term microvascular complications both in type 1 (10) and type 2 diabetes (11). Effective dietary strategies shown to decrease postprandial plasma glucose excursions include the use of high fiber and low glycemic index diets (12,13). The mechanism is presumed to involve slowing carbohydrate absorption (13). Based on recent population studies, these types of diets have been shown to have a protective role in preventing diabetes (14,15) and CHD (16). In the case of clinical studies, however, it is the viscous water-soluble fibers, which increase the viscosity of digesta in the human gut (17), that reduce glucose and lipid CHD risk factors (18). Whether soluble fiber is able to reduce a cluster of risk factors is speculative. Studies

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using soluble fiber as an adjunct to conventional treatment in individuals with two or more major CHD risk factors are scarce (19).

We therefore studied the effect of water-soluble Konjac-mannan (KJM) fiber in type 2 diabetic patients, as an adjunct to conventional treatment, on a cluster of CHD risk factors: hyperglycemia, hyperlipidemia, and hypertension. KJM was chosen as the fiber because it represents a polysaccharide with one of the highest viscosities (20). The physiologically active component is a high molecular weight glucomannan polymer that, when taken as a supplement, has been shown to have effects in lowering lipids (21–23), systolic blood pressure (sBP) (21), and glycemia (24,25). By incorporating it into commercially produced biscuits, we sought to determine whether the addition of high-viscosity fiber given in a palatable form would enhance conventional treatment outcomes, assessed primarily by total:HDL cholesterol, fructosamine, and sBP and secondarily by total, LDL, and HDL cholesterol, apolipoprotein (apo) A-1, apo B, and their ratio, glucose, insulin, and diastolic blood pressure (dbp).

RESEARCH DESIGN AND METHODS

Subjects

A total of 11 diabetic patients (5 men, 6 women) gave written informed consent to participate in the present study, which was approved by the human ethic committees of St. Michael's Hospital and the University of Toronto. All had hyperlipidemia, hypertension, and type 2 diabetes (mean serum C-peptide 701 ± 351 pmol/l), with a minimum of 3 years since the onset of all three conditions. They were taking medications to control each of the three risk factors, consuming a National Cholesterol Education Program (NCEP) Step 2 diet, not smoking, not taking alcohol, and leading sedentary lifestyles at recruitment. Two participants had a history of atherosclerotic heart disease, but none had evidence of recent myocardial infarction, unstable angina, or congestive heart failure. Exclusion criteria were a family history of premature CHD, hypothyroidism, or renal, hepatic, or gastrointestinal disease. Table 1 provides baseline demographic, anthropometric, and clinical characteristics of the study participants.

Study design

The study used a double-blind placebo-controlled crossover design, where all sub-

Table 1—Baseline characteristics of the study subjects according to sex

| | Men | Women |
|------------------------------------|-----------|-----------|
| <i>n</i> | 5 | 6 |
| Age (years) | 62 ± 8 | 59 ± 7 |
| Body weight (% desirable) | 133 ± 33 | 143 ± 22 |
| Android obesity (prevalence) | 5 | 4 |
| Baseline risk factor values | | |
| Serum total cholesterol (mmol/l) | 6.2 ± 0.4 | 5.9 ± 0.5 |
| Glycosylated hemoglobin (%) | 7.4 ± 2.1 | 8.3 ± 3.0 |
| sBP/dbp (mmHg) | 139/78 | 136/82 |
| Known duration of risk factors | | |
| Diabetes (years, self-reported) | 11.5 ± 9 | 18.1 ± 6 |
| Hypertension (years) | 7.1 ± 3 | 6.0 ± 2 |
| Hyperlipidemia (years) | 6.3 ± 3 | 5.6 ± 2 |
| Drug/insulin treatment, prevalence | | |
| Insulin | 1 | 3 |
| Sulfonylurea and/or metformin | 5 | 6 |
| Diuretics | 2 | 4 |
| Other antihypertensives | 4 | 3 |
| Lipid-lowering medications | 5 | 6 |

Data are means ± SD or *n*. Values for body weight were assessed using Metropolitan Life Insurance tables of 1983. Android obesity is indicated by a waist-to-hip ratio ≥ 0.9 for men and ≥ 0.8 for women. Lipid-lowering medications include bile acid sequestrants and/or hydro-3-methyl-glutaryl CoA reductase inhibitors.

jects were maintained on the same dosage of their medications throughout. The study began with an 8-week baseline period over which participants followed an NCEP Step 2 ad libitum diet, documented by 3 nonconsecutive days of food records every 2 weeks. This was followed by the experimental phase of the study, consisting of two successive 3-week treatment periods separated by a 2-week washout interval over which another 3-day food record was obtained. During the first treatment period subjects were randomly assigned to either the KJM (NCEP Step 2 metabolically controlled diet enriched with KJM fiber) or the control treatment (the same diet enriched with wheat bran [WB] fiber). For the second treatment period, subjects were crossed over. The study began with five subjects taking the KJM treatment and six the WB control treatment.

Diet

Both treatments consisted of a 3-day rotating NCEP Step 2 diet with three meals per day provided under metabolic conditions. All foods were preweighed, packaged, and couriered to participants for consumption at home or at work. The mean macronutrient profile conformed with an NCEP Step 2 diet. Energy intakes for weight maintenance were provided according to Lipid Research Clinics Tables with adjustment for physical activity (26). Total dietary fiber was administered at 2 g/412 kJ (100 kcal), with a mean daily intake, according to energy intake, ranging from 24 g to a plateau of 50 g for those consuming 2,500 kcal/day or more. The actual diet consumed is presented in Table 3.

The two treatments differed only in the type of fiber. Participants on the KJM treatment received KJM-enriched biscuits,

Table 2—Composition (g/100 g) of KJM and WB biscuits at a moisture content of 2.8 g/100 g

| Biscuit type | Protein | Fat | Available carbohydrate | KJM flour | Ash | Total dietary fiber | | Energy (kJ/100 g) |
|--------------|---------|------|------------------------|-----------|-----|---------------------|----------------------------|-------------------|
| | | | | | | Dietary fiber | Glucomannan from KJM flour | |
| WB | 6.8 | 14.4 | 66.5 | — | 1.4 | 2.8 | — | 1,011 |
| KJM | 6.2 | 13.9 | 61.2 | 15.3 | 1.3 | 2.3 | 10.6 | 944 |

Available carbohydrate values are calculated as follows: $100 - (\text{moisture} + \text{protein} + \text{fat} + \text{total dietary fiber} + \text{ash})$. Added sucrose was between 37 and 40% of the total available carbohydrate. Average values for dietary fiber in WB and flour were analyzed by the method of Prosky et al. (35). The glucomannan value represents 69% glucomannan polymer derived from KJM flour.

whereas those on the control treatment received an equal quantity of WB (placebo) biscuits. Subjects were instructed to eat an equal amount of biscuits along with an 8-oz beverage as a snack, three times daily, including once at bedtime. Both types of biscuits were produced and provided by Dicoform (Rome, Italy; KJM biscuits are commercially available in Italy as Dicoman biscuits). They had similar nutrient profiles (Table 2) and were indistinguishable in taste and appearance. KJM biscuits contained ~15% KJM flour, of which 69% was the active high-viscosity glucomannan, 15% other polysaccharides, and 16% excipients by weight. Because KJM flour comprised half (1 g/412 kJ [100 kcal]) of the total fiber on the KJM treatment, ~0.7 g/412 kJ (100 kcal) was glucomannan. WB biscuits, in contrast, had a lower proportion of fiber than KJM biscuits (Table 2). Therefore, ~14 g/day of WB fiber derived from standardized American Association of Cereal Chemist hard red wheat bran was added to the WB control diet to compensate for these fiber differences.

Any food from the metabolic diet together with study biscuits not consumed were brought to the clinic for weighing to measure compliance. Dietary changes found to occur during the first 3-week treatment period were duplicated before food delivery for the second treatment period for each participant.

Laboratory methods

Serum blood samples were immediately separated and stored in four aliquots at -70°C after collection. They were thawed at the end of the study for analysis of total cholesterol, HDL, and triglycerides measured enzymatically (27,28). LDL content was estimated by the formula of Friedewald et al. (29). Apo A1 and B were determined by rocket immunoelectrophoresis (30). Fasting blood glucose was analyzed by a hexokinase method using a Cobas Mira Autoanalyzer (Roche Diagnostic, Mississauga, Ontario, Canada). Serum fructosamine was analyzed in triplicate using the Cobas Fara II (31), and plasma insulin was measured in duplicate by radioimmunoassay (RIA) with reagent from ICN Biomedicals (Horsham, PA) (32). Finally, C-peptide was determined by RIA (33).

Physical measurements were obtained by standard techniques. Blood pressure was taken and expressed as the mean of three measurements to the nearest 2 mmHg on both arms. Fasting body weight was deter-

Table 3—Average intake of energy and nutrients before and during study periods

| | Baseline | KJM | WB | P |
|--------------------------------------|-------------------|-------------------|-------------------|--------|
| Total energy (kJ/day) | 7,671 \pm 1,760 | 8,907 \pm 2,250 | 9,134 \pm 1,006 | 0.23 |
| Total fat (% of energy) | 24.8 \pm 6.2 | 23.4 \pm 2.1 | 23.9 \pm 1.6 | 0.6 |
| Saturated fat (% of energy) | 8.2 \pm 2.4 | 4.1 \pm 0.4 | 3.9 \pm 0.2 | 0.73 |
| Monosaturated fat (% of energy) | 7.3 \pm 1.3 | 12.4 \pm 1.9 | 12.6 \pm 1.4 | 0.35 |
| Polyunsaturated fat (% of energy) | 9.1 \pm 2.1 | 7.1 \pm 0.2 | 7.6 \pm 0.3 | 0.24 |
| Cholesterol (mg/4,184kJ) | 87 \pm 17 | 44 \pm 18 | 36 \pm 11 | 0.12 |
| Total protein (% of energy) | 18.7 \pm 4.2 | 15.5 \pm 1.7 | 14.9 \pm 2.1 | 0.86 |
| Available carbohydrate (% of energy) | 56.5 \pm 14.3 | 60.5 \pm 8.6 | 61.2 \pm 6.5 | 0.4 |
| Sugar (% of energy) | 13.2 \pm 17.2 | 11.2 \pm 0.6 | 10.4 \pm 0.3 | 0.17 |
| Total fiber (g/day) | 27.4 \pm 14.2 | 39.3 \pm 11.4 | 40.1 \pm 12.5 | 0.9 |
| Water soluble (g/day) | 8.1 \pm 2.7 | 23.1 \pm 4.1 | 8.3 \pm 2.4 | <0.001 |
| Water insoluble (g/day) | 17.8 \pm 4.2 | 16.7 \pm 3.6 | 29.8 \pm 4.8 | <0.001 |
| Sodium (mg) | 4,540 \pm 1,350 | 2,820 \pm 348 | 2,708 \pm 420 | 0.878 |
| Potassium (mg) | 1,430 \pm 850 | 3,960 \pm 450 | 4,240 \pm 664 | 0.659 |
| Calcium (mg) | 630 \pm 442 | 1,150 \pm 185 | 1,370 \pm 246 | 0.552 |

Data are means \pm SD. KJM and WB diets are based on actual intake ($n = 11$). Baseline values are based on the mean of four 3-day food records. Differences between KJM and WB study periods were calculated by Student's *t* test for paired data.

mined using a beam scale in light clothing, with an emptied bladder and in bare feet. Waist and hip circumferences were measured by soft nonstretchable tape on the narrowest and widest parts of the trunk.

Energy and nutrient analysis of the diets was calculated using U.S. Department of Agriculture data (34). Nutrient composition of the treatment biscuits was analyzed using the Prosky method to determine fiber content (35).

Statistical analyses

Results are expressed as means \pm SEM, except for age, anthropometric measurements, and nutrient intake (means \pm SD). Data were analyzed by the Statistical Analysis System (SAS) (36). Differences in serum lipids, apolipoproteins, glycemia, blood pressure, and body weight between the beginning (week 0) and end (week 3) of each treatment (control and KJM) were assessed by two-tailed Student's *t* test for paired data (proc univariate). Analysis of covariance with the facility of the general linear model procedure (proc glm) was used to test for differences in these same parameters between the two treatments. Adjustment for multiple comparisons was made by the Bonferroni-Hochberg procedure (37) for primary (fructosamine, total:HDL cholesterol ratio, and sBP) and secondary (body weight, total, LDL, and HDL cholesterol, apo A-1, B, and A-1:B ratio, glucose, insulin, and dBp) end points separately. *P* values for each end point were

ordered sequentially and contrasted with the corresponding adjusted comparison-wise critical α -levels. Null hypotheses were rejected only if the *P* values were less than their corresponding α -values (37). Control of individual variation from the repeat measures aspect of the design was addressed by incorporating the random subject effect as well as the starting measurement. Diet, sex, and phase effects were also incorporated in this model. To test for confounding effects of body weight on study parameters, Pearson correlations were performed (proc corr).

RESULTS — All participants followed the experimental protocol with little difficulty. According to 3-day food records collected over the baseline and washout periods, subjects ate their usual low-fat (<25% energy) and high-fiber (>27 g/day) diets (Table 3). In addition, during the treatment periods, returned food and biscuits from metabolic diets indicated that subjects consumed an average of 93 and 95% of diet calories prescribed on the KJM and WB control treatments, respectively, and 88% (137 g/day) and 91% (142 g/day) of the KJM test and WB placebo biscuits, respectively. Consumption patterns translated into an insignificant decrease in body weight during both treatment periods (Table 4). There was no correlation between changes in weight and serum lipids, glucose, or blood pressure (data not shown). The only side effect experienced was a transient complaint of flatulence and

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soft stools reported by 37 and 24% of participants during the KJM and the WB control treatments, respectively, but none refused to continue the study.

Serum lipids

Blood lipids were improved during KJM treatment compared with the WB control treatment (Table 4). The primary lipid endpoint, total:HDL cholesterol, decreased significantly by $5.7 \pm 2.3\%$ ($P = 0.034$, $\alpha = 0.05$) during KJM treatment compared with an insignificant increase of $4.7 \pm 4.4\%$ ($P = 0.316$, $\alpha = 0.017$) during the WB control treatment. The resultant between-treatment decrease of $10 \pm 4.0\%$ in those on the KJM treatment was significant ($P = 0.028$, $\alpha = 0.05$). The secondary end points of total and LDL cholesterol also fell significantly by $16 \pm 2.7\%$ ($P = 0.001$, $\alpha = 0.005$) and $25 \pm 3.9\%$ ($P = 0.001$, $\alpha = 0.005$), respectively, during KJM treatment compared with $4.9 \pm 3.7\%$ ($P = 0.20$, $\alpha = 0.006$) and $4.8 \pm 5.9\%$ ($P = 0.45$, $\alpha = 0.008$), respectively, during the WB control treatment. Resultant between-treatment differences of $11 \pm 4.2\%$ ($P =$

0.025 , $\alpha = 0.005$) and $19 \pm 6.8\%$ ($P = 0.033$, $\alpha = 0.006$) were insignificant, however, after correction by the Bonferroni-Hochberg procedure. The combined fall in total cholesterol and LDL in those on the KJM treatment indicated reclassification of the lipid status from elevated to normal cholesterolemia (<5.2 mmol/l) (2) for 6 of 11 subjects. Values for LDL, however, were derived from only 9 subjects, because 2 of 11 participants had serum triglyceride levels >4.5 mmol/l, not allowing for calculation by the Friedewald equation.

Similar results were observed for apo B and the apo B:A-1 ratio. During KJM treatment, both fell significantly by $14 \pm 3.4\%$ ($P = 0.002$, $\alpha = 0.006$) and $8.6 \pm 2.3\%$ ($P = 0.004$, $\alpha = 0.007$), respectively, compared with $3.0 \pm 5.0\%$ ($P = 0.57$, $\alpha = 0.013$) and $3.0 \pm 4.8\%$ ($P = 0.55$, $\alpha = 0.01$) during the WB control treatment. These changes, however, resulted in insignificant between-treatment differences of $11 \pm 4.3\%$ ($P = 0.025$, $\alpha = 0.005$) and $5.6 \pm 4.5\%$ ($P = 0.24$, $\alpha = 0.008$) after correction by the Bonferroni-Hochberg procedure.

In contrast, such effects were not seen for HDL, apo A-1, or triglycerides. During KJM and WB control treatments, HDL and apo A-1 decreased insignificantly, for insignificant between-treatment changes. Similarly, during both treatments, triglycerides increased insignificantly, with no significant difference between treatments.

Glycemic control

Improvements in glycemic control were observed in those on the KJM treatment compared with those on the WB control treatment (Table 4). The primary glycemic end point, serum fructosamine, was reduced insignificantly during both the KJM and control treatments by $6.1 \pm 2.4\%$ ($P = 0.03$, $\alpha = 0.025$) and $0.5 \pm 1.4\%$ ($P = 0.751$, $\alpha = 0.05$), respectively, after correction by the Bonferroni procedure. The resultant between-treatment decrease of $5.7 \pm 1.7\%$ in those on the KJM treatment was nevertheless significant ($P = 0.007$, $\alpha = 0.017$). No significant between-treatment differences were seen for the secondary end points of insulin and glucose,

Table 4—Changes in primary and secondary end points of metabolic control during and between the KJM and WB control study periods

| Risk factor | KJM | | | WB | | | Between-treatments | | |
|--------------------------------|-----------------|-----------------|------------------|-----------------|-----------------|-----------------|--------------------|--------|----------|
| | Week 0 | Week 3 | Change (%) | Week 0 | Week 3 | Change (%) | Change (%) | P | α |
| Primary end points | | | | | | | | | |
| Total:HDL cholesterol (mmol/l) | 6.08 \pm 0.53 | 5.69 \pm 0.48 | -5.7 \pm 2.3* | 6.06 \pm 0.56 | 6.21 \pm 0.53 | 4.7 \pm 4.4 | -10 \pm 4.0 | 0.028* | 0.05 |
| Fructosamine (mmol/l) | 3.36 \pm 0.1 | 3.17 \pm 0.2 | -6.1 \pm 2.4 | 3.25 \pm 0.2 | 3.25 \pm 0.2 | -0.5 \pm 1.4 | -5.7 \pm 1.7 | 0.007* | 0.017 |
| sBP (mmHg) | 139.5 \pm 5.0 | 131.6 \pm 4.9 | -5.5 \pm 1.4* | 128.8 \pm 4.0 | 130.4 \pm 4.7 | 1.4 \pm 2.7 | -6.9 \pm 2.5 | 0.021* | 0.025 |
| Secondary end points | | | | | | | | | |
| Cholesterol (mmol/l) | | | | | | | | | |
| Total | 6.10 \pm 0.29 | 5.11 \pm 0.28 | -16 \pm 2.7* | 5.81 \pm 0.19 | 5.48 \pm 0.19 | -4.9 \pm 3.7 | -11 \pm 4.2 | 0.025 | 0.005 |
| LDL | 3.89 \pm 0.25 | 3.04 \pm 0.24 | -25 \pm 3.9* | 3.56 \pm 0.18 | 3.29 \pm 0.18 | -4.8 \pm 5.9 | -19 \pm 6.8 | 0.033 | 0.006 |
| HDL | 1.07 \pm 0.08 | 0.94 \pm 0.06 | -11 \pm 2.2 | 1.04 \pm 0.10 | 0.95 \pm 0.08 | -8.9 \pm 2.4* | -2.2 \pm 3.1 | 0.492 | 0.01 |
| Triglyceride (mmol/l) | | | | | | | | | |
| | 2.53 \pm 0.23 | 2.88 \pm 0.29 | 18.7 \pm 12.8 | 2.69 \pm 0.44 | 2.96 \pm 0.37 | 25.1 \pm 14.7 | -6.4 \pm 13.9 | 0.657 | 0.017 |
| Apolipoprotein (g/l) | | | | | | | | | |
| Apo A-1 | 1.47 \pm 0.07 | 1.37 \pm 0.06 | -6 \pm 3.1 | 1.48 \pm 0.08 | 1.48 \pm 0.10 | 0.7 \pm 3.8 | -6.7 \pm 4.3 | 0.154 | 0.007 |
| Apo B | 1.50 \pm 0.09 | 1.28 \pm 0.08 | -14 \pm 3.4* | 1.48 \pm 0.08 | 1.40 \pm 0.07 | -3.0 \pm 5.0 | -11 \pm 4.3 | 0.025 | 0.005 |
| Apo B/Apo A-1 | 1.05 \pm 0.09 | 0.96 \pm 0.08 | -8.6 \pm 2.3* | 1.05 \pm 0.10 | 0.99 \pm 0.08 | -3.0 \pm 4.8 | -5.6 \pm 4.5 | 0.235 | 0.008 |
| Glycemic control | | | | | | | | | |
| Glucose (mmol/l) | | | | | | | | | |
| | 9.63 \pm 0.89 | 8.62 \pm 0.95 | -11.0 \pm 3.0* | 9.29 \pm 0.74 | 8.99 \pm 0.78 | -1.5 \pm 6.1 | -9.7 \pm 6.1 | 0.141 | 0.006 |
| Insulin (pmol/l) | 142 \pm 32 | 140 \pm 31 | 2.1 \pm 11 | 154 \pm 38.6 | 150 \pm 32.8 | 9.58 \pm 9.8 | -7.5 \pm 12.4 | 0.559 | 0.013 |
| dBp (mmHg) | 79.1 \pm 2.0 | 77.5 \pm 1.8 | -1.6 \pm 2.8 | 78.3 \pm 1.6 | 78.4 \pm 2.7 | 0.4 \pm 3.6 | -2.0 \pm 5.2 | 0.706 | 0.025 |
| Body weight (kg) | 85.6 \pm 19 | 85.0 \pm 19 | -0.6 \pm 0.5 | 85.9 \pm 19 | 85.3 \pm 19 | -0.6 \pm 0.4 | -0.1 \pm 0.4 | 0.899 | 0.05 |

Data are means \pm SEM except for body weight, which is means \pm SD ($n = 11$). Between-treatment differences were assessed by analysis of covariance (PROC GLM). Comparison α -level was adjusted for multiple end point comparisons with the Bonferroni-Hochberg procedure for primary and secondary end points separately. LDL values are for nine subjects, since two subjects had triglycerides >4.5 mmol/l, preventing calculation by the Friedewald equation. *Significant after adjustment of α -level by the Bonferroni-Hochberg procedure. Null-hypotheses were rejected only if the P values were less than their corresponding α -value. P values for during-treatment changes were assessed by paired Student's t test.

although during the KJM treatment, fasting glycemia fell significantly by $11 \pm 3.0\%$ ($P = 0.004$, $\alpha = 0.008$) compared with $1.5 \pm 6.1\%$ ($P = 0.804$, $\alpha = 0.013$) in those on the control treatment.

Blood pressure

An improvement in blood pressure was also observed in those on the KJM treatment compared with those on the WB control treatment (Table 4). The primary blood pressure endpoint, sBP, decreased significantly in those on KJM supplementation by $5.5 \pm 1.4\%$ ($P = 0.003$, $\alpha = 0.017$) compared with $1.4 \pm 2.7\%$ ($P = 0.62$, $\alpha = 0.03$) in those on the WB control treatment, producing a significant between-treatment difference of $6.9 \pm 2.5\%$ ($P = 0.021$, $\alpha = 0.025$) or 9.4 ± 3 mmHg. During both treatments, however, dBP remained virtually unchanged with no significant difference between treatments. The result was a reclassification in sBP status from moderately high to normotensive (<135 mmHg) in 5 of 11 subjects after the KJM treatment.

CONCLUSIONS — The present study indicates that the addition of 0.7 g/412 kJ (100 kcal) of high-viscosity glucomannan in biscuit form to conventional CHD treatment (a low-saturated fat diet combined with drug therapy) improved metabolic control beyond the effect of conventional treatment alone in high-risk individuals with type 2 diabetes. We observed amelioration in three major CHD risk factors—hyperglycemia, hypertension, and hyperlipidemia—relative to a matched placebo control treatment, as measured by the primary end points of fructosamine, sBP, and total:HDL cholesterol, respectively. Differences in secondary glycemic, blood pressure, and lipid end points were insignificant after adjustment for multiple comparisons by the Bonferroni-Hochberg procedure. With greater power derived from a larger sample size, significance might have been achieved in these cases.

To achieve similar metabolic benefits, the most recent dietary recommendations of the American Diabetes Association have a change in emphasis from encouraging carbohydrate and less processed fiber foods to increased consumption of monounsaturated fat (38). The reasoning is that fiber has only very modest effects on LDL cholesterol and does nothing to raise HDL cholesterol levels. Nevertheless, the diet usually prescribed for the management of CHD risk factors in people with diabetes resem-

bles an NCEP Step 1 or 2 diet. The recommendations for these diets are as follows: for NCEP Step 1, $<30\%$ of total calories from fat, $<10\%$ from saturated fat, and $<10\%$ from polyunsaturated fat, with <300 mg/day of cholesterol; and for NCEP Step 2, the same except $<7\%$ of total calories from saturated fat with <200 mg/day of cholesterol. In the two well-controlled clinical studies in this area, limitations of the diets are evident. Hunninghake et al. (39), following hypercholesterolemic subjects on an NCEP Step 2 diet for 3 months, found that LDL was reduced by only 5%. Schaefer et al. (40) found a reduction in LDL in subjects provided an NCEP Step 2 diet on a metabolic basis to be as much as 17%, but with adverse effects on other lipid parameters and no effect on the total:HDL cholesterol ratio. A high inter-subject variability in LDL reductions was also noticed. These results are in agreement with our findings, but we also detected an improvement in lipid ratios in those on KJM treatment. The suggestion is that an NCEP Step 2 diet supplemented with KJM may confer additional benefits over this diet alone.

Lipids

Improvements in blood lipid control have previously been shown when NCEP Step 2 diets were supplemented with soluble fiber from different dietary sources (41) or fiber supplements (18,42). Although such studies have reported reduced total and LDL cholesterol concentrations, few, as has been the case for NCEP diets, have reported improved lipoprotein ratios. Out of the three lipid trials that used KJM (21–23), the former two did not show a significant change in these ratios. In contrast, Venter et al. (23) found 4.5 g/day glucomannan significantly improved both LDL and the LDL:HDL ratio in 18 hypercholesterolemic subjects. These last findings are supported by those of the present study, in which a significant $10 \pm 4.0\%$ decrease in the total:HDL cholesterol ratio was noticed in those on the KJM treatment compared with control subjects. The mechanism by which our KJM-supplemented biscuits had this lipid-lowering effect is not clear. It is likely similar to the mechanism proposed for other soluble fibers. Possibilities include an inhibition of cholesterol absorption in the jejunum (43), bile acid absorption in the ileum (44), or less postprandial stimulation of hydro-3-methyl-glutaryl CoA reductase (41). Other options include the

generation of short-chain fatty acids by colonic microflora, predominantly propionate, which may decrease hepatic cholesterol synthesis (45).

Glycemic control

Improvements in diabetes control after soluble fiber supplementation have also been shown (46). KJM, in particular, has been shown to have a beneficial effect after both acute (25) and long-term (24,25) administration. Our findings support these observations. In those on KJM treatment compared with control subjects, a $5.7 \pm 1.7\%$ reduction was observed in serum fructosamine, a short-term marker of diabetes control, with no effect on either fasting glucose or insulin concentrations. These results were not altered by excluding four subjects treated with insulin. An effect of the gel-forming KJM on digestion may explain this finding. It has been suggested that decreases in glucose and insulin levels after the consumption of water-soluble fibers are related to slower rates of food absorption in the small intestine associated with increased viscosity (47). KJM has been shown to have very high viscosity, ~ 5 times higher than guar gum (47) and considerably more than pectin (23). Consequently, in some studies it has been given at half the dosage relative to these other fibers (47).

Blood pressure

Finally, although few studies have demonstrated an effect of fiber on blood pressure, significant reductions in both sBP and dBP have been reported after consumption of guar granulates (48) and soluble dietary fiber supplements (49). The same effect has been shown for KJM, but only in sBP (21). This last finding agrees with results from the present study, in which KJM treatment significantly reduced sBP by 6.9% compared with WB control treatment but did not affect dBP. The commonly recommended oat bran, in contrast, has been shown to affect neither sBP nor dBP (50). A possible mechanism for the blood pressure-lowering effect of soluble fibers may involve increased insulin sensitivity (18), which may reduce blood pressure by influencing sodium absorption in the distal tubule, increasing sympathetic nervous system activity and peripheral vascular resistance (51). Unfortunately, this parameter was not measured.

The effect of KJM fiber supplements on the three CHD risk factors persists even in subjects who are concurrently taking con-

ventional drug therapy. Consistent with our findings, a combination of fiber and drugs has been shown to be more effective clinically in improving metabolic control than the drug given alone. Tuomilehto et al. (52) found that the viscous soluble fiber guar gum and gemfibrozil administered together reduced total cholesterol and the LDL:HDL ratio significantly more than gemfibrozil and placebo. Elsewhere this same effect has been noticed for blood glucose and blood pressure. A significant reduction was found in postprandial blood glucose after consumption of sulfonylurea (glibenclamide) and glucomannan with a test meal compared with sulfonylurea alone with the same test meal (53). Similarly, a significant decrease in dBP was noticed after administration of guar gum compared with placebo in patients receiving drug treatment for hypertension (19). Together these findings suggest that highly viscous soluble fiber may augment or potentiate the effect of drugs.

In conclusion, the application of KJM supplementation in our high-risk diabetic study group demonstrated simultaneous improvement in all three diet-modifiable risk factors, indicating a reduction in overall CHD risk (54). One of the benefits we foresee from this study is that KJM-supplemented therapy may lower required drug dosages and improve overall cost-effectiveness and acceptability of treatment. Although we agree that food should be the normal way to achieve an adequate fiber intake, we also consider that fiber-supplemented foods have advantages in the treatment of individuals at high risk for CHD and represent a possible intermediate step between diet and drug therapy. To maximize the therapeutic potential of KJM in CHD prevention, however, studies with larger sample sizes are needed. A determination of the optimal fiber dose in different categories of people and the rheological-biological relationship of KJM are also warranted.

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Effect of short-term ingestion of konjac glucomannan on serum cholesterol in healthy men^{1,2}

Anders Arvill and Lennart Bodin

ABSTRACT The effects of the soluble fiber konjac glucomannan (GM) on serum cholesterol concentrations were investigated in 63 healthy men in a double-blind crossover, placebo-controlled study. After a 2-wk baseline period, the subjects were given 3.9 g GM or placebo daily for 4 wk. After a washout period of 2 wk, crossover took place, followed by another 4 wk of treatment. The subjects were encouraged not to change their ordinary diets or general lifestyle during the investigation. GM fibers reduced total cholesterol (TC) concentrations by 10% ($P < 0.0001$), low-density-lipoprotein cholesterol (LDL-C) concentrations by 7.2% ($P < 0.007$), triglycerides by 23% ($P < 0.03$), and systolic blood pressure by 2.5% ($P < 0.02$). High-density-lipoprotein cholesterol (HDL-C) and the ratio of LDL-C to HDL-C did not change significantly. No change in diastolic blood pressure or body weight was observed. No adverse effects were observed. The results of this study show that GM is an effective cholesterol-lowering dietary adjunct. *Am J Clin Nutr* 1995;61:585–9

KEY WORDS Glucomannan, cholesterol, triglycerides, dietary fiber

Introduction

More than 50% of the population in most Western countries have cholesterol values >5.17 mmol/L and are, consequently, in the opinion of some experts, in need of treatment (1–5). The cornerstone of the treatment program for hypercholesterolemia consists of dietary changes toward a low-fat, low-cholesterol diet that is rich in dietary fiber (3). Partly because of cost, pharmacological treatment should be reserved for cases of hypercholesterolemia not responding satisfactorily to dietary changes. The long-term safety, however, of cholesterol-lowering drugs is not firmly established. In view of this, a dietary fiber with significant cholesterol-lowering effects, either as a dietary adjunct or as a natural component of the diet, has a large potential role in lowering cholesterol in the general population. A diet rich in fiber has been shown to lower plasma cholesterol by 10–15% in several studies (6–9). The nature of the dietary fiber is important. Water-soluble fibers such as pectins, gums, and mixed-linked β 1,3- and 1,4-D-glucans are capable of significantly lowering the plasma cholesterol concentration (9). However, one study suggested that the intrinsic cholesterol-lowering effect of oat bran was small (10). Glucomannan is a dietary fiber obtained from the tubers of *Amorphophallus konjac*. Konjac flour ($\approx 80\%$ glucomannan) has

traditionally been used as the chief ingredient of edible konyaku (konjac jelly). Purified glucomannan (now available under the name of PROPOL A, Shimizu Chemical Corporation, Hiroshima, Japan), is a polysaccharide consisting of repeating units of β -D-glucose and β -D-mannose joined together in a chain by 1,4 linkages (11–15).

The aim of the present study was to examine the hypocholesterolemic effect of supplementing the usual diets of normocholesterolemic or hypercholesterolemic but otherwise healthy men with glucomannan. We wanted to investigate whether glucomannan had any intrinsic cholesterol-lowering effect as a dietary adjunct. The subjects were, therefore, specifically instructed to keep their diet and physical activity unchanged throughout the study.

Subjects and methods

Subjects

Seventy male subjects with serum cholesterol values > 6.3 mmol/L (at screening) and aged between 25 and 65 y were selected from a group of ≈ 500 subjects responding to a local newspaper advertisement. Subjects being treated for hypercholesterolemia and subjects with secondary causes of hyperlipidemia such as diabetes mellitus, hypothyroidism, or renal disease were excluded from the study.

After a 2-wk baseline period, the 70 subjects were randomly divided into two groups. The study then consisted of two 4-wk treatment periods, with a double-blind, placebo-controlled crossover design. There was a 2-wk washout period between the treatment periods. The subjects were given identical gelatin capsules, each capsule containing 0.43 g glucomannan (active) or cornstarch (placebo) in addition to 66 mg lactose and 10 mg magnesium stearate. Three capsules were taken three times daily one-half hour before meals (total daily amount 3.9 g glucomannan) with a glass of water. Compliance with the dosage regimen was monitored by interview and by counting the capsules left at the end of each treatment period. The subjects were also independently interviewed about their food intake and physical activity during the trial, at the start and end

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of each period (four times), by the same person. No attempt however was made to describe the exact amount and composition of each individual meal.

From the original group, seven subjects were excluded during the study: one died, one had perforated appendicitis, one drastically reduced his food intake, two admitted taking additional cholesterol-lowering medicine, and two failed to complete the trial. Sixty-three subjects completed the 10-wk protocol. Baseline data for the group are shown in **Table 1**. The study was approved by the Medical Research Ethical Committee of Örebro, Sweden.

Measurements

Measurements were made at the beginning of the baseline period and at the end of period 1 (baseline-period 1), and the beginning and end of period 2 (washout-period 2). Body weight, blood pressure, and blood samples were thus taken four times during the study. Blood samples were collected after a 12-h overnight fast. Serum total cholesterol (TC) was determined enzymatically with a high-performance kit (Boehringer Mannheim, Mannheim, Germany), high-density-lipoprotein cholesterol (HDL-C) with the same kit after selective precipitation of the apo B-containing lipoproteins with manganese chloride and heparin, and triglyceride concentrations with an enzymatic colorimetric method (Boehringer Mannheim). Low-density-lipoprotein cholesterol (LDL-C) was calculated by using the following formula:

$$\text{LDL-C} = [(\text{TC}) - (\text{HDL-C}) - (\text{TG}/2.2)]$$

The upper limit of triglycerides for use in this formula was set at 4.6 mmol/L (16). The intraassay and interassay CVs were, respectively, 1.2% and 1.9% for TC, 1.9% and 4.1% for triglycerides, and 3.5% and 4.7% for HDL-C. The following were also determined on each of the testing occasions: serum concentrations of creatinine, bilirubin, glutamyltransferase, aspartate aminotransferase (ASAT), and alanine aminotransferase (ALAT).

Statistical analysis

The data were analyzed as a 2×2 crossover design by using a sequence of two-sample *t* tests, according to Jones and Kenward (17). Baseline and period 1, as well as washout and period 2, measurements were used. The testing sequence started by testing for first-order carryover effects, then second-order carryover effects, and finally for treatment effects con-

ditional on the outcome of the preceding test. If carryover effects were not verified, the test for treatment effect was based on contrasting period 1 and period 2 measurements. In the presence of carryover effects the treatment analysis was based on the comparison of baseline and period 1 measurements. **Figures 1 and 2** describe the two ways of analysis. The figures illustrate the mean values for TC and triglycerides over the four time points that measurements were taken; baseline, end of period 1, end of washout period, and end of period 2. The mean values at the four time points are represented by A, B, C, and D for group 1 and a, b, c, and d for group 2. Group 1 started with the treatment followed by placebo; in group 2 the order was reversed. The analysis of triglycerides represents a case of no carryover effect and the analysis of TC a case with a suspected carryover effect. In the case of no carryover effect, a point estimate of the treatment effect is given by $[(B - D) - (b - d)]/2$, for triglyceride $[(2.54 - 3.47) - (2.28 - 2.18)]/2$ or -0.51 . For those measurements for which a carryover effect cannot be rejected, the point estimate is $[(B - A) - (b - a)]$, which results in $[(6.51 - 6.93) - (6.76 - 6.51)]$, or -0.67 for TC. In **Tables 2 and 3** these estimates are given together with 95% CIs, *P* values in the test for no treatment effect, and a percentage difference calculated as the effect estimate divided by the mean of the baseline values for the two groups.

Results

A possible carryover effect was found in the analysis of cholesterol, LDL-C, and HDL-C. Therefore, point estimates and CIs for these outcomes were calculated only from period 1 and baseline readings (Table 2). For other outcomes there was no suggestion of carryover effects. Hence, the specific feature of the design could be fully used in the estimation of the treatment effect, ie, data from both periods were used (Table 3).

Four weeks of ingestion of GM fibers reduced TC concentrations by 10.0% ($P < 0.0001$), LDL-C concentrations by 7.2% ($P < 0.007$), triglycerides by 23% ($P < 0.03$), and systolic blood pressure by 2.5% ($P < 0.02$). HDL-C and the ratio of LDL-C to HDL-C were not significantly different from baseline. No change in diastolic blood pressure or body weight was observed. No adverse effects were observed.

TABLE 1
Baseline characteristics at start of treatment¹

| | Value (n = 63) |
|----------------------------------|----------------------|
| Age (y) | 47 ± 8.2 (26-62) |
| Weight (kg) | 90 ± 12.8 (65-128) |
| Height (cm) | 177 ± 6.9 (158-194) |
| Systolic blood pressure (mm Hg) | 140 ± 17.6 (110-190) |
| Diastolic blood pressure (mm Hg) | 85 ± 10.2 (70-110) |
| Total cholesterol (mmol/L) | 6.7 ± 1.0 (5.2-12.0) |
| LDL cholesterol (mmol/L) | 4.5 ± 1.3 (3.2-5.9) |
| HDL cholesterol (mmol/L) | 1.2 ± 0.3 (0.7-2.4) |
| Triglycerides (mmol/L) | 2.2 ± 1.7 (0.7-11.9) |

¹ $\bar{x} \pm \text{SD}$; range in parentheses.

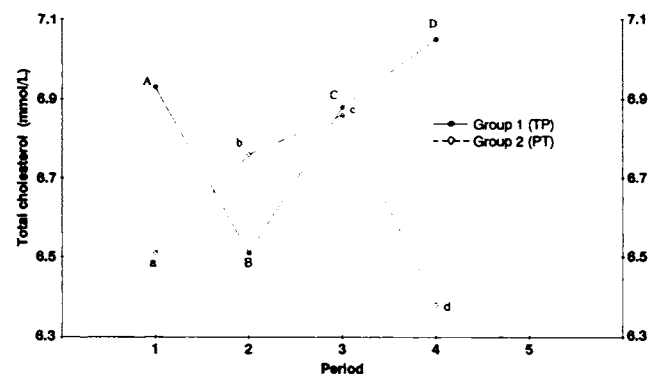


FIGURE 1. Mean values for total serum cholesterol for group 1 (treatment/placebo) and group 2 (placebo/treatment) for four time points: 1, baseline; 2, period 1; 3, washout; and 4, period 2.

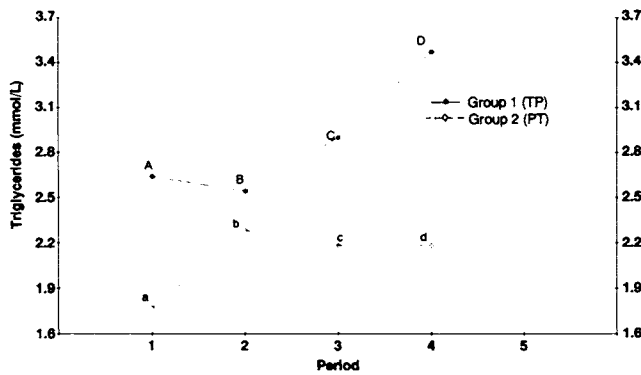


FIGURE 2. Mean values for triglycerides for group 1 (treatment/placebo) and group 2 (placebo/treatment) for four time points: 1, baseline; 2, period 1; 3, washout; and 4, period 2.

Discussion

The cholesterol-lowering effect of glucomannan fiber reported in this study is 10% after 4 wk of treatment, a remarkable reduction considering the relatively small doses used and the short time of treatment. The study design allowed for inclusion of different concentrations of serum cholesterol, as well as of mild to moderate obesity and hypertension. Men between 25 and 65 y of age with serum cholesterol concentrations ≥ 6.3 mmol/L at the initial screening were eligible. However, the cholesterol concentrations of some subjects sank after their initial screening and the range at baseline was 5.2–12.0 mmol/L. The baseline range was considered acceptable for the purpose of the study and the deviation from the screening range was judged to be part of normal variability. Besides, a lower initial range (including normal or near normal serum cholesterol concentrations) would seem to augment the demands on glucomannan as far as detectable treatment effects were concerned. Statistical evaluation using only the cholesterol values within the range 6.3–12 mmol/L [Table 2: group 1 ($n = 24$) and group 2 ($n = 19$); Table 3: group 1 ($n = 24$) and group 2 ($n = 19$), except LDL-C—group 1 ($n = 21$) and group 2 ($n = 18$)] did not change the results significantly. On the other hand the estimate of the percentage change could be affected by regression to the mean if the initial values were restricted to higher values. Therefore, the percentage change was estimated also for the complementary group with initial cholesterol values in the range 5.2–6.2 mmol/L. The percentage decrease for TC due to glucomannan treatment was then estimated to be 5.6%. On the other hand the estimate of decrease in triglycerides was estimated to be 44%. Five subjects turned out to have hypercholesterolemia phenotype IIB, with a mean triglyceride concentration of 5.98 ± 1.84 mmol/L (range 4.4–8.7), and a mean serum cholesterol concentration of 8.66 ± 1.01 mmol/L (range 7.4–10.3). None of the type IIB subjects had diabetes. On average the group as a whole ($n = 63$) was 15–30% overweight.

The method of analysis chosen is a fairly robust technique with relatively few assumptions. No assumption of the covariance structure has to be made, apart from that of equal variance for the contrast in each group. In one case that assumption was not fulfilled, and therefore the *t* test with separate variance estimation and a reduced number of degrees of freedom was

used. This partial imbalance was present as a result of the randomization. Two individuals with very high triglyceride values had both been allocated to the group with initial treatment. Because no other significant imbalance in the randomization was found, the small differences in the groups at baseline and the allocation of individuals were accepted, and thought not to influence the validity of the analysis.

The physical-chemical structure of glucomannan may be an important determinant of its cholesterol-lowering ability. Glucomannan particles, derived from the konjac root, are tasteless, odorless, and pure white. They consist of extremely long thread-like macromolecules tangled together. On contact with water the particles swell to ≈ 200 times their original volume, turning glucomannan into a viscous liquid. The highest viscosity is reached 5 or 6 h after glucomannan is placed in water, and it will maintain this viscosity for >120 h (18, 19). The mechanism of action of dietary fiber on plasma lipids is still a matter of debate. Promotion of bile-acid excretion in the stool and/or blockage of cholesterol absorption are possible mechanisms (20–23).

The effect of the gelatin capsule on the release of glucomannan fibers showed a time delay of ≈ 30 min as compared with glucomannan powder, according to the manufacturer. Further study is needed, though, on the optimal way of dispensing glucomannan. Glucomannan treatment lowered TC by 10%, LDL-C by $\approx 7\%$, and HDL-C by 6% (NS). Triglycerides were reduced by $\approx 20\%$, which is remarkable, although the great variability in triglyceride concentrations should be kept in mind. It is interesting to note that studies using psyllium mucilloid showed no significant changes in triglycerides (24, 25).

The statistical analysis has shown that the results are significantly different between glucomannan intake and placebo intake. This result is valid. One explanation of this result is of course the different treatments. There could also be other explanations. It is not impossible that changes in total energy or composition of the food could have occurred during this period. The trial was a double-blind crossover study. It is not likely that changes in food intake would have been distributed differently during the study periods and over the two groups, and the most obvious explanation for the differences seems thus to be the glucomannan treatment. Body weight was constant in both groups throughout the study, also supporting this statement. Statistical analysis showed a carryover treatment effect between groups, indicating that a 2-wk washout period is too short. The mechanism of this prolonged treatment effect is not known.

This study used gelatin capsules to dispense the glucomannan and the placebo, thus eliminating intolerance due to bulky powders of slimy consistency. Glucomannan was well tolerated and no side effects were reported. It might well be ideally suited for the large number of people with uncomplicated type II hypercholesterolemia, a group that is clearly too big for intensive pharmacological treatment. This study concentrated on the cholesterol-lowering ability of glucomannan as a dietary adjunct. Throughout the study the subjects claimed that they continued their usual diets, which traditionally are rich in fat and poor in dietary fiber (very little grain, fruits, or vegetables). Consequently, any synergistic effects of glucomannan together with a prudent diet have not been examined. It might well be that glucomannan plus a low-fat ($\approx 25\%$ fat) diet rich in fiber (>4.76 g/MJ), would lower cholesterol to satisfactory concentrations in the vast majority of cases of uncomplicated type II hypercholesterolemia.



TABLE 2

Effect of 4 wk of treatment with glucomannan fiber on lipid concentrations of subjects from groups 1 ($n = 32$) and 2 ($n = 31$), baseline and period 1 only

| | Baseline | Glucomannan | Baseline | Placebo | Treatment effect | 95% CI | <i>P</i> | Percent difference ¹ |
|-----------------------------|--------------------------|-------------|-------------|-------------|------------------|--------------|----------|---------------------------------|
| | % | | | | | | | |
| Total cholesterol (mmol/L) | 6.93 ± 1.22 ² | 6.51 ± 0.85 | 6.51 ± 0.72 | 6.72 ± 0.67 | -0.67 | -0.99, -0.35 | 0.0001 | -10.0 |
| LDL-C (mmol/L) ³ | 4.57 ± 0.73 | 4.28 ± 0.69 | 4.49 ± 0.67 | 4.54 ± 0.71 | -0.33 | -0.56, -0.09 | 0.007 | -7.2 |
| HDL-C (mmol/L) | 1.18 ± 0.28 | 1.14 ± 0.26 | 1.22 ± 0.35 | 1.25 ± 0.39 | -0.07 | -0.17, +0.02 | 0.125 | -6.1 |
| LDL-C:HDL-C | 3.90 ± 0.90 | 3.85 ± 1.01 | 3.93 ± 1.13 | 3.88 ± 1.13 | +0.009 | -0.34, +0.36 | 0.959 | +0.2 |

¹ Treatment effect in relation to the mean of the baseline for groups 1 and 2.

² $\bar{x} \pm$ SD at the end of each period.

³ Group 1 ($n = 29$), group 2 ($n = 30$).

TABLE 3

Effect of 4 wk of treatment with glucomannan fiber on subjects from groups 1 and 2 combined ($n = 63$)

| | Baseline | Glucomannan | Baseline | Placebo | Treatment effect | 95% CI | <i>P</i> | Percent difference |
|----------------------------------|-------------|-------------|-------------|-------------|------------------|--------------|----------|--------------------|
| | % | | | | | | | |
| Triglyceride (mmol/L) | 2.42 ± 1.88 | 2.37 ± 1.59 | 2.34 ± 1.59 | 2.88 ± 2.32 | -0.51 | -0.95, -0.06 | 0.026 | -23 |
| Systolic blood pressure (mm Hg) | 138 ± 16.7 | 133 ± 15.9 | 136 ± 18.5 | 136 ± 17.9 | -3.43 | -6.21, -0.67 | 0.016 | -2.5 |
| Diastolic blood pressure (mm Hg) | 85 ± 9.6 | 83 ± 9.1 | 86 ± 10.2 | 81 ± 16.5 | -0.27 | -2.32, +1.79 | 0.796 | -0.3 |
| Body weight (kg) | 89.6 ± 12.8 | 89.4 ± 12.9 | 89.4 ± 12.9 | 89.7 ± 12.9 | -0.29 | -0.74, -0.16 | 0.209 | -0.3 |

The dose-response curve of glucomannan should be further examined as well as its role as a cholesterol-lowering agent in other patient categories (eg, those with obesity or hyperglycemia). Thus, in summary, we think that glucomannan is an interesting cholesterol-lowering agent. In view of the facts that studies (26) have shown regression of atherosclerosis with treatment of hyperlipidemia and that a moderate reduction in serum cholesterol in the population would probably lead to a significant reduction in cardiovascular morbidity and mortality (3), glucomannan may have an important role in the future. ■

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Original Research

A Glucomannan and Chitosan Fiber Supplement Decreases Plasma Cholesterol and Increases Cholesterol Excretion in Overweight Normocholesterolemic Humans

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Key words: chitosan, glucomannan, cholesterol, fecal fat, bile acids, humans

Objective: Both chitosan and glucomannan have demonstrated hypocholesterolemic effects. A recent study in rats indicates that the combination of the two is also a potent hypocholesterolemic agent that increases fecal fat excretion. The objective of the present study was to determine the hypocholesterolemic effect of a supplement containing equal amounts of chitosan and glucomannan on blood lipid concentrations and fecal excretion of fat, neutral sterols and bile acids.

Methods: Twenty-one overweight normocholesterolemic subjects (11 males and 10 females) were fed 2.4 g/day of a supplement containing equal amounts of chitosan and glucomannan. Prior to taking the supplement (initial period) and after 28 days (final period), blood was drawn for measurement of serum lipids and a three-day fecal sample collected for determination of fat, neutral sterol and bile acid excretion. Subjects maintained their normal dietary and activity patterns during the study.

Results: Caloric intake and intake of fat and dietary fiber (excluding the supplement) did not differ between the initial and final periods. Serum total, HDL and LDL cholesterol concentrations were significantly lower ($p < 0.05$) in the final period compared to the initial period. Serum triacylglycerol concentration did not change between periods. There was a trend towards greater fecal excretion of neutral sterols and bile acids ($p = 0.13$ and 0.16 , respectively) in the final period. However, fecal fat excretion did not differ between periods.

Conclusions: Serum cholesterol reduction by a chitosan/glucomannan supplement is likely mediated by increased fecal steroid excretion and is not linked to fat excretion.

INTRODUCTION

An elevated plasma cholesterol concentration has long been recognized as an independent risk factor for ischemic heart disease. It is now believed that reducing plasma cholesterol concentration decreases the risk of myocardial infarctions [1]. Water-soluble fibers such as psyllium, guar gum, oat bran and pectin have been shown to reduce plasma cholesterol concentration [2,3]. Although the mechanism by which these fibers have their hypocholesterolemic effect is still uncertain, many

studies indicate that increased bile acid excretion and/or decreased cholesterol absorption is responsible [4].

Konjac mannan is a dietary fiber from the tuber *Amorphophallus konjac*. It is a highly branched viscous glucomannan that has a demonstrated hypocholesterolemic effect in animals [5,6] and humans [7,8]. It is highly fermentable within the large intestine. Chitosan, although not derived from plants, is similar to dietary fiber in being a polysaccharide that is indigestible by mammalian digestive enzymes. Chitosan is the deacetylated form of chitin, an aminopolysaccharide found in

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the exoskeleton of arthropods and certain fungi [9]. Several studies have also shown chitosan to be hypocholesterolemic in both animal models [10–13] and humans [14].

Although both glucomannan and chitosan are hypocholesterolemic, few studies have examined the mechanism by which these two materials exert this effect. Maezaki *et al.* [14] reported increased fecal excretion of two bile acids, cholic and chenodeoxycholic acid, in males subjects consuming 3 to 6 g/day of chitosan. In rats, chitosan increased [11] or had no effect [15] on fecal neutral sterol excretion. In a recent study in rats, both chitosan and glucomannan, either alone or in combination, reduced liver cholesterol, with the combination tending to be more effective [16]. Both materials decreased cholesterol absorption, whereas only chitosan led to greater excretion of bile acids, relative to a cellulose-containing diet. Further, fecal fat excretion was greater with chitosan feeding, but not with glucomannan feeding. The greater fecal fat excretion with chitosan feeding is of particular interest in light of studies in humans showing that chitosan supplements accelerate weight loss in subjects consuming hypocaloric diets [17,18].

The objective of the present study was to examine the hypocholesterolemic effect of consuming a supplement containing equal amounts of chitosan and glucomannan in overweight humans. Additionally, we determined whether this supplement would increase the fecal excretion of bile acids, neutral sterols and fat.

METHODS

Subjects

Twenty-two overweight subjects enrolled in the study, which was conducted at the University of Utah, Salt Lake City, Utah. The study was approved by the University of Utah Institutional Review Board. Subject characteristics are shown in Table 1. Subjects ranged in age from 18 to 50 years and had a mean body mass index (\pm SD) of 28.0 ± 4.6 . Twenty-one

subjects, 11 male and 10 female, completed the study, as one subject dropped from the study for personal reasons.

Subjects with eating disorders, gastrointestinal disturbances or on chronic drug therapy were excluded from the study, as were pregnant or lactating women. All subjects were given multivitamins while taking the fiber supplement to compensate for any increased loss of fat-soluble vitamins.

Experimental Design

Beginning on day 1, subjects recorded three days of food intake. On days 4 to 6, subjects made a quantitative 72 hour fecal collection. Ingestion of the fiber supplement began on day 6. The fiber supplement was provided in capsules. Subjects were instructed to take five capsules three times a day with a glass of water 30 minutes before breakfast, lunch and dinner for 28 days. Each capsule contained equal amounts of chitosan and glucomannan (Propol™, from *Amorphophallus konjac*). The fifteen capsules taken daily provided 2.4 g of material. The subjects also recorded one day food intakes five times during the period of fiber supplementation, on days 5, 10, 15, 20 and 33. A second 72 hour fecal collection was begun on day 31.

Blood samples were taken via venipuncture to assess blood lipid levels on day 7 (initial period) and day 35 (final period). Subjects fasted for at least 12 hours prior to the blood draw. Blood was drawn at the University of Utah Health Sciences Center outpatient lab by qualified phlebotomists. Analyses of serum total, HDL and LDL cholesterol and serum triacylglycerol concentrations were done by a clinical laboratory by standard methods (ARUP Laboratories, Salt Lake City, Utah).

Feces were collected for analysis of fecal fat, neutral sterols and bile acids. Subjects were provided with airtight plastic containers to defecate in, and gloves were provided to aid in cleanliness. All fecal samples during the 72-hour fecal collection were collected separately in new containers for each defecation. Each subject's daily collection was kept cold on blue ice in an insulated carrier while subjects were away from their residences. Fecal samples were stored refrigerated at the subjects' residence or turned in daily to the nutrition laboratory at the University of Utah.

A percentage moisture analysis was conducted on each sample in each container. Two small (approximately 1 g) portions of feces from different ends of the sample were dried in a drying oven at 120°F for approximately three to four hours. After drying, the samples were removed from the oven and immediately weighed. The two subsamples from each stool sample were averaged and percent moisture calculated as the difference realized between the average wet and dry weights divided by the total wet weight, multiplied by 100.

Each subject's three-day fecal collections were weighed, diluted 1:4 (w/v) with distilled water and homogenized. One aliquot of the homogenate was shipped to the Department of Food Science and Nutrition at the University of Minnesota on dry ice and stored at -20°C until freeze-drying and analyzed

Table 1. Characteristics of study subjects: Combined, males and females^a

| | Combined (n = 21) | Males (n = 11) | Females (n = 10) |
|---|----------------------|-------------------|---------------------|
| Age (years) | 28.9 \pm 9.8 | 30.6 \pm 9.9 | 27.7 \pm 10.1 |
| Height (cm) | 172.9 \pm 9.0 | 179.9 \pm 5.4 | 168.2 \pm 7.9 |
| Weight (kg) | 84.4 \pm 17.7 | 88.9 \pm 17.7 | 81.3 \pm 17.9 |
| Body mass index (kg/m ²) | 28.0 \pm 4.6 | 27.4 \pm 4.7 | 28.5 \pm 4.7 |
| Body fat (%) | 37.2 \pm 10.7 | 27.9 \pm 10.5 | 43.8 \pm 3.7 |
| Lean muscle mass (kg) | 48.7 \pm 11.2 | 58.5 \pm 7.3 | 41.8 \pm 7.8 |
| Fat mass (kg) | 31.3 \pm 12.7 | 25.6 \pm 14.9 | 35.3 \pm 9.7 |

^a Mean \pm SD.

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for fecal fat and fecal bile acids. A second aliquot of the homogenate was sent to the Department of Nutritional Science and Dietetics and the University of Nebraska and stored at -20°C until analyzed for fecal neutral steroids.

Analytical Methods

Bile acids were extracted from dried feces using organic solvents [19] and total bile acids measured enzymatically essentially as described by Sheltawy and Lowowsky [20]. Fecal fat was determined gravimetrically after extraction with organic solvents. Fecal neutral steroids were analyzed as previously described [21].

Statistics

Results were analyzed by a paired t test, comparing initial to final period values. Differences due to gender were analyzed by one-way ANOVA. A probability of 0.05 or less was considered statistically significant.

RESULTS

Caloric, fat and dietary fiber intake (exclusive of the supplement) did not differ significantly between the initial and final periods (Table 2). Thus, subjects appeared to maintain their habitual diet during the study. The initial and final weights for all subjects were 84.82 kg and 84.81 kg, respectively, indicating no change in body weight during the course of the study.

There were no statistically significant differences between males and females for any blood lipid or fecal output parameter measured. Therefore, results are reported only for males and females combined.

Both serum total and LDL cholesterol concentrations were significantly lower at the final period of the experiment (day 35) than at the initial period (day 7) (Table 3). Total serum cholesterol was reduced by approximately 7% and LDL cholesterol by 10%. There was a slight but statistically significant reduction of approximately 4% in serum HDL cholesterol in the final period relative to the initial period. However, serum

Table 2. Intake during baseline and study periods of calories, fat and dietary fiber¹

| | Period | |
|------------------------------------|----------------|----------------|
| | Initial | Supplement |
| Calories (kcal/day) | 2050 \pm 200 | 1985 \pm 149 |
| Fat (g/day) | 71.9 \pm 8.6 | 70.3 \pm 6.5 |
| Dietary fiber (g/day) ² | 15.7 \pm 1.9 | 14.5 \pm 1.2 |

¹ Values are means \pm SEM. There were no statistically significant differences in intake between baseline and study periods for any parameter.

² Excludes dietary fiber from supplement.

Table 3. Serum lipid concentrations¹

| | Period | | <i>p</i> value ² |
|----------------------------|-----------------|-----------------|-----------------------------|
| | Initial | Final | |
| Total cholesterol (mmol/L) | 4.29 \pm 0.22 | 4.00 \pm 0.18 | 0.002 |
| HDL cholesterol (mmol/L) | 1.11 \pm 0.05 | 1.06 \pm 0.05 | 0.008 |
| LDL cholesterol (mmol/L) | 2.61 \pm 0.19 | 2.36 \pm 0.15 | 0.003 |
| Triacylglycerol (mmol/L) | 1.19 \pm 0.14 | 1.27 \pm 0.16 | 0.358 |

¹ Values are means \pm SEM, n = 21.

² Probability of difference between initial and final period.

triacylglycerol concentrations did not differ between the initial and final periods of the study.

Ingestion of the supplement resulted in a strong trend towards a greater fecal dry weight ($p = 0.052$) (Table 4). There were also tendencies towards greater daily fecal excretion of both bile acids ($p = 0.16$), neutral sterols ($p = 0.13$), and total steroid excretion ($p = 0.13$) in the final period compared to the initial period. In particular, there was a strong trend toward increased fecal excretion of cholesterol ($p = 0.064$), whereas excretion of other neutral sterols was essentially unchanged. The supplement did not significantly alter daily fecal fat excretion.

DISCUSSION

In this study, overweight subjects with initial serum cholesterol concentrations within the normal clinical range consumed 2.4 g/day of a supplement containing equal amounts of chitosan and glucomannan for twenty-eight days in a non-placebo-controlled study. Consumption of the supplement resulted in significant reductions of serum total, HDL and LDL cholesterol concentration, but no change in serum triacylglycerol concentration. These results are consistent with the hypocholesterolemic effect of chitosan and glucomannan reported in other human studies [7,8,14]. It is notable that in the present study

Table 4. Daily fecal excretion¹

| | Period | | <i>p</i> value ² |
|---|----------------|-----------------|-----------------------------|
| | Initial | Final | |
| Dry wt (g/day) | 64.5 \pm 6.8 | 79.7 \pm 10.7 | 0.052 |
| Fat (g/day) | 13.8 \pm 1.4 | 14.3 \pm 1.7 | 0.764 |
| Total bile acids ($\mu\text{mol/day}$) | 2569 \pm 299 | 3251 \pm 488 | 0.161 |
| Coprostan-3-ol ($\mu\text{mol/day}$) | 863 \pm 179 | 868 \pm 225 | 0.220 |
| Coprostan-3-one ($\mu\text{mol/day}$) | 111 \pm 63 | 207 \pm 93 | 0.495 |
| Dihydrocholesterol ($\mu\text{mol/day}$) | 312 \pm 93 | 182 \pm 82 | 0.455 |
| Cholesterol ($\mu\text{mol/day}$) | 922 \pm 174 | 1613 \pm 344 | 0.064 |
| Total neutral sterols ($\mu\text{mol/day}$) | 2448 \pm 337 | 3080 \pm 524 | 0.134 |
| Total steroids ($\mu\text{mol/day}$) | 5263 \pm 611 | 6551 \pm 958 | 0.126 |

¹ Values are means \pm SEM, n = 15–16.

² Probability of difference between initial and final period.

these reductions were obtained with lower amounts of material than has been used in other studies. The two previous studies in humans using glucomannan employed amounts of 3 to 3.9 g/day [7,8], whereas the previous chitosan feeding study gave 3 to 6 g/day [14]. There does appear, however, to be a lower limit to the efficacy of chitosan. Subjects consuming approximately 1.2 g/day of chitosan for four weeks found supplementation to be ineffective in lowering serum cholesterol [22], whereas an eight week supplementation with 2.4 g/day of chitosan led to only a marginally significant reduction in LDL cholesterol and no reduction in total cholesterol [23]. From the present study it cannot be determined which of the two materials, glucomannan or chitosan, is more potent in lowering cholesterol; however, our recent studies in rats suggest that the two materials are equipotent on a weight basis [16].

Relative to other soluble dietary fiber sources, the supplement used in this study appears to be a more potent hypocholesterolemic agent. Brown *et al.* [24], in a meta-analysis of the cholesterol lowering effect of various dietary fibers, reported net changes per g of soluble fiber of -0.029 mmol/L/g LDL cholesterol (95% CI: -0.035 , -0.022). In the present study, the change in LDL cholesterol was -0.104 mmol/L/g. Our study did not utilize a placebo group, unlike the studies cited in the meta-analysis of Brown *et al.* [24]. However, examination of changes in total serum cholesterol in 20 of the studies used in their analysis indicates an average change of only 0.16% in the groups given a placebo, a value not different from zero (data not shown). Thus, inclusion of a placebo group would not likely have resulted in a significant adjustment in the final cholesterol concentrations.

It is of interest that the relatively large reduction in serum total and LDL cholesterol was obtained using subjects that are likely relatively resistant to diet-induced changes in their serum cholesterol, that is, overweight subjects with initially normal serum cholesterol concentrations. Both these factors appear to independently make individuals resistant to the effects of cholesterol lowering diets. For example, Jansen *et al.* [25] found that moderately overweight men (BMI > 25 kg/m²) had no significant reductions in total or LDL cholesterol when fed either an NCEP-I or high MUFA diet, relative to a high saturated fat diet. In contrast, men of normal weight (BMI < 25 kg/m²) had significant cholesterol reductions with both diets. Similar results were found by Bronsgeest-Schoute *et al.* [26], who noted that normal weight men and women experienced a significant reduction in total serum cholesterol when eggs were removed from their diet, whereas obese individuals showed no change. In a large study of hypercholesterolemic subjects (>6000) treated with fibrates, the degree of reduction in LDL cholesterol was inversely and significantly related to BMI at baseline [27]. Two studies have demonstrated that in women fed low cholesterol, reduced fat diets, only lean women experience significant reductions in LDL cholesterol [28,29]. Recently, in a study comparing the cholesterol-lowering effect of margarine relative to butter, initial BMI was inversely related to

the degree of reduction of LDL cholesterol [30]. Initial serum cholesterol concentrations also appear to influence responsiveness. Individuals with initially normal cholesterol concentrations have been found less responsive to a cholesterol lowering diet than those with initially high cholesterol concentrations [31]. The finding that the chitosan + glucomannan supplement used in this study reduced serum cholesterol to a degree beyond that of most soluble dietary fibers, and did so in a population that was likely relatively unresponsive, suggests that this supplement is a potent cholesterol lowering agent.

Fecal excretion of bile acids and neutral sterols was determined to ascertain whether enhanced steroid excretion could be responsible for the hypocholesterolemic effect of the supplement. Excretion of bile acids and neutral sterols, measured after twenty-eight days of consumption of the supplement, tended to be increased, but the difference relative to the initial period did not achieve statistical significance ($p = 0.16$ and $p = 0.13$, respectively). This increase, however, is consistent with other studies. Gallaher *et al.* [16] found that an equal mixture of chitosan and glucomannan, fed at 7.5% of the diet, reduced cholesterol absorption and increased bile acid excretion in rats relative to a cellulose-based diet. Sugano *et al.* [32] noted an increase in cholesterol excretion in rats fed 5% chitosan, relative to cellulose. They further noted a change in the composition of the fecal sterols, with rats consuming chitosan excreting relatively more cholesterol and less coprostanol. In the present study, we found a strong trend for increased cholesterol excretion, with no change in excretion of other neutral sterols. Chitosan is known to have antimicrobial properties [33,34]. The change in the profile of fecal neutral sterols could therefore be due to a change in the type of colonic microflora or inhibition of their metabolic activities induced by the chitosan. This is also suggested by our previous study, in which we found a greater cecal pH in rats fed chitosan, with or without glucomannan, relative to a cellulose-based diet [16]. A higher cecal pH would be indicative of decreased activity of the microflora.

In this study no increase in fecal fat was detected after consumption of the chitosan + glucomannan supplement. This is in contrast to our previous study in rats, where consumption of the same supplement led to large increases in fecal fat excretion [16]. This increase could be attributed to the chitosan, as glucomannan alone did not increase fecal fat excretion. Further, others have reported that chitosan greatly reduces fat digestibility in rats [35,36] and chickens [37] when fed at 5% and 1.5% of the diet, respectively. The failure of the chitosan + glucomannan supplement to increase fat excretion in the present study may be due to the dose given, which was considerably less than that used in the animal studies. The reduction in serum cholesterol and increase in fecal cholesterol excretion in the absence of an increase in fecal fat excretion indicates that these two phenomena are not linked and, therefore, must act through different mechanisms. The trend toward increased bile acid excretion coupled with the demonstrated ability of chitosan to bind bile acids, both *in vitro* [38,39] and *ex vivo* [40],

Cholesterol Reduction by Chitosan + Glucomannan

would favor bile acid binding, with subsequent micelle disruption and decreased cholesterol solubilization, as the mechanism of cholesterol lowering in the present study. However, glucomannan is a highly viscous dietary fiber and increasing intestinal contents viscosity decreases cholesterol absorption [41]. It would thus appear that a higher dietary concentration of chitosan is required to decrease fat digestibility than to achieve cholesterol lowering.

CONCLUSIONS

The present study confirms the hypocholesterolemic effect of a chitosan + glucomannan supplement reported in rats [16] and extends the finding to humans. The trend toward increased steroid excretion with supplement consumption suggests this is the primary mechanism for the effect. The failure to increase fecal fat excretion and the lack of change in body weight after 28 days of consumption of the supplement suggests that, at the dose used, this supplement would likely not be effective in accelerating weight loss.

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Review

Konjac-Mannan and American Ginseng: Emerging Alternative Therapies for Type 2 Diabetes Mellitus

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Key words: type 2 diabetes mellitus, konjac-mannan, American ginseng

Despite significant achievements in treatment modalities and preventive measures, the prevalence of diabetes has risen exponentially in the last decade. Because of these limitations there is a continued need for new and more effective therapies. An increasing number of people are using dietary and herbal supplements, even though there is a general lack of evidence for their safety and efficacy. Consequently, science based medical and government regulators are calling for more randomized clinical studies to provide evidence of efficacy and safety. Our research group has selected two such promising and functionally complementary therapies for further investigation as potentially emerging alternative therapies for type 2 diabetes: Konjac-mannan (KJM) and American ginseng (AG). We have generated a mounting body of evidence to support the claim that rheologically-selected, highly-viscous KJM, and AG with a specific composition may be useful in improving diabetes control, reducing associated risk factors such as hyperlipidemia and hypertension, and ameliorating insulin resistance. KJM has a demonstrated ability to modulate the rate of absorption of nutrients from the small bowel, whereas AG has post-absorptive effects. Consequently, it appears that KJM and AG are acting through different, yet complementary, mechanisms: KJM by increasing insulin sensitivity and AG likely by enhancing insulin secretion. Before the therapeutic potential of KJM and AG as novel prandial agents for treatment of diabetes can be fully realized, further controlled trials with larger sample sizes and of longer duration are required. A determination of the active ingredients in AG, and the rheology-biology relationship of KJM are also warranted.

Key teaching points:

- With an epidemic of obesity and prolonged life expectancy, an increasing number of people are predicted to develop diabetes and die prematurely due to coronary heart disease (CHD).
- Despite substantial efforts in developing conventional medical therapies, the prevention and treatment of diabetes remain unsatisfactory, thus requiring the development of new treatment modalities.
- Substantial evidence is available to support the hypothesis that dietary fiber and herbs may be useful in the alleviation of diabetes, but the evidence is far from conclusive.
- Highly viscous dietary fiber, such as konjac-mannan (KJM) selected by rheological procedures, may ameliorate glycemic control and associated CHD risk factors in type 2 diabetes.
- Emerging evidence for the use of American ginseng (AG) in the control of diabetes and high blood pressure appears to be encouraging.
- Alternative therapies such as KJM and AG might be particularly effective in controlling the metabolic and physiologic manifestations of diabetes. They are acting through different, but complementary, mechanisms; KJM by increasing insulin sensitivity and AG likely by enhancing insulin secretion. Both insulin resistance and limited insulin secretion are important in the pathophysiology of diabetes.

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INTRODUCTION

Diabetes is a major health problem in North America reaching epidemic proportions. In the past decade, the United States has seen a dramatic 33% rise in diabetes coupled to increases in obesity and inappropriate lifestyle [1,2]. This increase in diabetes has occurred in spite of major inroads in understanding the pathophysiology and treatment of this insidious disease. Current therapies seem to be insufficient to prevent diabetic complications in type 2 diabetes, with a two- to fourfold likelihood for developing cardiovascular events [3]. Because of these limitations, there is a continuous need for the development of novel health promotion strategies and therapeutic modalities.

Conventional Diabetes Therapies

Type 2 diabetes is a dual chronic disorder that, in the majority of patients, arises from defects in both peripheral insulin action (insulin resistance) and insulin secretion (β -cell dysfunction), resulting in fasting and postprandial hyperglycemia [4]. The disease often co-exists with hypertension and dyslipidemia in the same individual, with devastating consequences to the cardiovascular system. Amelioration of any of these risk variables will markedly decrease the risk of cardiovascular disease (CVD) [5]. To achieve this goal, current treatment involves numerous therapies [6]: 3–4 medications for the regulation of blood glucose [7,8], 1–2 for lipids [9], and 4 to control blood pressure [10]. When hormone replacement therapy, smoking patches and aspirin [11] are added to the above, the number of required therapies increases even further. Despite this large armamentarium, the progressive deterioration of diabetes control is such that treatment is still insufficient, with the majority of type 2 diabetes patients eventually requiring insulin therapy to achieve targeted glycemic levels [12], and an estimated 75% dying of diabetes related complications from CVD [13].

Controversies

The value of current therapies is unequivocal, yet inadequate. While physicians advocate aggressive use of drugs to tighten glucose control and attenuate CVD risk factors, many patients are more inclined toward use of alternative therapies that include diet, food supplements and herbal medicine. When considering new recommendations for the treatment of diabetes [14], major health agencies and governmental authorities have largely ignored the role of diet, especially dietary fiber, and/or herbs with hypoglycemic characteristics, due to the paucity of data available. However, use of “popular” diets, nutritional supplements and botanicals is increasing among consumers. Only a minority of patients has begun to approach their physician about these types of therapies, with over 60% of patients failing to report usage of these products to their physician [15].

Alternative Diabetes Therapies

Insufficiency of current therapies for the treatment of diabetes, combined with both a lack of trust in conventional medical treatment and an inability of the economy to absorb the cost of pharmaceuticals, have created a growing public interest in dietary supplements and botanicals. The use of herbs has more than tripled over the last 10 years [15], and a whole new industry referred to as “nutraceuticals” has evolved. Similarly, consumption of dietary fibers such as wheat bran, psyllium and oats has increased significantly, due mainly to the conduct of research promoting their health properties and providing evidence to permit the approval of health claims by the FDA [16]. While therapeutic potential of dietary fibers in reducing serum cholesterol and maintenance of colonic health has been well recognized, their hypoglycemic effects are much less well established. In the case of herbs, the safety and efficacy of alternative therapies for the treatment of diabetes remain largely unknown. A vast abundance of knowledge is present and is based on open case studies, animal studies and in vitro experiments, false claims, paraherbalism and soft science. The medical literature and popular press are replete with anecdotal evidence both with respect to the efficacy and detrimental effects of herbs and novel fibers for the treatment of diabetes. The medical community and governmental agencies have responded with a call for more controlled clinical assessments of the efficacy and safety of nutritional supplements and botanicals [17].

Research Objectives

With a clear clinical need to investigate novel strategies, we endeavored to probe the efficacy and safety of two therapies as possible adjuncts and/or alternatives to conventional treatment for diabetes mellitus. The first therapy involves the use of a novel fiber extracted from the root of the Konjac plant (*Amorphophallus Konjac*, K. Koch). This is a highly viscous fiber that targets gut absorption phenomena and possibly increases insulin economy [18,19]. The second alternative therapy under development is American ginseng (AG) (*Panax quinquefolius* L.), a popular herbal medicine that may target post-absorptive physiological mechanisms and might have insulin secretagogue properties. These treatment modalities were selected by our laboratory for further investigation based upon our years of experience studying the relationship between the rheological properties and physiological effects of soluble fiber, and more recent work into the physiological effects of adaptogenic and hypoglycemic herbs.

KONJAC-MANNAN (KJM)

Background

For a thousand years in Asia, the tuber root of the konjac plant has been used as a foodstuff and remedy. KJM flour is

Novel Diabetes Therapies

obtained from grinding the konjac plant root and is traditionally made into a rubbery gel and eaten. Only recently has purified KJM flour been used as a stabilizer or gelling agent in variety of food applications, and as a food supplement in the production of health food products [20]. It has generally recognized as safe status (GRAS) in the U.S., and “novel” food status in Canada. Its main constituent is highly viscous glucomannan, a polysaccharide chain containing glucose and mannose in a molar ratio of 1:1.6 with β -1-4 linkages. When taken as a supplement, it has been shown to reduce serum lipids and systolic blood pressure [21], postprandial glycemia [22], and body weight [23].

Rheological Studies

Viscous fibers, as a result of their rheological (flow) properties, reduce postprandial increases in plasma glucose and insulin concentrations in normal and diabetic subjects [24–27]. There is now convincing evidence that the effectiveness of gel-forming fibers seems to relate mainly to their capacity to hydrate rapidly and thus increase the viscosity of digesta in the stomach and small intestine. These properties are dependent on fiber concentration, molecular weight, and also size-distribution of the fiber-gum particles [28].

KJM is very important in this regard for, when properly selected, it may have the highest viscosity amongst polysaccharides. We determined the viscosity of KJM (92% glucomannan), psyllium (95% purity), and xanthan using a Brookfield viscometer. When measured at 1% concentration, shear rates of 6, 12 and 30 sec^{-1} , using spindle setting F and 22 degrees centigrade, the apparent viscosity for KJM was 12×10^{-1} cp, which was twofold higher than xanthan 6.2×10^{-1} cp, and almost six times that of the psyllium 2.1×10^{-1} cp [26]. The flattening of postprandial glycemia, following 20 grams of glucose challenge and 3 grams of fiber added, closely mirrored the relative viscosity of the fibers, with KJM demonstrating the greatest effect followed by xanthan and psyllium (Fig. 1) [26]. In the selection of KJM material for our clinical studies we used glucomannan that had both a high level and a homogeneous distribution of molecular weight, in addition to a high presence of branching. The target molecular weight of KJM fiber typically used in our clinical experiment exceeds 100×10^{-4} , determined by light scattering measurements.

Furthermore, we exploited the ability of KJM to act synergistically with other polysaccharides, forming a gel with unique viscoelastic properties [20,26]. An interaction of the cellulosic backbone of other polysaccharides and the mannan backbone of KJM results in a considerable increase in viscosity of the mixed KJM polymer, and thus significant improvements in lipid and carbohydrate metabolism in humans (Proprietary Technology: Provisional U.S. Patent #60/208,090). We studied the effect on glycemic response of incorporating our high viscosity proprietary KJM-polysaccharide mix in a group of seven type 2 diabetic individuals with mean \pm SD age = 54 ± 7 , BMI = 27 ± 3 , and HbA1C = $7.6 \pm 1.2\%$. Three grams of

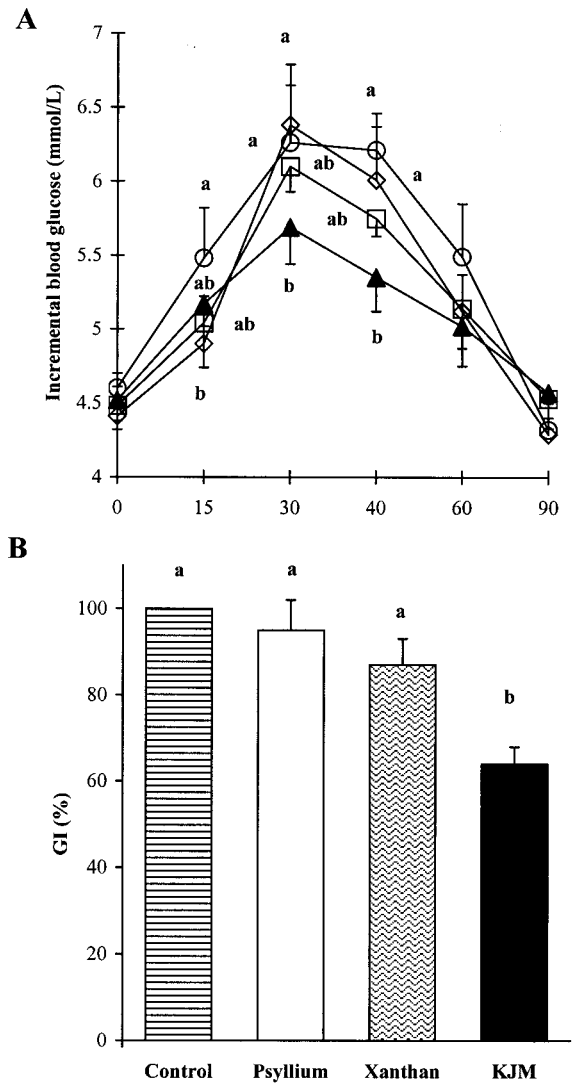


Fig. 1. Postprandial glycemic responses to a 20 g oral glucose challenge done alone (○) or following 3 g of psyllium (◇), xanthan (□), or konjac mannan (▲) (A) and the calculated glycemic indexes of three fibers relative to oral glucose alone (B). GI was expressed as the area under the curve (AUC) for each fiber divided by the AUC for oral glucose alone multiplied by 100. Points or bars with different letters are significantly different (repeated measures ANOVA adjusted for multiple pairwise comparisons with the Newman Keuls procedure, $p < 0.05$). Statistics expressed for GI differences were done for the differences in the absolute AUC values. Data are mean \pm SEM. Reference [26].

proprietary KJM mix were added to a 50 gram available carbohydrate portion of test biscuit and compared to matched control biscuits consumed on two different occasions. Blood glucose was measured over two hours following consumption of the test meals, with postprandial glycemia calculated as the incremental area under the glucose response curve expressed as a percent of mean of control biscuits. The glycemic index was 42 ± 5 [27]. This exceptional reduction, achieved with a relatively low, almost pharmacological concentration of KJM

mix, indicates that KJM offers great potential for use in a variety of functional foods for the management/treatment of diabetes.

From acute glucose challenge studies we moved to test the potential effect of this fiber as part of a well-controlled long-term study. The KJM polymer, which had been proven to be the most potent, was incorporated into the palatable test biscuits and matched with control biscuits that were substituted into a National Cholesterol Education Program (NCEP) step 2 diet in two long-term studies. Both types of biscuits were provided by Dicofarm S.p.a., Rome, Italy. The two studies conducted were both randomized, placebo-controlled, metabolic feeding (food delivered to the study participants) trials, with crossover phases during which participants maintained their habitual body weight and medications.

Study 1: KJM and Type 2 Diabetes

The first study was conducted in high-risk subjects with type 2 diabetes receiving concurrent pharmacological treatment for diabetes, hypertension, and dyslipidemia [29]. The KJM treatment was well tolerated with only transient effects on the colon as observed from increased flatulence and rare cases of mild diarrhea. The main findings included significant improvements in glycemic control, serum lipids and systolic blood pressure compared to placebo biscuits (Fig. 2). Because these improvements were seen beyond the NCEP Step 2 diet and medications alone, it was suggested that KJM might augment conventional dietary and pharmacological treatment safely in people with type 2 diabetes with associated CVD risk factors.

Study 2: KJM and Insulin Resistance Syndrome

Similar results were found in the second study in subjects selected for the full cluster of features of the insulin resistance syndrome: impaired glucose tolerance, dyslipidemia (low HDL, elevated triglycerides), central obesity, mild hypertension, and increased apolipoprotein (apo) B [30]. Reductions were observed in glycemia, blood lipids, and lipid ratio, and improvements were found in apolipoproteins compared with placebo (Fig. 3).

An improvement was also observed in whole body insulin sensitivity as calculated by equation of Matsuda *et al.* [31]. These measurements were calculated and compared using post-prandial glucose and insulin profiles taken after KJM or control mixed meal challenges consumed at the beginning and end of each 3 week study period [32]. It was concluded that, beyond a NCEP step 2 diet alone, KJM supplementation improved features of the insulin resistance syndrome including insulin action and LDL-apo B.

KJM Versus Other Therapies

These effects of KJM compare well against other therapies. Although KJM improved glycemic control only mildly, the

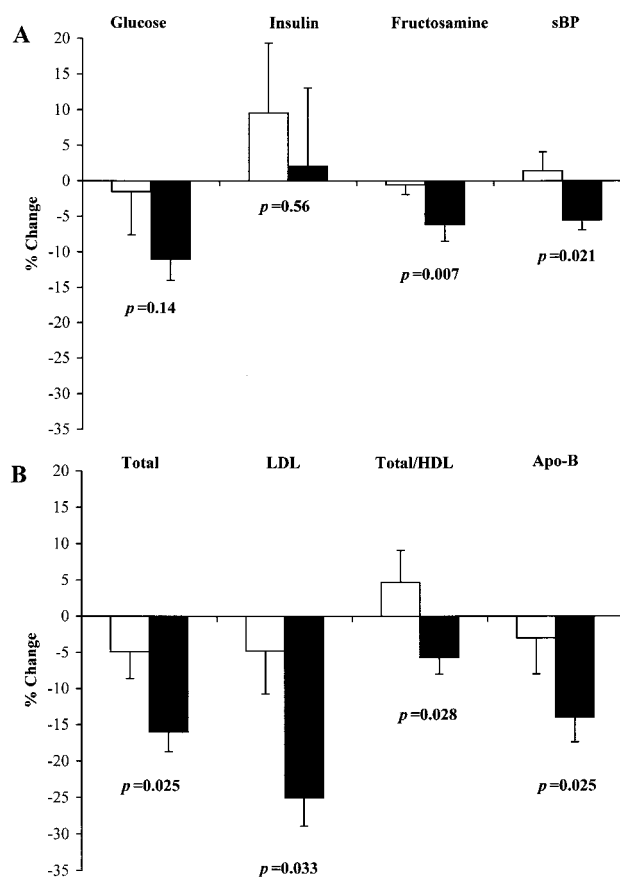


Fig. 2. Percent change in (A) measures of glycemic control (fasting plasma glucose, plasma insulin, and serum fructosamine) and systolic blood pressure and (B) measures of serum cholesterol (total, LDL, total:HDL ratio, and apolipoprotein B-100 [Apo-B]) after 3-weeks of supplementation with either konjac mannan (KJM, ■) or wheat bran (WB) control (□) biscuits in 11 subjects with type 2 diabetes mellitus, hyperlipidemia, and hypertension receiving a metabolically controlled National Cholesterol Education Program (NCEP) step 2 diet. *p*-values are for a GLM ANCOVA, adjusted for repeated measures, starting value, randomization sequence, diet, age, and gender. Data are mean \pm SEM. Reference [29].

reductions were comparable to those found with oral hypoglycemic agents such as alpha-glucosidase inhibitors (i.e. *Acarbose*) [33]. KJM also demonstrated very strong lipid lowering effects. It had an effect greater than that of other refined but “non-rheologically selected” KJM varieties [21,33,34]. Lipid lowering effects of KJM seen in our two studies were comparable to those of low dose statin drugs. Compared to lipid lowering effects of major gel-forming fibers such as psyllium, oat, or guar [35], KJM has three- to fivefold stronger effects (Fig. 4), expressed as a change in cholesterol per gram of soluble fiber consumed.

Proposed Mechanisms

The mechanism by which KJM improves metabolic control likely involves its rheological properties. It has been repeatedly

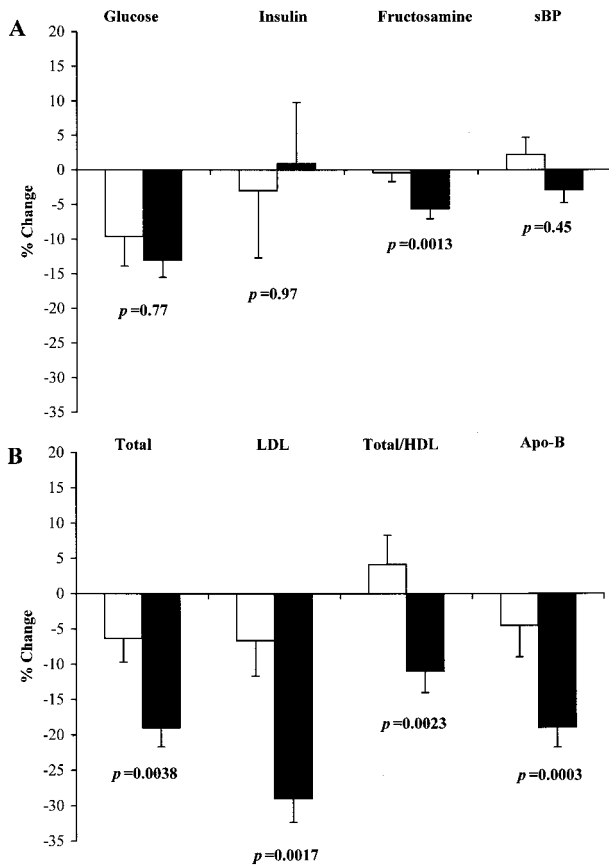


Fig. 3. Percent change in (A) measures of glycemic control (fasting plasma glucose, plasma insulin, and serum fructosamine) and systolic blood pressure and (B) measures of serum cholesterol (total, LDL, total:HDL ratio, and apolipoprotein B-100 [Apo-B]) after 3-weeks of supplementation with either konjac mannan (KJM, ■) or wheat bran (WB) control (□) biscuits in 11 subjects with the insulin resistance syndrome (IGT, dyslipidemia, central obesity, mild hypertension) receiving a metabolically controlled National Cholesterol Education Program (NCEP) step 2 diet. *p*-values are for GLM ANCOVA, adjusted for repeated measures, starting value, randomization sequence, diet, age, and gender. Data are mean \pm SEM. Reference [30].

shown that measures of viscosity and hardness of KJM and other soluble fibers are inversely correlated with postprandial glycemia [16,24–26]. It is hypothesized that the gel forming KJM, like other soluble fibers, increases the viscosity of the digesta slowing the rate of food absorption in the small intestine, thereby decreasing postprandial glucose and insulin surges. This in turn may result in a long-term improvement in peripheral insulin sensitivity. These effects may also explain KJM's cholesterol lowering properties. KJM also has been shown to inhibit cholesterol absorption in the jejunum [36] and bile acid absorption in the ileum [37], contributing to improvements in plasma LDL and apoB levels. However, these effects may also be mediated by decreased shunting of glucose and fatty acids through the liver and decreased VLDL synthesis.

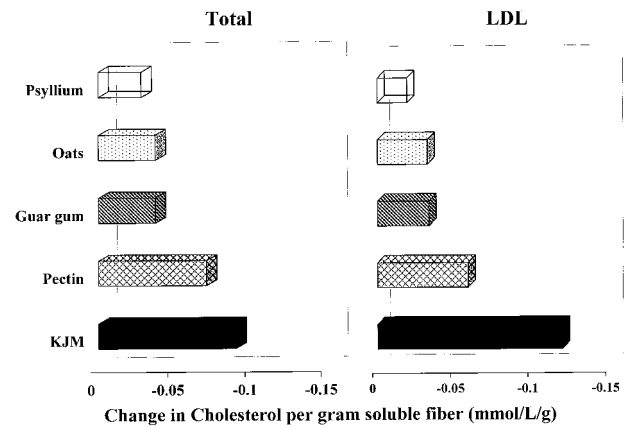


Fig. 4. Comparison of the total and LDL cholesterol lowering ability of the 4 main dietary soluble fibers (psyllium, oats, guar gum, and pectin) versus KJM. Values for the 4 fibers are taken from the meta-analysis of Brown *et al.* [35] and values for KJM represent the mean reduction in cholesterol taken from the two studies by Vuksan *et al.* [29,30]. Data are presented as change in cholesterol (mmol/L) per gram of soluble fiber.

Thus a series of major vascular and CVD risk factors are improved such as dysglycemia, dyslipidemia, and hypertension in people with type 2 diabetes, and glucose, lipid control and insulin resistance in people with the insulin resistance syndrome. If KJM is operating through this mechanism, then its higher viscosity compared to other soluble fibers may explain its higher lipid lowering capacity. Another physiological response, which may be a response to consumption of KJM fiber, might be blood pressure. The attenuated increased insulin sensitivity [38] might reduce blood pressure by influencing sodium absorption in the distal tubule, increasing sympathetic nervous system activity and decreasing peripheral vascular resistance [39]. Such an improvement in insulin sensitivity might have been mediated by sustained slowed absorption during the KJM treatment.

AMERICAN GINSENG (AG)

Background

For the last 3000 years of Chinese traditional medicine, the root of ginseng species has been used as a tonic with supposed curative, restorative and aphrodisiac properties. Trust in health properties of ginseng is best supported by consumption, which exceeds \$300 million in the USA alone [15]. However, most of the claims made for ginseng are anecdotal, or based on cellular and molecular research, as well as animal studies, with lack of demonstrated effect in humans for any of the claimed therapeutic properties [40]. There are fourteen species of ginseng, including AG (*Panax quinquefolius* L.), Asian (*Panax ginseng* C.A. Meyer), Japanese (*Panax Japonicus* CA Meyer), san-chi

(*Panax Notoginseng* [Burk.] F.H. Chen), and the non-panax species Siberian (*Eleutherococcus Senticosus*). Only recently have tests of their effects using rigorous scientific techniques begun in humans. From the little that has been learned from these tests, the WHO continues to endorse ginseng as an herb without known side-effects [41]. Other investigators, however, have cited side effects that include increased blood pressure, nausea, headache, insomnia, nervousness, and diarrhea [42]. Interaction with “blood thinning” agents is another non-confirmed possibility [43]. According to the American Herbal Products Association’s Botanical Safety Handbook, most of these adverse effects can be attributed to Asian ginseng, with no reported adverse effects for AG [44].

Growing evidence from in vitro and animal models indicates that ginseng might have a viable use in diabetes. North American [44–46], Chinese [46,47], Siberian, Sanchi, and Korean Red (steam treated *Panax ginseng* C.A. Meyer) [47] ginsengs have been shown to possess significant hypoglycemic action in rodent models. The same is true for some of their fractions: saponins (ginsenosides), peptidoglycans (panaxans for the panax species and eleutherans for *Eleutherococcus senticosus*), and the water (DPG-3-2) and methanol (EPG-3-2) extracted fractions of Chinese ginseng [48]. The sole human long-term study that investigated ginseng in diabetes also offers support. Supplementation for eight weeks with 200 mg/day of an unspecified type of ginseng extract resulted in an improvement in long-term glycemic control measured by hemoglobin

A1c [49]. This observation however was complicated by significant weight reduction.

Acute Studies

Using traditional Chinese medical teachings to establish starting points for ginseng dosing and timing applications, we evaluated the efficacy of AG on postprandial metabolism in a series of four acute studies (Table 1). AG was administered at doses from 1 to 9 grams and at times of administration from 0 to 120 minutes before an oral glucose challenge in people with and without type 2 diabetes [50–53]. Taken together, AG demonstrated a good acute safety profile. Neither group of subjects reported side effects, with the exception of insomnia reported by a diabetic patient after AG in our first study [50]. The data also suggested that escalation of dose and time of administration offered no added benefit in people with diabetes. Doses of 3, 6, and 9 grams and administration times of 120, 80, 40, and 0 minutes before a 25 gram oral glucose challenge were equally as efficacious at lowering postprandial blood glucose from 15–20% compared to placebo [51]. These reductions were achieved without an effect on glycemia before the oral glucose challenge. Effects were also observed beyond the oral hypoglycemic medications in which 6 of 9 subjects remained constant in the first acute study and 7 of the 10 remained constant in the second study. Taken together, the data suggested the

Table 1. Summary of Four Acute American Ginseng (AG) Studies in People with and without Type 2 Diabetes Mellitus

| Study | Sample | Treatments | OGTT | AUC Reductions | <i>p</i> value |
|----------------------|--|---|------|---|------------------------------------|
| Arch Intern Med [50] | 10 NGT (Age: 34 ± 7 years, BMI: 25.6 ± 3 kg/m ²) | 3 g AG vs. placebo @ 0 min | 25 g | – | <i>p</i> = NS |
| | | 3 g AG vs. placebo @ –40 min 3 g AG vs. placebo @ 0 min | 25 g | 18% 19% | <i>p</i> < 0.05 <i>p</i> < 0.05 |
| J Am Coll Nutr [53] | 10 NGT (Age: 41 ± 13 years, BMI: 24.8 ± 3.5 kg/m ²) | 3 g AG vs. placebo @ –40 min Dosing: 3, 6, or 9 g AG vs. placebo | 25 g | 22% 26.6, 29.3, 38.5% for 3, 6, and 9 g | <i>p</i> < 0.05 <i>p</i> < 0.05 |
| | | Timing: –40 min vs. –120 or –80 min | – | – | <i>p</i> = NS |
| Diabetes Care [51] | 10 T2DM (Age: 63 ± 2 years; BMI: 27.7 ± 1.5 kg/m ² ; HbA _{1c} : 7.3 ± 0.3%) | Dosing: 3, 6, or 9 g AG vs. placebo | 25 g | 19.7, 15.3, 15.9% for 3, 6, and 9 g | <i>p</i> < 0.05 |
| | | Timing: –120, –80, –40 or 0 min | – | – | <i>p</i> = NS |
| Am J Clin Nutr [52] | 12 NGT (Age: 42 ± 7 years, BMI: 24.1 ± 1.1 kg/m ²) | Dosing: 1, 2, or 3 g AG vs. placebo | 25 g | 14.4, 10.6, 9.1% for 1, 2, and 3 g | <i>p</i> < 0.05 |
| | | Timing: –40 min vs. –20, –10 or 0 min | – | 14.1, 15.0, 9.2% for –40 min | <i>p</i> < 0.05 |

NGT, T2DM, OGTT, and AUC denote normal glucose tolerance, type 2 diabetes mellitus, oral glucose tolerance test and area under the curve, respectively. AUC reductions are for the doses versus placebo and for –40 min versus the other times of administration. *p*-values are for comparisons between absolute values not the percent reductions, using repeated measures ANOVA adjusted for multiple pairwise comparisons with the Newman Keuls procedure. Data are mean ± SD.

possibility for an adjunctive role of AG in lowering postprandial glycemia without the fear of precipitated preprandial hypoglycemia. This last safety feature may confer a benefit of AG over the sulfonylurea drugs and hormones, which currently are common treatment in type 2 diabetes.

Similar findings were observed in people without diabetes, with one exception. Again there appeared to be no dose response. In one study, doses of 1, 2, and 3 grams of AG were equally efficacious at lowering postprandial glycemia compared to placebo [52], while in another study the same was true for doses of 3, 6, and 9 grams [53]. People without diabetes however appeared sensitive to the time of ginseng administration. Reductions were achieved when times of administration were 40, 80, and 120 minutes before the oral glucose challenge [54], but not closer to the challenge. Times of administration of 20, 10, or 0 minutes before the challenge did not result in postprandial blood glucose reductions [52]. Again, reductions were achieved without an effect on glycemia before the oral glucose challenge in all cases. It was concluded that the dose response for AG probably lies below 1 gram and that AG's blood glucose lowering effect appears time dependent in people without diabetes.

The AG used in all four acute studies originated from the same batch. The composition of this specific AG was characterized by a higher portion of protopanaxadiols relative to protopanaxatriols, with ratios of Rg₁/Re and Rb₂/Rc smaller than 1. Because it is difficult to establish that the ginsenoside profile of ginseng is responsible for its effects in the absence of similar studies using ginseng with varying ginsenoside composition, we were reluctant to draw such a conclusion.

Long-term Study

Armed with our dosing and timing response data, we conducted a long-term study in people with type 2 diabetes [54]. We hypothesized that the postprandial blood glucose lowering effects we observed following 1 gram of AG could be sustained safely in type 2 diabetic subjects. This hypothesis was tested using a double blind, placebo-controlled crossover trial. Twenty-four well-controlled (HbA_{1c} = 7.1 ± 0.1%) type 2 diabetic subjects (F = 11; M = 13; Age = 64 ± 7; BMI = 28 ± 5 kg/m²) were randomized to consume 1 gram of a standardized AG extract (CNT2000 produced by Chai-Na-Tai Corporation from Langley, BC, Canada) or placebo before each meal three times daily for eight weeks while following a Canadian Diabetes Association diet. Seventeen of the 24 subjects who were having their diabetes treated pharmacologically were also maintained constant on their medications throughout. After the first treatment phase, all subjects were washed out for at least 4 weeks and then crossed over to receive the alternate treatment. Plasma HbA_{1c}, glucose, and insulin were measured as primary endpoints. Because numerous articles, commentaries, and editorials have cautioned that ginseng may increase blood pressure, this safety parameter and others were measured as

secondary endpoints. Preliminary results from the study [54] demonstrated that consumption of AG extract modestly but significantly reduced HbA_{1c} compared with placebo. As well, fasting blood glucose significantly decreased (0.95 mmol/L; $p < 0.027$) with eight weeks of AG treatment, while insulin increased nonsignificantly compared to placebo. The unexpected finding was a significant decrease in blood pressure on AG, with an end difference between AG and placebo for systolic blood pressure of 5.6 ± 2.7 mmHg ($p = 0.001$, adjusted for age, gender and starting value). It is important to mention that 15 subjects were taking hypotensive medications. Liver and kidney functions were not affected by either treatment. We concluded that an AG extract added to the conventional treatment of diabetes significantly improved glycemic and blood pressure control beyond conventional treatment alone.

Proposed Mechanisms

Although the mechanisms underlying AG's hypoglycemic action are still elusive, animal data support several possibilities that may work alone or together. These include three possibilities: (1) modulation of glucose disposal [55–57], (2) insulin secretion [58,59], and (3) digestion [60]. The last of these possibilities seems unlikely. Whereas KJM might have modulated digestion through a gut effect, our blood glucose data from the acute studies would seem to suggest that AG does not. The reductions in glycemia were observed consistently in the final 60–90 minutes of the oral glucose challenges. If AG were able to slow digestion, then, as seen with soluble dietary fiber and *Acarbose*, we also would have expected lower values in the first 15–30 minutes, the absorptive phase of the blood glucose profile. Preliminary mechanistic trials that include acute insulin data on eight male and female nondiabetic subjects (age: 34 ± 3; BMI: 24.6 ± 0.8 kg/m²) offer stronger support for post-absorptive effects, such as an enhancement of insulin secretion [61]. We observed that 6 grams of AG administered 40 minutes before a 75 gram oral glucose test (75g-OGTT) increased postprandial insulin concentrations ~2-fold in the first 45 minutes following the challenge compared to the 75g-OGTT done alone previously (Fig. 5). As the first 60 minutes of a 75 gram oral glucose challenge is considered to be representative of the early phase of insulin secretion, these data suggest that AG may be able to increase this phase, the loss of which is a primary defect in type 2 diabetes. Also offering support to an insulin enhancing effect of AG is the nearly significant ($p = 0.084$) ~25% increase that was observed in fasting insulin after eight weeks of AG supplementation in the long-term study.

Involvement of ginsenosides may play an important mechanistic role [56–60]. The 20 (S)-protopanaxadiol ginsenoside Rb₁, measured in our studies, was found to increase glucose uptake into sheep erythrocytes in a dose dependent manner. Another protopanaxadiol we measured, Rb₂, was also shown to

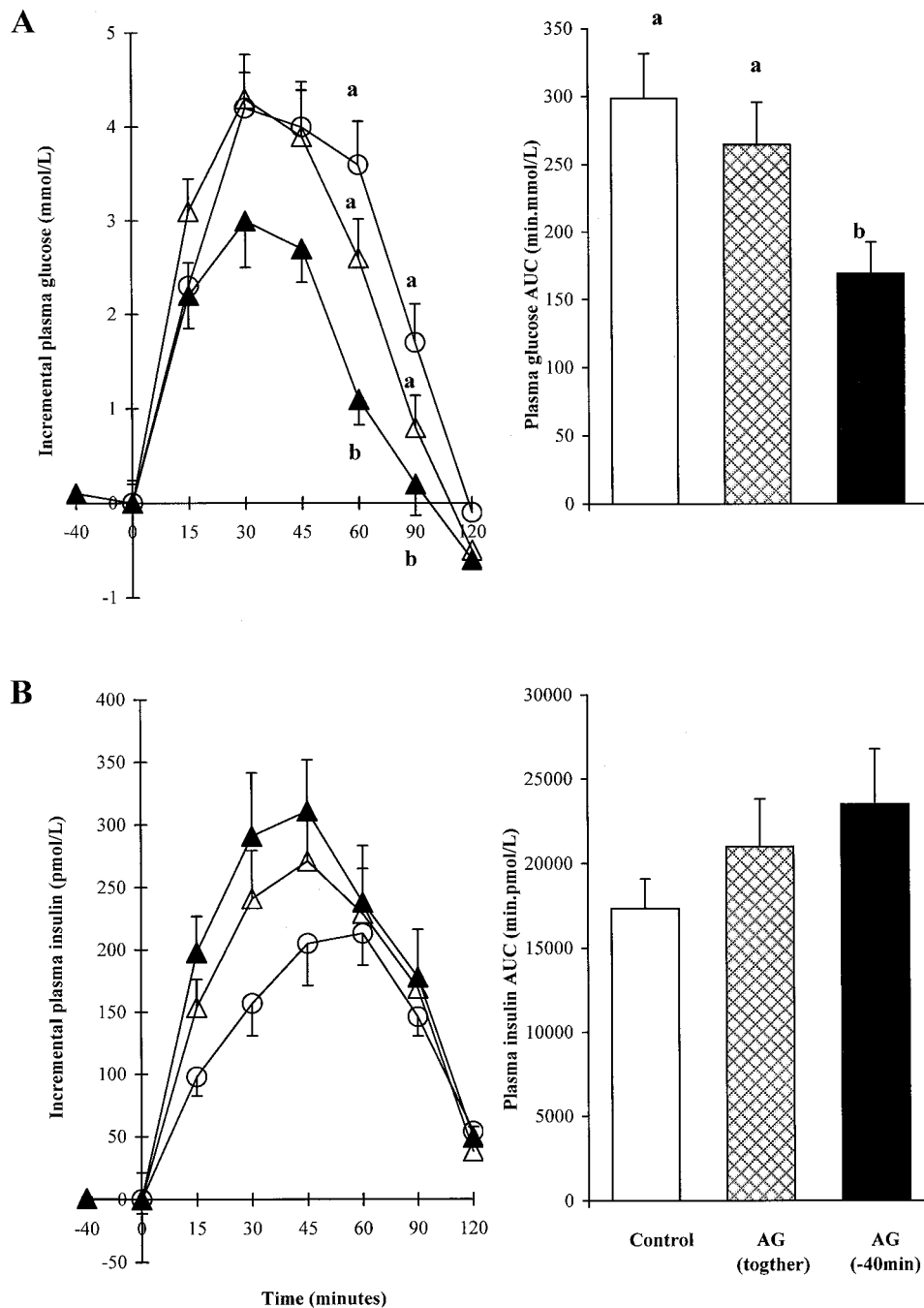


Fig. 5. Incremental change and area under the curve (AUC) in plasma (A) glucose and (B) insulin following America ginseng (AG) taken 40 minutes before (\blacktriangle) or together (\triangle) with a 75 g oral glucose tolerance test (75 g-OGTT), or a 75 g-OGTT done alone (\circ) in 8 nondiabetic subjects. Points or bars with different letters are significantly different (repeated measures ANOVA adjusted for multiple pairwise comparisons with the Newman Keuls procedure, $p < 0.05$). Data are mean \pm SEM. Reference [61].

increase the activity of the rate limiting glycolytic enzymes, glucokinase and phosphofructokinase, while decreasing the activity of the rate limiting gluconeogenic enzyme glucose-6-phosphatase in rat liver preparations [56–58]. Taken together, it is tempting to suggest that these ginsenosides present in our AG

might be responsible for the observed reductions in postprandial glycemia and improvements in glycemic control over the eight weeks of our study. However, evidence is insufficient to make this extrapolation. Neither studies that investigated the effect of isolated ginsenosides on carbohydrate metabolism in humans, nor

direct investigations of the hypoglycemic activities of the more than 20 other ginsenosides can be found in the literature.

CONCLUSIONS

Our preliminary data indicate that both KJM and AG may have therapeutic promise in the treatment of diabetes. These two alternative therapies provided benefits to a number of physiological risk variables that worked independently of the diet and in addition to concurrent medications. Overall, KJM and AG both target meal related metabolic excursions safely, with mechanisms that appear to be different but complementary to each other; KJM by decreasing nutrient absorption rates and increasing insulin sensitivity and AG by enhancing insulin secretion.

IMPLICATIONS

Although our data suggest that the concurrent use of KJM or AG with other oral agents to treat diabetes, hypertension, and dyslipidemia might improve treatment outcomes safely, an interaction with other therapies remains an unconfirmed possibility. Since both KJM and AG exert their effects beyond conventional treatment, there is a suggestion that adverse outcomes may be precipitated. These might include undesired postprandial hypoglycemia, although this has not been observed in any of our controlled studies. Whether these therapies are helpful in the long run is not known. Practitioners should therefore make themselves aware of any alternative treatments used by their patients since the patients may choose to use KJM and AG as a preemptive measure to drug therapy or adjunct to conventional drug treatment. However, before physicians can prescribe these as “mainstream alternative therapies” much more research is needed. The mechanisms for each and their long-term effects are areas requiring more study. Other avenues of investigation include exploring ways to enhance the metabolic effects of KJM through modulation of its rheological characteristics, development of new products, and initiation of longer-term studies. Confirming the unexpected blood pressure lowering effect of AG and the mechanisms involved is of extreme interest and gives credence to the overall health benefits of ginseng, which is sometimes referred to as an adaptogen or “normalizer” of multiple physiological functions [62]. Another study of great potential is a “head-to-head” comparison of various ginsengs to determine whether the effects observed with AG hold for other varieties and species, while shedding light on potentially interesting chemical composition differences as they relate to physiological effects. Finally, the isolation and optimization of active components from AG specific to various physiologic variables will provide much interesting work for years to come.

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Original Research

Konjac Supplement Alleviated Hypercholesterolemia and Hyperglycemia in Type 2 Diabetic Subjects—A Randomized Double-Blind Trial

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Key words: konjac glucomannan, diabetes, hypercholesterolemia, hyperglycemia, bile acid

Objectives: The present study was designed to evaluate effects of konjac glucomannan (KGM) supplement (3.6 g/day) for 28 days on blood lipid and glucose levels in hyperlipidemic type 2 diabetic patients and the possible mechanism for the reductions in blood lipid levels.

Methods: Twenty-two diabetic subjects (age 64.2 ± 8.4 years, BMI 25.5 ± 3.2 kg/m²) with elevated blood cholesterol levels (fasting glucose between 6.7–14.4 mmol/L), but currently not taking lipid-lowering medication, were recruited to participate in a two 28-day period, randomized, double-blind, crossover clinical trial. Fasting blood samples drawn on the initial and final days of each period were determined for plasma lipids and glucose levels. Feces collected at the end of each experimental period were analyzed for neutral sterol and bile acid contents.

Results: Compared with placebo, KGM effectively reduced plasma cholesterol (11.1%, $p = 0.0001$, adjusted $\alpha = 0.006$), LDL-cholesterol (20.7%, $p = 0.0004$, adjusted $\alpha = 0.006$), total/HDL cholesterol ratio (15.6%, $p = 0.0005$, adjusted $\alpha = 0.007$), ApoB (12.9%, $p = 0.0001$, adjusted $\alpha = 0.006$) and fasting glucose (23.2%, $p = 0.002$, adjusted $\alpha = 0.008$). Plasma triglyceride, HDL-cholesterol, LDL/HDL cholesterol, postprandial glucose and body weight were not significant after adjustment by the Bonferroni-Hochberg procedure. Fecal neutral sterol and bile acid concentrations were increased by 18.0% ($p = 0.004$) and 75.4% ($p < 0.001$), respectively, with KGM supplement.

Conclusions: The KGM supplement improved blood lipid levels by enhancing fecal excretion of neutral sterol and bile acid and alleviated the elevated glucose levels in diabetic subjects. KGM could be an adjunct for the treatment of hyperlipidemic diabetic subjects.

INTRODUCTION

Elevated blood cholesterol levels are a major risk factor for cardiovascular disease [1], a leading cause of worldwide morbidity and mortality [2–3]. Cardiovascular disease also is a long-term complication of diabetes mellitus, a disease of rapidly increasing incidence in some populations [3]. The American Diabetes Association recognized the interrelatedness of diabetes and cardiovascular disease in its most recent nutrition recommendations, in which goals included optimal serum lipid

levels, as well as maintenance of near-normal blood glucose levels [4]. Sources of soluble dietary fiber that are viscous lower blood cholesterol levels [5] and modulate blood glucose concentrations [6]. Thus, these food supplements have the potential to reduce cardiovascular disease and control hyperglycemia in individuals with diabetes.

Konjac, *Amorphophallus Konjac* C. koch, a tuber of Oriental origin, is rich in glucomannan polysaccharide [7]. The viscous, water-soluble glucomannan is extracted from the tubers with water, dried and made into rubbery jelly, noodles and

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other food products. Glucomannan has been used for over 1000 years in Japan and now is popular in Taiwan. Konjac glucomannan (KGM) lessened the rise in blood glucose levels when given as part of a test meal in healthy adults and in diabetics [8]. In addition, a KGM supplement has been reported to lower blood cholesterol levels in healthy and hypercholesterolemic adults [9,10]. Two recent studies further evaluated both the hypocholesterolemic and hypoglycemic benefits of KGM-rich meals in individuals with diabetes or insulin-resistant syndrome [11,12]. Daily ingestion for three weeks of a KGM-rich diet (0.7 g KGM/100 kcal intake) effectively improved hypercholesterolemia, fasting fructosamine levels in high-risk type 2 diabetics [11]. In another study by the same research group, KGM-rich diet (0.5 g/100 kcal intake) again lowered blood cholesterol and fasting fructosamine levels in prediabetic, insulin-resistant patients [12].

Our primary objective was to determine the roles of KGM supplement in hypercholesterolemic, type 2 diabetic patients who were not taking lipid-lowering medication. The daily dose of KGM used in most of previous studies was 8–13 g/day [8,11–12], nearly 1/3 of the recommended fiber intake [4]. This study was aimed to explore the effectiveness of low dose of KGM supplement (3.6 g KGM per day) in type 2 diabetic subjects. Furthermore, the possible mechanism by which the KGM supplement exerted hypocholesterolemic effects was investigated by determining bile acid excretion.

SUBJECTS AND METHODS

Experimental design

This randomized, double blind, placebo-controlled, crossover study consisted of a two-month run-in period and two 28-day experimental periods.

Hypercholesterolemic diabetic subjects who potentially met our criteria had been advised to keep dietary habits according to the National Cholesterol Education Program (NCEP) from the run-in period throughout the study [13]. The run-in period was to screen patients who stayed hypercholesterolemic even with an NCEP dietary regimen and to allow patients to adapt to the dietary pattern. Following the run-in period, twenty-two subjects recruited into the study were randomly assigned to consume either placebo (12 subjects) or KGM (10 subjects) capsules for 28 days and, without a washout period, were immediately switched to the other treatment for another 28 days. Gelatin capsules each contained 0.5 g konjac powder (catalogue number T18, <60 mesh; Fukar International Company, Ltd., Taipei, Taiwan) or 0.5 g food-grade corn starch (Chungman Trading Co., Ltd., Korea) were taken three times daily, one half hour before each meal with a glass of water, as done by Arvill *et al.* [9]. The dose of glucomannan fiber increased progressively from 1.2 (for 3 days), 2.6 (for 3 days), to 3.6 g per day for 22 days.

The composition of the konjac powder was (on dry weight basis) 80% glucomannan, 8.0% starch, 3.4% protein, 3.8% lipid, 1.7% ash and 3.1% moisture, as analyzed using AOAC method. Starch was quantified using amylase method [14]. Protein was determined by Kjeldahl analysis for nitrogen and conversion to protein using 6.25 [15]. Lipid was extracted with ether using a Soxhlet apparatus [16]. Ash was determined by heating at 550°C overnight [17]. The moisture was determined by vacuum-drying at 110°C overnight [17]. The glucomannan content was calculated by subtracting the contents of moisture, starch, protein, fat and ash.

Blood was drawn and body weight was measured for each subject on days 0, 28 and 56 of the study. In the morning of blood drawing, a test meal (376 kcal, 48 g available carbohydrate, 15 g protein and ~14 g lipid) consisting of white toast (President, Tainan, Taiwan), spreading margarine (Meiji Milk, Tokyo, Japan) and imitated pork shred (Kwang Da Shaun Food Co., Taiwan) was given to subjects after the fasting blood sample had been obtained. The contribution of carbohydrate, protein and lipid to the energy of this test meal was 51.3%, 13.8% and 32.8%, respectively. Two-hour postprandial blood samples were then obtained for glucose analysis. Subjects were asked to record the symptoms of intestinal discomfort every day. Subjects were asked to maintain constant dietary pattern, exercise and lifestyle during the investigation. Compliance of subjects was monitored by phone-interview every week, two-day diet record, exercise record and returned capsules at the end of each study period. The study protocol was approved by the Chung Shan Medical University Teaching Hospital, and all subjects gave their written, informed consent.

Subjects

Outpatients aged above 45 years admitted in the Department of Medicine (Taichung Veteran's General Hospital, Taichung, Taiwan) were screened for the following criteria: type 2 diabetes mellitus, receiving oral hypoglycemic medicine for at least one year, fasting glucose concentration ≤ 260 mg/dL (14.4 mmol/L), total plasma cholesterol concentration of ≥ 200 mg/dL (5.17 mmol/L) without taking lipid lowering medication, willingness to comply the treatments, and absence of heart, hepatic and renal failure. Twenty-two subjects finished the study with no dropouts. The participants (10 male, 12 female) were ambulatory, with plasma cholesterol (mean \pm SD, range) of 6.2 ± 0.7 , 5.2–7.5 mmol/L; triglyceride of 2.0 ± 0.9 , 0.6–4.0 mmol/L; fasting glucose of 9.1 ± 1.9 , 6.7–14.4 mmol/L; age of 64.2 ± 8.3 , 52–77; BMI (kg/m^2) of 25.5 ± 3.2 , 21.0–32.6 on day 0 of the study. The oral hypoglycemic agents administered included glibenclamide (5 subjects), metformin (2 subjects), glipizide (1 subject), or combination of glipizide and metformin (3 subjects), of glibenclamide and metformin (6 subjects), of glipizide and metformin (3 subjects), of glibenclamide and insulin (1 subject), and of glibenclamide, metformin and acorbose (1 subject). The dose of medication

stayed constant during the investigation. None of the participants took lipid-lowering medication during the study.

Dietary Assessment

Subjects were advised for NCEP regimen and closely monitored by the investigators throughout the entire study. Subjects were asked to keep diary records for only two days in each period because five out of 22 subjects were illiterate. The energy, macronutrient, fatty acids profile and dietary fiber consumed as the average of two days was calculated for each period based on local food tables [18].

Blood Analysis

Blood samples (10 mL) were collected into tubes containing disodium EDTA on the days 0, 28 and 56. Plasma samples were collected after centrifugation at 3000 rpm for 10 minutes and were then stored in -70°C until analysis at the end of the study. Plasma total cholesterol, triglyceride and glucose concentrations were measured enzymatically on the Express Clinical Chemistry Analyzer (Ciba Corning Diagnostics Corp., Oberlin, OH) with respective calibrator and biological standards. The measurement errors were consistently within limits set by the CDC standardization program. High-density-lipoprotein (HDL) cholesterol was measured after heparin-manganese precipitation of plasma [19]. Low-density-lipoprotein (LDL) cholesterol was calculated from the formula of Friedewald *et al.* [20]. Apolipoprotein B (apo B) concentration in plasma was determined with immunoassay (Randox Laboratories, San Francisco, CA). Every analysis was conducted in duplicate.

Analysis of Fecal Neutral Sterol and Bile Acid

Subjects produced a stool at their regular clinical appointment on days 28 and 56. Two aliquots of 15 g each were collected with a spatula from the middle of the stool. Fecal samples were dried in a vacuum oven at 70°C overnight and then ground. Neutral steroids and bile acids were extracted from feces with 20 volume of mixture of chloroform and methanol (2:1 v/v) at 60°C for 2 hours. Neutral steroids were quantified using Libermann-Burchard reagent (acetic anhydride:sulfuric acid:acetic acid = 20:1:10) [21]. Bile acids were quantified using the reaction catalyzed by 3 α -hydroxysteroid dehydrogenase (EC1.1.1.50; Randox Laboratories, San Francisco, CA) [22]. The known amounts of cholesterol/chenodeoxycholic acid were added into a fecal sample, which was extracted with identical way of its blank counterpart that was not added with cholesterol/chenodeoxycholic acid.

The recovery was determined as the following equation:

Recovery (%) of cholesterol

$$= \frac{\text{Cholesterol}_{\text{the added sample}} - \text{Cholesterol}_{\text{blank}}}{\text{Cholesterol}_{\text{added}}} \times 100\%$$

The extraction efficiencies for neutral cholesterol and bile acid were 98% and 85%, respectively.

Statistical Analyses

Results were expressed as means \pm SD and analyzed using by the Statistical Analysis System (SAS) [23]. The carryover effect of treatment was not observed since $p > 0.1$ as analyzed by 2×2 crossover method [24]. The within-treatment differences in plasma lipids, ratio of apolipoprotein cholesterol, apolipoprotein B, fasting glucose, postprandial glucose and body weight between the beginning (week 0) and end (week 4) of each treatment (placebo and KGM) were expressed as % change of the final (day 28 or 56) to initial (day 0 or 28) measurements and analyzed by two-tailed Student's *t* test for paired data (proc univariate). The between-treatment effects (KGM vs. placebo) for each parameter were analyzed by the general linear model procedure (proc glm). Control of individual variation from the repeat measures aspect of the design was addressed by incorporating the random subject effect as well as the diet, gender and phase effects into the model. Adjustment for multiple comparisons was made by the Bonferroni-Hochberg procedure for the end points of metabolic controls [25]. *p* values for each end point were ordered sequentially and contrasted with the corresponding adjusted α -value. Null hypotheses were rejected only if the *p* values were less than their corresponding α -value [25]. Dietary intakes as the means of two days during the run-in, placebo and KGM periods were analyzed with one-way ANOVA, followed by Dunnett's test using run-in period for the comparison, respectively. The fecal neutral steroid and bile acid excretions between treatments were analyzed using Student's paired *t* test. $p < 0.05$ indicates significant difference for Student's paired *t* test, one-way ANOVA and Dunnett's test.

RESULTS

All participants followed the experimental protocol with good compliance. Returned capsules from subjects indicated that subjects consumed 95% of KGM prescribed. One subject developed minor gastric discomfort in the beginning and adapted well to the supplement on the fifth day of the KGM period.

Energy and Nutrient Intakes

The daily energy and nutrient intakes during the run-in, placebo and KGM periods is shown in Table 1. The average energy consumed during each period was similar, around 1500 kcal/day. The proportion of energy contributed by fat, protein and carbohydrate were similar between study periods. Protein and carbohydrate contributed to $\sim 17\%$ and 53% to 55% of the total energy ingested. Dietary fat, fatty acid profile and cholesterol intakes complied with the NCEP step 1 diet guideline.

Table 1. Daily Energy and Nutrient Intakes during the Study¹

| Energy and Nutrients | Run-in | Placebo | Konjac Glucomannan |
|------------------------------------|--------------|--------------|--------------------|
| Energy (Kcal/day) | 1516 ± 191 | 1495 ± 149 | 1511 ± 172 |
| Total Fat (% energy) | 28.2 ± 2.8 | 27.2 ± 2.9 | 27.0 ± 3.8 |
| Saturated Fat (% energy) | 6.6 ± 2.3 | 6.7 ± 2.4 | 6.6 ± 2.6 |
| Monounsaturated Fat (% energy) | 9.0 ± 2.7 | 8.5 ± 2.7 | 8.5 ± 2.5 |
| Polyunsaturated Fat (% energy) | 10.2 ± 3.0 | 8.9 ± 1.9 | 9.1 ± 2.2 |
| Protein (% energy) | 16.8 ± 2.9 | 17.2 ± 3.0 | 17.2 ± 3.4 |
| Carbohydrate (% energy) | 52.9 ± 4.9 | 54.2 ± 4.6 | 55.1 ± 4.7 |
| Cholesterol (mg/day) | 252.4 ± 26.3 | 210.2 ± 29.3 | 228.3 ± 25.7 |
| Dietary Fiber ² (g/day) | 11.4 ± 4.2 | 12.5 ± 5.0 | 11.7 ± 5.6 |

¹ Data based on 2-day food records during run-in and each experimental period were expressed as means ± SD. No significant differences were found between groups as analyzed using 1-way ANOVA followed by Dunnett's test using run-in period for comparison.

² Dietary fiber ingested from KGM was not included in the calculation.

Total fat and saturated fatty acid contributed to less than 30% and less than 10% of total energy intake, respectively. In fact, saturated, monounsaturated and polyunsaturated fatty acids each contributed <7%, ~9% and 9% to 10% of total energy, respectively, during each period. Daily consumption of cholesterol did not exceed 300 mg/day for all three periods. Dietary fiber consumed from the meal excluding the KGM fiber was in the range of 11–13 g/day (7.5–8.4 g/Mcal).

Plasma Lipids, Apolipoprotein, Glycemia and Body Weight

The changes of plasma lipid, apolipoprotein, glucose and body weight during KGM and placebo periods are shown in Table 2. Blood lipids except triglyceride were improved during KGM period. Concentrations of total cholesterol and LDL-cholesterol fell significantly by 8.2% ($p < 0.001$) and 10.7% ($p = 0.023$) during KGM treatment compared with 2.9% ($p = 0.27$) and 9.9% ($p = 0.11$) during the control treatment. The between-treatment differences were significant, $-11.1%$ ($p = 0.0001$, adjusted $\alpha = 0.006$) for total cholesterol and $-20.7%$

($p = 0.0004$, adjusted $\alpha = 0.006$) for LDL-cholesterol. HDL cholesterol concentration was elevated by 4.5% ($p = 0.034$) during KGM treatment compared with $-0.5%$ ($p = 0.49$) during the placebo period. However, the difference in HDL cholesterol levels between treatments was insignificant ($p = 0.392$, adjusted $\alpha = 0.05$). The total/HDL-cholesterol and LDL/HDL-cholesterol ratios were significantly reduced by 11.6% ($p < 0.001$) and 13.6% ($p = 0.01$), respectively, during KGM period. While compared with the effect during the control period, the changes in total/HDL-cholesterol was significant, $-15.6%$ ($p = 0.0005$, adjusted $\alpha = 0.007$). However, the difference between treatments was insignificant for LDL/HDL cholesterol ($p = 0.011$, adjusted $\alpha = 0.010$). The apo B concentration was significantly reduced during the KGM treatment by 9% ($p = 0.134$). The between-treatment difference for apo B level was observed ($-12.9%$, $p = 0.001$, adjusted $\alpha = 0.006$).

Fasting blood glucose concentration in the KGM period was significantly decreased by 12.3% ($p = 0.002$) compared to a 10.2% ($p = 0.017$) increase in the placebo period (Table 2). The between treatment difference was observed ($p = 0.002$,

Table 2. Changes in End Point of Metabolic Control during and between the Konjac Glucomannan and Placebo Study Periods¹

| | Konjac Glucomannan | | | Placebo | | | Between-Treatments | | |
|-----------------------|--------------------|------------|---------------|------------|------------|--------------|--------------------|---------|----------|
| | Week 0 | Week 4 | Change (%) | Week 0 | Week 4 | Change (%) | Change (%) | p | α |
| Triglyceride (mmol/L) | 1.8 ± 0.6 | 1.6 ± 0.5 | -5.9 ± 21.2 | 2.0 ± 0.8 | 1.8 ± 0.7 | -2.5 ± 23.6 | -3.8 ± 27.6 | 0.078 | 0.017 |
| Cholesterol (mmol/L) | | | | | | | | | |
| Total | 6.1 ± 0.8 | 5.6 ± 0.8 | -8.2 ± 7.8* | 6.0 ± 0.8 | 6.2 ± 0.8 | 2.9 ± 10.1 | -11.1 ± 14.7 | 0.0001* | 0.006 |
| LDL | 4.0 ± 0.9 | 3.5 ± 0.8 | -10.7 ± 23.3* | 3.9 ± 0.8 | 4.2 ± 0.9 | 9.9 ± 24.7 | -20.7 ± 38.2 | 0.0004* | 0.006 |
| HDL | 1.2 ± 0.2 | 1.2 ± 0.2 | 4.5 ± 9.3* | 1.2 ± 0.2 | 1.2 ± 0.2 | -0.5 ± 7.7 | 5.0 ± 14.4 | 0.392 | 0.05 |
| Total:HDL | 5.3 ± 0.8 | 4.7 ± 0.9 | -11.6 ± 10.2* | 5.2 ± 1.0 | 5.3 ± 0.8 | 3.9 ± 13.0 | -15.6 ± 18.9 | 0.0005* | 0.007 |
| LDL:HDL | 3.5 ± 0.8 | 3.0 ± 0.8 | -13.6 ± 26.1* | 3.4 ± 0.8 | 3.5 ± 0.8 | 6.4 ± 23.3 | -20.1 ± 35.3 | 0.011 | 0.01 |
| Apo B (g/L) | 1.5 ± 0.3 | 1.4 ± 0.5 | -9.0 ± 17.8* | 1.4 ± 0.5 | 1.5 ± 0.4 | 3.8 ± 18.0 | -12.9 ± 28.5 | 0.0001* | 0.006 |
| Glucose (mmol/L) | | | | | | | | | |
| Fasting | 9.4 ± 2.3 | 8.0 ± 1.8 | -12.3 ± 15.2* | 8.7 ± 1.8 | 9.6 ± 2.4 | 10.2 ± 18.7* | -23.2 ± 28.65 | 0.002* | 0.008 |
| 2-Hour Postprandial | 13.8 ± 4.6 | 11.5 ± 3.2 | -12.2 ± 25.5* | 13.0 ± 3.7 | 14.3 ± 4.3 | 12.6 ± 32.0 | -27.8 ± 49.8 | 0.014 | 0.013 |
| Body Weight (kg) | 64.3 ± 9.0 | 63.8 ± 8.8 | -0.6 ± 1.4 | 64.0 ± 8.8 | 64.2 ± 8.7 | 0.2 ± 1.7 | -0.7 ± 2.5 | 0.115 | 0.025 |

¹ $\chi \pm$ SD, $n = 21$. Between-treatment differences were assessed by analysis of covariance (PROC GLM). Comparison-wise α -level was adjusted for multiple end point comparisons with the Bonferroni-Hochberg procedure for end points of metabolic control separately.

* Significant after adjustment of α -level by the Bonferroni-Hochberg procedure. Null hypothesis were rejected if the p values were less than their corresponding α -value. p values for during-treatment changes were assessed by paired Student's t test.

Table 3. Fecal Neutral Sterol and Bile Acid Contents of Subjects in this Study¹

| | Placebo | KGM ² |
|---------------------------------|---------------|------------------|
| Neutral Sterol (mg/g dry feces) | 44.33 ± 12.55 | 52.31 ± 14.76* |
| Bile Acid (mg/g dry feces) | 2.57 ± 1.30 | 4.16 ± 1.98* |

¹ $\chi \pm$ SD, n = 20.² KGM, konjac glucomannan.* Significantly different ($p < 0.05$) between two groups as analyzed using Student's paired t test.

adjusted $\alpha = 0.008$). The postprandial glucose level was also significantly decreased by 12.2% ($p = 0.006$) compared with a 12.6% ($p = 0.077$) increase during the placebo control period. However, the between treatment effect were insignificant ($p = 0.014$, adjusted $\alpha = 0.013$). The body weight decreased slightly during the period of KGM supplementation, and the between-treatment effect was insignificantly ($p = 0.115$, adjusted $\alpha = 0.025$), compared with a 0.2% increase during the control period.

Fecal Neutral Sterol and Bile Acid Contents

The fecal neutral sterol and bile acid contents are shown in Table 3. The concentrations of fecal neutral sterols and bile acids (mg/g dry feces) were both increased with KGM treatment by $19.4 \pm 25.0\%$ ($p = 0.004$) and $75.4 \pm 81.5\%$ ($p < 0.001$), respectively, in relative to the placebo treatment.

DISCUSSION

This study demonstrated three beneficial aspects of KGM supplement (in capsule) for type 2 diabetic patients whose hypercholesterolemia could not be normalized solely by the National Cholesterol Education Program diet. First, the low dose of KGM (1.2 g KGM before each meal) was compliant for these subjects. Secondly, we demonstrated that this low dose of KGM supplement (0.24 g/100 kcal), compared with 0.7 g/100 kcal and 0.5 g/100 kcal in previous studies [11–12], successfully alleviated the elevated cholesterol, LDL-cholesterol, apo B and ratios of total/HDL-cholesterol in our subjects who were not treated for hypercholesterolemia. Thirdly, the fasting blood glucose levels were also improved with KGM supplement while the dose of medication remained constant throughout the study.

Although this study was not metabolically controlled, the diet consumed by the subjects throughout the study was relatively constant in energy, lipid, fatty acid, protein, carbohydrate, cholesterol and dietary fiber contents (Table 1). Although the two-day diary records obtained from our subjects might not be as accurate as three-day diary records, we observed less than 15% variation between the two day in energy intake. The average dietary fiber intake in our subjects was in the range of 7.6–8.4 g/Mcal or 11.4–12.5 g/day, which was relatively lower

than the American Diabetic Association's recommendation, 12.5/Mcal or 20–35 g/day [4]. This low level of fiber intake was not surprising compared with only ~5 g crude fiber intake in Taiwanese aged 55–64 (n = 1005) [26] or 8.8 g dietary fiber intake for the senior population aged over 70 (n = 313) [27]. The additional KGM fiber (3.6 g/day, 2.4 g/Mcal) was ~22%–24% of the total dietary fiber ingested during the KGM.

The American Diabetic Association recently recommended the optimal blood lipid levels for diabetic patient with dyslipidemia [28]. The concentrations of LDL-cholesterol was suggested to be lower than 2.59 mmol/L (100 mg/dL), of HDL-cholesterol greater than 1.16 mmol/L (45 mg/dL), and of triglyceride <2.26 mmol/L (200 mg/dL). All of our subjects were hypercholesterolemic, of which six also had elevated triglyceride level (>2.26 mmol/L) on day 0 of this study. During the 28-day KGM supplementation, plasma total cholesterol level was lessened for ~11%, as compared to placebo, and resulted in normalization of total cholesterol level in six out of twenty-two subjects. Three of 22 subjects obtained LDL-cholesterol <2.59 mmol/L as recommended at the end of KGM period. Furthermore, 10 subjects raised their HDL-cholesterol over 1.16 mmol/L after KGM treatment. Three of them obtained triglyceride level as recommended by ADA after consuming KGM supplement. Thus, this study confirmed the short-term (three week to one month) hypocholesterolemic effects of KGM as demonstrated previously in healthy, high-risk-for-type-2-diabetes and prediabetic insulin-resistant subjects [9,11,12]. Although the effect of long term (over one month) KGM supplement on the blood cholesterol profile remains to be investigated, this study suggests the potential of low dose (3.6 g/day, 0.24 g KGM fiber/100 kcal) KGM as part of the lipid-lowering treatment for type 2 diabetic patients.

Several studies have pointed out gel-forming dietary fibers such as pectin, guar gum and psyllium reduced blood cholesterol concentrations in rats [29–31]. In humans, psyllium and guar have been shown to elicit cholesterol-lowering effects, ranging from 4% to 20% for total cholesterol and 6% to 27% for LDL-cholesterol [32]. However, the changes in the HDL-cholesterol and triglyceride levels did not always accompany the decrease in total and LDL cholesterol levels [32]. The soluble fiber KGM reduced total and LDL cholesterol by 11% and 21% in this study, respectively, which were within the ranges exerted by psyllium and guar. Although the mechanism has not yet been fully explored, it is postulated that dietary fiber decreases blood lipid and cholesterol by increasing fecal sterol or bile acid output. This theory is supported by animal studies [29,33], but clinical studies are as yet scanty. A recent clinical study by Chandalia *et al.* [5] indicated that increase in mainly soluble fiber intake from a mixed diet significantly decreased cholesterol absorption by 10% and increased fecal bile acid excretion by 41% in diabetic patients [5]. Adding a larger amount of oat bran fiber (16 g) to a controlled diet caused a very large increase (115%) in fecal bile acid excretion [34]. Results from the present study showed that KGM significantly

increased fecal neutral sterol content by 19%, and fecal bile acid content by 75%, respectively, in relative to the placebo treatment (Table 3). Although the bile acids were analyzed chemically in previous studies [5,34], differently from the biochemical method used in our study, our results agreed with the previous studies that the increases in fecal sterol excretion might mediate the cholesterol-lowering effect of fiber.

In this study, the fasting glucose was significantly elevated at the end of the placebo periods ($p = 0.017$). The postprandial glucose (~13%), total-cholesterol (~3%), LDL-cholesterol (~10%) and apo B (~4%) levels also tended to increase during the placebo period in this study. These increases in glycemia, cholesterol and apo B levels by the placebo treatment in this study were observed especially in patients who took KGM first for 28 days and, without any washout period, immediately took the placebo. Since konjac supplementation effectively reduced glycemia, cholesterol and apo B levels on day 28 (the final day of KGM period) as compared to the level obtained in the beginning of the study (end of the run-in period), the increases in the measurements on day 56 as compared to day 28 indicated that effects of KGM supplement were not sustained to day 56 (the final day of the placebo period). We also could not exclude the possibility that diseases progressed while patients took consistent doses of hypoglycemic medication and did not take any lipid-lowering medication throughout the study.

Nevertheless, the changes in the fasting and two-hour postprandial blood glucose concentrations were significantly lowered after KGM supplement, even when not compared to the effect of placebo (Table 2). These observations agreed with many previous studies in which soluble dietary fibers improved glycemic control [6,8,11,12,35,36]. The hypoglycemic effect of guar gum has been extensively evaluated and been shown to reduce fasting and postprandial glucose levels in type 2 diabetics [35] and reduced the need for insulin in healthy men [36]. A single dose of KGM has been shown to alleviate the rise in postprandial blood glucose concentration, with greater effect than the same dose of guar gum [8]. Konjac-rich diets have also been shown to effectively decrease fasting fructosamine in high-risk diabetes [11] and insulin-resistant patients [12]. The possible mechanism for the hypoglycemic effects of KGM may be due to its rheological property, which hampers the rate of carbohydrate digestion and absorption and further reduces the increment of plasma glucose after a meal [6,8]. The KGM capsule ingested before the meal in this study, different from KGM incorporated into meals [8,11,12], could provide a layer of unstirred water prior to any metabolism of dietary nutrients. These preventive effects for rapid absorptions of lipid and glucose could explain why low dose of KGM in this study, compared with relatively higher dose in previous studies [11–12], could also exert benefit effects in alleviating hypercholesterolemia and hyperglycemia. The benefits of KGM powder administered before meals in this study supports its use in the management of glycemia in type 2 diabetic patients.

In conclusion, our findings suggest that a small dose of

KGM supplement (3.6 g/day, 0.24 g/100 Kcal) could be an adjunct for treating type 2 diabetes as it could alleviate hypercholesterolemia by enhancing fecal excretion of cholesterol and bile acid and improved glycemia in hyperlipidemic type 2 diabetic patients.

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Beneficial Effects of Viscous Dietary Fiber From Konjac-Mannan in Subjects With the Insulin Resistance Syndrome

Results of a controlled metabolic trial

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OBJECTIVE— Dietary fiber has recently received recognition for reducing the risk of developing diabetes and heart disease. The implication is that it may have therapeutic benefit in prediabetic metabolic conditions. To test this hypothesis, we investigated the effect of supplementing a high-carbohydrate diet with fiber from Konjac-mannan (KJM) on metabolic control in subjects with the insulin resistance syndrome.

RESEARCH DESIGN AND METHODS— We screened 278 free-living subjects between the ages of 45 and 65 years from the Canadian-Maltese Diabetes Study. A total of 11 (age 55 ± 4 years, BMI 28 ± 1.5 kg/m²) were recruited who satisfied the inclusion criteria: impaired glucose tolerance, reduced HDL cholesterol, elevated serum triglycerides, and moderate hypertension. After an 8-week baseline, they were randomly assigned to take either KJM fiber-enriched test biscuits (0.5 g of glucomannan per 100 kcal of dietary intake or 8–13 g/day) or wheat bran fiber (WB) control biscuits for two 3-week treatment periods separated by a 2-week washout. The diets were isoenergetic, metabolically controlled, and conformed to National Cholesterol Education Program Step 2 guidelines. Serum lipids, glycemic control, and blood pressure were the outcome measures.

RESULTS— Decreases in serum cholesterol (total, $12.4 \pm 3.1\%$, $P < 0.004$; LDL, $22 \pm 3.9\%$, $P < 0.002$; total/HDL ratio, $15.2 \pm 3.4\%$, $P < 0.003$; and LDL/HDL ratio, $22.2 \pm 4.1\%$, $P < 0.002$), apolipoprotein (apo) B ($15.1 \pm 4.3\%$, $P < 0.0004$), apo B/A-1 ratio ($13.1 \pm 3.4\%$, $P < 0.0003$), and serum fructosamine ($5.2 \pm 1.4\%$, $P < 0.002$) were observed during KJM treatment compared with WB-control. Fasting blood glucose, insulin, triglycerides, HDL cholesterol, and body weight remained unchanged.

CONCLUSIONS— A diet rich in high-viscosity KJM improves glycemic control and lipid profile, suggesting a therapeutic potential in the treatment of the insulin resistance syndrome.

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Abbreviations: apo, apolipoprotein; CHD, coronary heart disease; IGT, impaired glucose tolerance; KJM, Konjac-mannan; NCEP, National Cholesterol Education Program; WB, wheat bran.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Abnormal glucose tolerance and insulin resistance are related to multiple cardiovascular risk factors, especially reduced HDL cholesterol, elevated serum triglycerides, and hypertension (1). When clustered, these abnormalities increase the risk of coronary heart disease (CHD) morbidity and mortality, an effect that is independent of other conventional risk factors (2). Co-occurrence is usually present in insulin-insensitive individuals (3) and is often described in relation to visceral adiposity (4) and lack of physical activity (5). The estimated prevalence ranges from 3% (2) to ~30% (1,6) depending on how this insulin resistance syndrome is defined and in which population it is measured.

Although it has been extensively described (1–5), followed up (6), and had its prevalence determined (1,2), no specific recommendations for treatment of this syndrome have been proposed by health agencies. In practice, initial therapy of individual risk factors such as moderate dyslipidemia, hypertension, or hyperglycemia is non-pharmacological. Treatment will often include behavioral changes to reduce body weight, increase physical activity, and moderate alcohol consumption. To achieve nutritional goals, there are three main approaches: a high-carbohydrate/low-fat diet (7), sharing calories between monounsaturated fat and complex carbohydrate at the expense of saturated fat (8), or supplementing a high-carbohydrate/low-fat diet with exercise (9).

Evidence suggests that fiber may also be used in a therapeutic role. Recent epidemiological findings confirm the relationship between high dietary fiber intake and lower risk of developing both diabetes (10,11) and CHD (12). Soluble dietary fiber, in particular, has been shown clinically to reduce the need for insulin (13), improve glycemia (14), and reduce serum LDL cholesterol (15). Its viscosity is proposed as an important mechanistic factor (16). We recently demonstrated that a metabolically controlled low-fat diet supplemented with the high-viscosity Konjac-

mannan (KJM) simultaneously improved three major CHD risk factors in type 2 diabetic subjects (17).

In the present study, we tested the hypothesis that the same intervention would improve the control of conventional and emerging CHD risk factors in prediabetic individuals with a full cluster of metabolic abnormalities that define the insulin resistance syndrome. KJM flour is obtained by grinding the tuber root of the *Amarophallophallus Konjac C. Koch.* plant and is traditionally used as a food and remedy in the Far East. In addition to our previous findings (17), other findings have shown it to improve cholesterol levels (18,19), hypertension, and glycemia (20,21).

RESEARCH DESIGN AND METHODS

Subjects

We screened 278 free-living subjects from the Canadian-Maltese Diabetes Study between the ages of 45 and 65 years. This population is known to have one of the highest rates of diabetes (22). Of the subjects, 38 satisfied the initial inclusion criteria: impaired glucose tolerance (IGT) (23); clinical absence of CHD; BMI <30 kg/m²; not taking medications for hyperglycemia, hyperlipidemia or hypertension; not smoking; nor consuming more than two alcoholic drinks per day. These subjects were further screened for the presence of the full insulin resistance syndrome (2). This included moderate hypertension (>135/85 and <145/95 mmHg), dyslipidemia (low HDL cholesterol [<0.9 mmol/l for men and <1.2 mmol/l for women], and elevated triglycerides [>2.3 mmol/l and <4.5 mmol/l]). Based on power analysis from the previous study (17), 11 subjects (5 men, 6 women) who qualified were recruited. In addition to meeting the above criteria, their fasting (98 ± 13 pmol/l) and 2-h postprandial (439 ± 68 pmol/l) plasma insulin levels were greater ($P < 0.05$) than 2 SDs of the initial screening pool (71 ± 8 and 316 ± 47 pmol/l, respectively). All 11 also had moderately high serum cholesterol (5.2 – 6.7 mmol/l) and were sedentary, with a mean (\pm SD) age of 55 ± 4 years (range: 46–61); a BMI of 28 ± 3 kg/m²; a waist-to-hip ratio of 0.98 ± 0.2 (waist: 96 ± 12 cm) in men and 0.91 ± 0.4 (waist: 87 ± 19 cm) in women. They gave written informed consent to participate in the current study that was approved by the Human Ethics Committees of St. Michael's Hospital and the University of Toronto.

Study design

The study employed a double-blind placebo-controlled crossover design identical to that used on our previous study (17). It began with an 8-week baseline period during which participants followed a National Cholesterol Education Program (NCEP) Step 2 (8) ad libitum diet, documented by three nonconsecutive days of food records every 2 weeks. This run-in phase was included to eliminate possible effects of dietary change on metabolic parameters. The experimental phase of the study followed. This phase consisted of two successive 3-week treatment periods, separated by a 2-week washout interval over which a Step 2 diet was followed and documented by another 3-day food record. During the first treatment period, subjects were randomly assigned to either the KJM (Step 2 metabolically controlled diet enriched with KJM fiber) or the control treatment (the same diet enriched with wheat bran [WB] fiber). For the second treatment period, the subjects were crossed over. Blood collection, weight, blood pressure, and waist and hip measurements were done at the beginning and end of each 3-week treatment period. The study began with five subjects taking the KJM treatment and six the control.

Diet

Both treatments consisted of a 3-day rotating Step 2 diet with three meals per day provided under metabolic conditions. All foods were pre-weighed, packaged, and delivered by courier to participants for consumption at home or at work. The mean macronutrient profile closely conformed to a Step 2 diet (<30% of calories from total fat, <7% from saturated fat, and <300 mg/day cholesterol) (8). Energy intakes for weight maintenance were provided according to Lipid Research Clinics Tables with adjustment for physical activity (24). Total dietary fiber was administered at 1.5 g/100 kcal, with a mean daily intake according to energy intake ranging from 24 g to a plateau of 40 g for those consuming $\geq 2,800$ kcal per day. The actual diet consumed is presented in Table 1.

The two treatments differed only in the type of fiber. On the KJM treatment, participants received KJM-enriched test biscuits, whereas on the WB-control treatment they received an equal quantity of WB control biscuits. Subjects were instructed to eat an equal amount of biscuits together with an 8-oz. beverage three times daily as a snack,

including once at bedtime. Both were provided by Dicofarm S.p.A. (Rome). The biscuits had similar nutrient profiles and were indistinguishable in taste and appearance. KJM biscuits contained $\sim 10\%$ KJM flour, of which 69% was the active high-viscosity glucomannan, 15% other polysaccharides, and 16% excipients by weight (17). Because KJM flour comprised half (0.75 g/100 kcal) of the total fiber on the KJM treatment, ~ 0.5 g/100 kcal (8–13 g/day) was glucomannan. WB biscuits, in contrast, had a lower proportion of total dietary fiber than KJM biscuits. Therefore, ~ 11 g/day of wheat bran fiber derived from standardized American Association of Cereal Chemists hard red wheat bran was, therefore, added to the WB-control diet to compensate for these fiber differences. Subjects were instructed to sprinkle the additional fiber on cereal, yogurt, and/or other compatible foods to improve the fiber's palatability.

Any foods from the metabolic diet together with study biscuits not consumed during the study were returned to the clinic for weighing to measure compliance. Dietary changes found to occur during the first 3-week treatment period were duplicated in the diets for the second treatment period for each participant.

Laboratory methods

Laboratory methods were identical to those used in our previous study (17). In brief, blood samples were separated immediately and stored as serum in four aliquots at -70°C after collection. They were thawed at the end of the study for analysis of total cholesterol, HDL cholesterol, and triglycerides measured enzymatically. LDL cholesterol content was estimated by the formula of Friedewald et al. Apolipoprotein (apo) A1 and B were determined by rocket immunoelectrophoresis. Fasting blood glucose was analyzed by a hexokinase method using a Cobas Mira Autoanalyzer (Roche Diagnostic, Mississauga, Canada). Serum fructosamine was analyzed in triplicate using Cobas Fara II and plasma insulin in duplicate by radioimmunoassay with reagent from ICN Biomedicals (Horsham, PA). C-peptide was determined by radioimmunoassay.

Statistical analyses

Results are expressed as means \pm SEM, except for age, anthropometric measurements, and nutrient intake (means \pm SD). Data were analyzed by the Statistical Analysis System (SAS Institute, Cary, NC). Differences between the diets were assessed by

two-tailed Student's *t* test for paired data (univariate procedure). This same statistic also assessed differences in serum lipids, apolipoproteins, glycemia, blood pressure, and body weight between the beginning (week 0) and end (week 3) of each treatment (WB-control and KJM). Analysis of covariance (ANCOVA) with general linear model (GLM) procedure was used to test for differences in these same parameters between the two treatments. Control of individual variation from the repeated-measures aspect of the design was addressed by incorporating the random subject effect as well as the starting measurement. Diet, sex, and phase effects were also incorporated in this model. Adjustment for multiple comparisons was made by the Bonferroni-Hochberg procedure (25). *P* values for each end point were ordered sequentially and contrasted with the corresponding adjusted comparisonwise critical alpha (α) levels. The null hypotheses were rejected only if *P* values were less than their corresponding α values.

RESULTS — All participants followed the experimental protocol with little difficulty. Returned food from metabolic diets indicated that subjects consumed an average of 96% and 95% of diet calories prescribed on the KJM and WB-control treatments, respectively. Returned biscuits indicated they consumed 81% (97 g/day) of KJM and 86% (103 g/day) of WB-control biscuits. Consumption patterns translated into an insignificant decrease in body weight during both treatment periods with no difference between treatments (Table 2). The only side effect experienced was a transient complaint of flatulence and soft stools reported by three and two of the participants during the KJM and the WB-control treatments, respectively, but none chose to discontinue the study.

Serum lipids

Blood lipids improved during KJM compared with WB-control treatment (Table 2). Total and LDL cholesterol fell significantly by $19 \pm 2.7\%$ ($P < 0.0001$) and $29 \pm 3.4\%$ ($P < 0.0001$) during KJM treatment compared with $6.3 \pm 3.4\%$ ($P = 0.088$) and $6.6 \pm 5.0\%$ ($P = 0.231$) on control treatment. The between-treatment differences were $12.4 \pm 3.1\%$ ($P < 0.005$) and $22 \pm 3.9\%$ ($P < 0.003$), respectively. The combined fall in total cholesterol from 6.2 ± 0.3 to 5.0 ± 0.2 mmol/l and LDL from 3.9 ± 0.2 to 2.8 ± 0.2 mmol/l on KJM treatment indicated

Table 1—Average intake of energy and nutrients before and during study periods in 11 subjects

| Parameters | Baseline | KJM | WB |
|--------------------------------------|-------------------|-----------------|-----------------|
| Total energy (kcal/day) | 2,070 \pm 700 | 2,579 \pm 628 | 2,355 \pm 420 |
| Total fat (% of energy) | 30.5 \pm 4.3 | 29.3 \pm 3.2 | 28.7 \pm 2.4 |
| Saturated fat (% of energy) | 7.2 \pm 4.7 | 6.7 \pm 0.8 | 6.4 \pm 0.7 |
| Monounsaturated fat (% of energy) | 10.3 \pm 5.1 | 12.7 \pm 2.1 | 12.2 \pm 2.6 |
| Polyunsaturated fat (% of energy) | 13.0 \pm 5.7 | 9.9 \pm 1.8 | 10.1 \pm 0.9 |
| Cholesterol (mg/day) | 328 \pm 102 | 219 \pm 48 | 236 \pm 77 |
| Total protein (% of energy) | 14.6 \pm 8.2 | 16.2 \pm 2.7 | 15.6 \pm 3.2 |
| Available carbohydrate (% of energy) | 54.9 \pm 21 | 54.5 \pm 9.4 | 55.7 \pm 7.3 |
| Sugars (% of energy) | 13.3 \pm 3.6 | 11.2 \pm 0.9 | 9.2 \pm 1.4 |
| Fiber (g/day) | | | |
| Total | 24.2 \pm 11 | 34.7 \pm 8.4 | 33.4 \pm 9.6 |
| Water-soluble | 6.9 \pm 3.2 | 23.4 \pm 1.7 | 9.9 \pm 3.2* |
| Water-insoluble | 17.3 \pm 7.3 | 11.2 \pm 3.8 | 23.1 \pm 2.6* |
| Sodium (mg) | 5,810 \pm 2,384 | 3,162 \pm 648 | 3,380 \pm 647 |
| Potassium (mg) | 3,882 \pm 713 | 4,530 \pm 611 | 4,840 \pm 872 |
| Calcium (mg) | 1,366 \pm 193 | 1,260 \pm 238 | 1,487 \pm 446 |

Data are means \pm SD. KJM and WB-control diets are based on actual intake. Baseline values are based on the mean of four 3-day food records. * $P < 0.001$ for differences between KJM and WB-control treatments (Student's *t* test for paired data).

reclassification of the lipid status of the group (8 of 11 subjects) from elevated to normal cholesterolemia (7). Similar results were observed for apo B. During KJM treatment, apo B fell significantly by $19 \pm 2.8\%$ ($P < 0.0004$) compared to $4.5 \pm 4.5\%$ ($P = 0.34$) on control, for a significant difference of $15.1 \pm 4.3\%$ ($P < 0.0004$) between the treatments.

In contrast, such effects were not seen in apo A-1 or triglycerides. During KJM and control treatments, HDL cholesterol decreased significantly on both treatments: $8.5 \pm 2.2\%$, $P < 0.04$ on KJM diet and $9.6 \pm 2.2\%$, $P < 0.003$ on WB-control, with an insignificant between-treatment change ($P = 0.98$). Similarly, during both treatments, triglycerides increased insignificantly, with no significant difference between treatments.

Despite this lack of effect of KJM treatment on HDL cholesterol, apo A-1, or triglycerides, the decreases in total cholesterol and apo B were sufficient to improve lipid ratios. During KJM treatment, total/HDL, LDL/HDL, and apo B/A-1 ratios decreased by $11 \pm 3.0\%$ ($P < 0.005$), $22 \pm 3.7\%$ ($P < 0.0002$), and $13 \pm 3.0\%$ ($P < 0.003$), respectively. This compares to an insignificant increase of $4.1 \pm 4.1\%$ in total/HDL ratio, $0.2 \pm 6.3\%$ in LDL/HDL ratio, and $0.7 \pm 3.6\%$ in apo B/A-1 on WB-control. The resulting between-treatment differences were $15.2 \pm 3.4\%$ ($P < 0.003$) for total/HDL cholesterol, $22.2 \pm 4.1\%$ ($P < 0.002$) for LDL/HDL chole-

sterol, and $13.1 \pm 3.4\%$ ($P < 0.0003$) for apo B/A-1.

Glycemic control

An improvement in glycemic control was observed on the KJM compared with WB-control treatment (Table 2). Serum fructosamine was reduced during the KJM treatment by $5.6 \pm 1.5\%$ ($P < 0.003$), compared with $0.39 \pm 1.3\%$ ($P = 0.77$) on control treatment, with a between-treatment difference of $5.2 \pm 1.4\%$ ($P < 0.002$). No significant between-treatment differences were seen for insulin or glucose concentrations. On KJM, however, fasting glycemia fell by $13 \pm 2.5\%$ ($P < 0.0001$) compared with $9.6 \pm 4.3\%$ ($P < 0.05$) on control.

Blood pressure

No change in systolic or diastolic blood pressure was observed on either treatment or between treatments (Table 2).

All above results remained unchanged after adjustment for multiple comparisons by the Bonferroni-Hochberg procedure.

CONCLUSIONS — This preliminary study demonstrated that the addition of 0.5 g/100 kcal (8–13 g/day) of high-viscosity glucomannan in biscuit form to a high-carbohydrate/low-saturated fat NCEP Step 2 diet improved metabolic control beyond diet alone in individuals with the insulin resistance syndrome. We observed significant reductions in hyperglycemia as

Konjac-mannan and insulin resistance

Table 2—Changes in serum lipids, glycemia, blood pressure, and body weight during and between the KJM and WB-control study periods in 11 subjects

| Risk factor | KJM | | | WB-control | | | Between treatments | |
|-----------------------|-------------|-------------|--------------|-------------|-------------|--------------|--------------------|---------|
| | Week 0 | Week 3 | Change (%) | Week 0 | Week 3 | Change (%) | Change (%) | P |
| Cholesterol (mmol/l) | | | | | | | | |
| Total | 6.2 ± 0.3 | 5.0 ± 0.2 | −19 ± 2.69* | 6.0 ± 0.2 | 5.6 ± 0.2 | −6.3 ± 3.36 | −12.4 ± 3.1 | 0.0038* |
| LDL | 3.9 ± 0.2 | 2.8 ± 0.2 | −29 ± 3.37* | 3.8 ± 0.2 | 3.5 ± 0.2 | −6.6 ± 5.04 | −22.3 ± 3.9 | 0.0017* |
| HDL | 1.0 ± 0.1 | 0.9 ± 0.1 | −8.5 ± 2.19* | 1.0 ± 0.1 | 0.9 ± 0.1 | −9.6 ± 2.24* | 1.2 ± 2.2 | 0.9812 |
| Triglyceride (mmol/l) | 2.8 ± 0.2 | 3.0 ± 0.2 | 10.1 ± 9.92 | 2.9 ± 0.4 | 3.0 ± 0.3 | 12.1 ± 14 | −1.6 ± 10 | 0.7317 |
| Apolipoprotein (g/l) | | | | | | | | |
| Apo A-1 | 1.4 ± 0.1 | 1.4 ± 0.1 | −6.5 ± 2.46* | 1.5 ± 0.1 | 1.4 ± 0.1 | −4.8 ± 3.38 | −1.8 ± 3.1 | 0.3622 |
| Apo B | 1.6 ± 0.1 | 1.3 ± 0.1 | −19 ± 2.78* | 1.6 ± 0.1 | 1.5 ± 0.1 | −4.5 ± 4.47 | −15.1 ± 4.3 | 0.0003* |
| Lipid ratios | | | | | | | | |
| Total/HDL cholesterol | 6.5 ± 0.5 | 5.7 ± 0.4 | −11 ± 3.02* | 6.2 ± 0.4 | 6.4 ± 0.5 | 4.14 ± 4.16 | −15.2 ± 3.4 | 0.0023* |
| Apo B/apo A-1 | 1.1 ± 0.1 | 1.0 ± 0.1 | −13 ± 3.02* | 1.1 ± 0.1 | 1.1 ± 0.1 | 0.72 ± 3.61 | −13.1 ± 3.4 | 0.0002* |
| LDL/HDL | 4.2 ± 0.4 | 3.2 ± 0.3 | −22 ± 3.72* | 3.9 ± 0.3 | 3.9 ± 0.4 | 0.22 ± 6.27 | −22.2 ± 4.1 | 0.0012* |
| Glycemic control | | | | | | | | |
| Glucose (mmol/l) | 6.8 ± 0.5 | 5.9 ± 0.3 | −13 ± 2.48* | 6.6 ± 0.3 | 5.9 ± 0.4 | −9.6 ± 4.27 | −3.8 ± 3.6 | 0.7653 |
| Fructosamine (mmol/l) | 286 ± 13.6 | 269 ± 11.9 | −5.6 ± 1.46* | 279 ± 11.7 | 278 ± 12.6 | −0.39 ± 1.3 | −5.2 ± 1.4 | 0.0013* |
| Insulin (pmol/l) | 94.8 ± 16.6 | 91.1 ± 16.5 | 0.91 ± 8.88 | 99.2 ± 16.5 | 88.5 ± 11.4 | −3.0 ± 9.67 | 3.9 ± 8.9 | 0.9683 |
| Blood pressure (mmHg) | | | | | | | | |
| Systolic | 139 ± 2.0 | 135 ± 3.6 | −2.9 ± 1.88 | 135 ± 2.6 | 138 ± 3.7 | 2.2 ± 2.5 | −5.1 ± 2.2 | 0.448 |
| Diastolic | 85.4 ± 1.8 | 84.8 ± 1.5 | −0.26 ± 2.55 | 85.5 ± 1.7 | 86.5 ± 1.5 | 1.33 ± 1.49 | −1.4 ± 2.1 | 0.2647 |
| Body weight (kg) | 80.7 ± 5.1 | 80.6 ± 5 | −0.17 ± 0.14 | 81 ± 5.3 | 80.6 ± 5.1 | −0.29 ± 0.35 | 0.1 ± 0.2 | 0.5303 |

Data are means ± SEM, except for body weight, which is mean ± SD. Within-treatment differences (week 0 vs. week 3) were assessed by paired Student's *t* test and between-treatment differences by ANCOVA (general linear model procedure). *Significant after adjustment of α level by the Bonferroni-Hochberg procedure. Null-hypotheses were rejected only if the *P* values were less than their corresponding adjusted α level.

measured by the short-term marker of glycemic control, fructosamine, although the clinical significance of the observed changes remains to be demonstrated. We also observed significant reductions in hyperlipidemia as measured by total, LDL, LDL/HDL, and total/HDL cholesterol, and apo B and apo B/A-1, relative to a matched WB-control treatment. These findings represent the first to demonstrate such improvements using soluble fiber in subjects with this particular cluster of risk factors that also includes the intermediate diabetic classification, IGT.

Because of the strong implications of insulin resistance syndrome, a more aggressive approach has been suggested to achieve similar reductions. Diabetes and heart disease share common precursors for the development of atherosclerosis that often co-occur. Long before diabetes becomes manifest, the clustering of metabolic abnormalities exerts a synergistic effect on the atherosclerotic process (26). Based on findings from Trevisan and colleagues, cardiovascular disease (CVD) risk appears to increase linearly with an increase in the number of these risk factors. It is recommended therefore that insulin-resistant patients have their

CHD risk factors managed as if they have established CHD (27).

Low-fat/high-carbohydrate diets may still have promise as a therapeutic approach. Although there has been a shift away from their advocacy in favor of those rich in monounsaturated fat (8), these diets supplemented with fiber may have similar metabolic advantages. Guar gum, pectin, oat products, and psyllium added to high-carbohydrate diets have been shown to improve total and LDL cholesterol significantly, with no improvement to triglycerides and slight or no adverse effects on HDL (16). Both guar (14) and KJM (17,18) supplementation have also been shown to improve other risk factors, including glycemia and blood pressure. This has led to support for the use of guar in the treatment of the insulin resistance syndrome (13). Evidence further suggests that supplementation with these soluble fibers may augment concurrent drug therapy. Improvements in these assorted risk factors following supplementation have been noticed beyond what was achieved by drugs alone in subjects receiving hypolipidemic (14,17,28), hypoglycemic (14,17,29), and hypotensive (17,30) medications.

The ability of soluble fiber to improve a high-carbohydrate/low-fat diet is supported by the findings of the present study. Total and LDL cholesterol were decreased and glycemic control was improved significantly. Also, although HDL, apo A-1, and triglycerides were unaffected, as has been noticed with other fibers, this was balanced by the significant improvements in the other lipid end points, leading to significant reductions in all three lipid ratios: total/HDL, LDL/HDL, and apo B/A-1. Similar improvements in these ratios have rarely been reported using dietary interventions (28,29). Overall, the suggestion is that an NCEP Step 2 diet supplemented with KJM may confer additional benefits over the Step 2 diet alone, benefits that may be comparable to strategies using monounsaturated fat.

KJM may be better suited than the other major soluble fibers to improving outcomes with high-carbohydrate/low-fat diets. Although meta-analyses use variance-adjusted values that tend to underestimate effectiveness, KJM can be compared to other soluble fibers in terms of its lipid-lowering ability per gram of fiber, using recent meta-analytical data (15). Daily intake of glu-

commanan from KJM on this and our previous study (17) produced an average net change in total and LDL cholesterol of -0.084 and -0.119 mmol/l per gram of fiber, respectively. These reductions represent approximately triple the lipid-lowering capacity of psyllium (-0.028 and -0.029 mmol/l, respectively), oat products (-0.037 and -0.032 mmol/l), and guar gum (-0.037 and -0.033 mmol/l) (15). In the case of pectin, they represent comparable total cholesterol-lowering capacity (-0.070 mmol/l) and approximately twice the LDL-lowering capacity (-0.055 mmol/l) (15). The very high viscosity of KJM may explain these differences. It has been shown to be approximately five times higher than that of guar gum (31) and beta-glucan (32), and considerably more than that of pectin (19).

Contributions made by KJM's rheological properties may offer insight into the proposed mechanism by which the KJM-supplemented biscuits had their beneficial effects. Possibilities for its lipid-lowering action may include an inhibition of cholesterol absorption in the jejunum (19) and bile acid absorption in the ileum (33) mediated by viscosity or less postprandial stimulation of 3-hydroxy 3-methylglutaryl CoA reductase (34). Other options include the generation of short-chain fatty acids, predominantly propionate, by colonic microflora that may decrease hepatic cholesterol synthesis (35). The improvement in glycemic control may be attributable to an effect of the gel-forming KJM on rate of digestion. It has been suggested that decreases in glucose and insulin levels after the consumption of water-soluble fibers are related to slower rates of food absorption in the small intestine associated with increased viscosity (16). This mechanism may explain why we observed a reduction in serum fructosamine, but did not observe concomitant reductions in fasting glycemia and insulinemia: KJM may be exerting its effect mainly postprandially.

In conclusion, the results from the current study support the role of KJM and other viscous dietary fiber as a means for improving high-carbohydrate diets in the amelioration of the insulin resistance syndrome. Improved metabolic control resulted in the correction of several risk factors that characterize the syndrome and figure prominently in the etiology of atherosclerotic CHD. Before the therapeutic potential of KJM can be fully realized in this or other situations, however, further controlled studies with larger sample sizes and of longer duration

are required; these requirements are both major caveats of the present study. Determinations of the optimal fiber dose in different categories of subjects, of the rheological-biological relationship of KJM, and of KJM's effects on insulin sensitivity and thrombotic factors are also warranted.

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