

Beneficial Effects of a Soy-Based Dietary Supplement on Lipid Levels and Cardiovascular Risk Markers in Type 2 Diabetic Subjects

KJELD HERMANSEN, MD, DMSC
METTE SØNDERGAARD, MD
LARS HØIE, MD

MARIUS CARSTENSEN, MD
BIRGITTE BROCK, MD, PHD

OBJECTIVE — Consumption of soy protein has recently been shown to improve the blood lipid levels in nondiabetic subjects. The purpose of this study was to evaluate if a dietary supplement of soy protein, isoflavones, and cotyledon fiber (Abalon) affects cardiovascular risk markers, blood glucose, and insulin levels in type 2 diabetic subjects.

RESEARCH DESIGN AND METHODS — Twenty type 2 diabetic subjects participated in a crossover trial. They were randomized to double-blind supplementation for 6 weeks with Abalon (soy protein [50 g/day] with high levels of isoflavones [minimum 165 mg/day] and cotyledon fiber [20 g/day]) or placebo (casein [50 g/day] and cellulose [20 g/day]), separated by a 3-week wash-out period.

RESULTS — The results are expressed as means \pm SD. The percentage mean treatment difference between Abalon and placebo demonstrated significantly lower mean values after Abalon for LDL cholesterol ($10 \pm 15\%$, $P < 0.05$), LDL/HDL ratio ($12 \pm 18\%$, $P < 0.05$), apolipoprotein (apo) B100 ($30 \pm 38\%$, $P < 0.01$), triglycerides ($22 \pm 10\%$, $P < 0.05$), and homocysteine ($14 \pm 21\%$, $P < 0.01$), whereas the total cholesterol value tended to be less significant but still lower ($8 \pm 15\%$, $P < 0.08$). No change occurred in HDL cholesterol, apo B100/apo A1 ratio, plasminogen activator inhibitor 1, factor VIIc, von Willebrand factor, fibrinogen, lipoprotein(a), glucose, HbA_{1c}, or 24-h blood pressure.

CONCLUSIONS — These results indicate beneficial effects of dietary supplementation with Abalon on cardiovascular risk markers in type 2 diabetic subjects. This improvement is seen even in individuals with near-normal lipid values.

Diabetes Care 24:228–233, 2001

Coronary artery disease (CAD) is much more prevalent among adults with type 2 diabetes than in the general population (1,2) with a four- to sixfold greater cardiovascular mortality (3). A two to three times higher CAD risk is seen in diabetic subjects at every level of total cho-

lesterol (4). The serum lipid abnormalities in type 2 diabetes are characterized by decreased HDL cholesterol and hypertriglyceridemia, whereas total cholesterol and LDL cholesterol levels are similar to those in nondiabetic subjects. Also, altered coagulation with increased concentrations

and activity in blood of procoagulants including fibrinogen, coagulation factor VIIc, and von Willebrand factor, as well as attenuated fibrinolysis, with increased plasminogen activator inhibitor 1 (PAI-1) activity may contribute indirectly and directly to macrovascular disease (5,6). Both clinical and experimental studies have suggested that mild increases in plasma homocysteine may be an independent risk factor for CAD (7,8). A recent study in type 2 diabetes also demonstrated a clear relationship between increased homocysteinemia and increased risk of CAD (9). Hyperhomocysteinemia may be an even stronger risk factor for CAD in subjects with type 2 diabetes than in nondiabetic subjects (10).

In recent years, approaches to control CAD have largely focused on drug therapy in people with CAD. Still, lifestyle modifications including changed dietary pattern and increased exercise play an important role. The intake of diets low in fat and high in complex carbohydrates from grains, fruits, and vegetables is associated with a lower risk of cardiovascular disease (11). A diet with a high content of dietary fiber and low glycemic load is also associated with reduced incidence of type 2 diabetes (12,13). Dietary recommendations for type 2 diabetic subjects largely target reducing total and saturated fat and replacing the fat with complex carbohydrates (14). This dietary therapy is also generally recommended for lowering plasma cholesterol before resorting to drug treatments. Interestingly, the major components of soybean flour (i.e., soy proteins, soy cotyledon fiber, and isoflavones) appear to independently decrease serum cholesterol (15). A recent meta-analysis of 38 controlled clinical trials indicated that soy protein was effective in lowering plasma cholesterol, LDL cholesterol, and triglyceride concentrations (16). In a small acute study, supplementation of soy fibers for obese type 2 diabetic subjects also seemed to reduce the rise of postprandial plasma triglycerides and mildly lower the blood glucose response without affecting the insulin lev-

From the Department of Endocrinology and Metabolism (K.H., M.S., M.C., B.B.), Aarhus University Hospital, Aarhus, Denmark; and Nutri Pharma ASA (L.H.), Oslo, Norway.

Address correspondence and reprint requests to Kjeld Hermansen, MD, DMSc, Department of Endocrinology and Metabolism, Aarhus Amtssygehus, Aarhus University Hospital, Tage-Hansens Gade 2, DK-8000 Aarhus C, Denmark. E-mail: kjeld.hermansen@dadlnet.dk.

Received for publication 25 May 2000 and accepted in revised form 20 October 2000.

L.H. is on the Board of Directors of, is paid consulting fees by, and holds stock in Nutri Pharma ASA.

Abbreviations: apo, apolipoprotein; BP, blood pressure; CAD, coronary artery disease; ELISA, enzyme-linked immunosorbent assay; Lp(a), lipoprotein(a); PAI-1, plasminogen activator inhibitor 1.

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

Table 1—Subject characteristics of 20 type 2 diabetic subjects (14 men and 6 women) at the start of and after 6 weeks treatment

	Control		Abalon	
	Start	6 weeks	Start	6 weeks
Weight (kg)	88.3 ± 11.8	89.0 ± 12.3	88.7 ± 11.9	89.3 ± 11.9
BMI (kg/m ²)	30.1 ± 4.2	30.3 ± 4.2	30.2 ± 4.2	30.4 ± 4.2
Waist (cm)	103.1 ± 8.7	103.5 ± 8.7	102.9 ± 8.9	103.6 ± 8.6
Waist-to-hip ratio	0.96 ± 0.07	0.97 ± 0.07	0.96 ± 0.07	0.97 ± 0.07
Systolic BP (mmHg)	130 ± 9	129 ± 10	130 ± 9	130 ± 10
Diastolic BP (mmHg)	78 ± 6	77 ± 6	78 ± 5	77 ± 7
Pulse rate	79 ± 11	79 ± 9	76 ± 10	77 ± 9
HbA _{1c} (%)	6.7 ± 1.3	6.9 ± 1.7	6.6 ± 1.2	6.6 ± 1.2
Plasma glucose (mmol/l)	7.0 ± 2.0	7.7 ± 2.9	6.9 ± 2.3	7.3 ± 2.8
Insulin (pmol/l)	72 ± 30	68 ± 41	68 ± 37	74 ± 45

Data are means ± SD.

els (17). This raises the question if soy products may improve the glycemic control in type 2 diabetic subjects.

The purpose of the present study was to compare the effects of a soy-based dietary supplement Abalon (containing soy protein and a high-fixed level of isoflavones and soy cotyledon fibers) with a control supplement (containing casein and cellulose fibers) taken twice a day as a beverage with regular meals for a 6-week period. The effects studied are cardiovascular risk markers, glucose, and insulin responses in type 2 diabetic subjects.

RESEARCH DESIGN AND METHODS

Subjects

Of the 25 individually randomized type 2 diabetic subjects, 20 completed the study. Two subjects receiving control did not complete the study for the following reasons: one subject developed headaches and vertigo, and one did not tolerate phlebotomy. Three subjects in the soy product phase did not complete for the following reasons: one subject had diarrhea after the first visit, one had previously unrecognized brain metastases, and one had liver metastases. The mean age of the remaining 20 subjects (14 men and 6 women) was 63.6 ± 7.5 years, and time from diagnosis of type 2 diabetes was 3.0 ± 2.7 years. Twelve subjects started on active treatment and eight on the control treatment. Clinical characteristics are given in Table 1. None of the subjects had diabetic complications except background retinopathy; 11 were treated with diet alone and 9 received additional oral antidiabetic drugs (3 sulfonylureas, 3 metformin, and 3

sulfonylureas and metformin). They took the prescribed medicine throughout the study and, with the exception of one patient who increased the metformin dose 8 days before the last visit, all other subjects kept an unchanged dose of medicine. None were taking insulin, hypolipidemic agents, β -blocking agents, or acetylsalicylic acid. Subjects were asked to maintain their habitual diet and level of physical activity throughout the study. All were in good general health and had normal liver and renal function. The experimental protocol was approved by the local ethical committee of Aarhus County. Informed written consent was obtained from each subject. The study was monitored by the Good Clinical Practice (GCP) unit of Aarhus University Hospital.

Study design

A controlled double-blind crossover study was conducted on outpatients. Twelve patients were randomly allocated to a 6-week treatment with Abalon and 8 patients to a 6-week treatment with placebo. After a 3-week wash-out period, the participants received the alternative treatment for 6 weeks. The soy product (Abalon; Nutri Pharma ASA, Oslo, Norway) provided a daily amount of 50 g isolated soy protein (Supro; Protein Technologies, St. Louis, MO) with a high isoflavone content (total isoflavones >165 mg) and 20 g soy cotyledon fiber (Supro). The control provided a daily amount of 50 g casein and 20 g cellulose. Both products containing low-energy flavoring (aspartame, maltodextrin, and cacao taste) were packaged in foils. Subjects were instructed to mix half of their daily supplement in 250 ml water before

breakfast and half before the evening meal and to consume as a beverage with the current meals.

For each patient, the diets were isocaloric and had similar macronutrient composition up to the start of Abalon and the control treatment. Before each study period and during the last week of the 6-week periods, participants were instructed by a registered dietitian to weigh and record their food for 2 working days and 1 weekend day to estimate the energy intake and composition. The dietary records were validated by the dietitian using models and photo collections. The food records were coded by the dietitian, and the nutrient content was calculated using the computer program Dankost (Danish Catering Center, Herlev, Denmark) based on information from the Danish Veterinary and Food Administration (18). All foods ingested were registered in this database. The participants were weighed weekly and their caloric intake adjusted by the dietitian if body weight differed >1 kg from the weight at the beginning of the study. The nutrient composition after the 6-week treatment is given in Table 2. Blood samples were obtained after an overnight fasting period before the study and on the last day of the two intervention periods. The samples were stored at 20°C until assayed. Clinical auscultatory and 24-h ambulatory blood pressures (BPs) were measured on the last day of the two intervention periods. Ambulatory BP and pulse were measured with a portable automatic monitor (SpaceLabs model 90202; SpaceLabs, Redmond, WA). The equipment measures BP by oscillometry and was programmed for cuff insufflation every 20 min from 0600 to 2400 and every hour during the night. A 24-h urine sample was collected concomitantly with the 24-h BP measurement and was analyzed for glucose, creatinine, potassium, sodium, and calcium.

To evaluate the effect on blood glucose and insulin of Abalon and control, we measured 4-h profiles of glucose and insulin during a test meal of white bread, ham, and butter containing 360 kcal (carbohydrate 50%, fat 30%, and protein 20% energy) taken together with either Abalon (25 g soy protein, 10 g cotyledon fibers, and 83 mg isoflavones) or the control supplement (25 g casein and 10 g cellulose). This was conducted after an overnight fasting from 0800 on the last day during the 6-week treatment with Abalon and the control supplement.

Analytical methods

Plasma and urinary glucose levels were measured by the glucose oxidase method. Serum insulin was determined by an enzyme-linked immunosorbent assay (ELISA) method (19). HbA_{1c} was measured by a commercial kit (Bio-Rad, Richmond, CA) (normal 3.5–5.5%). Free fatty acids were determined by a standard enzymatic colorimetric assay method using a commercial kit (Boehringer Mannheim, Mannheim, Germany). Triglycerides, total cholesterol, and HDL were measured on a Roche/Hitachi 917 Automatic Analyzer (Roche Diagnostics, Mannheim, Germany). LDL cholesterol was calculated. The functional activity of factor VII was determined by a coagulation procedure (20) and the functional concentration of fibrinogen with a modified Clauss assay (21). The protein concentration of fibronectin was determined with an ELISA method from American Diagnostica (Greenwich, CT). PAI-1 was determined with the Imulysse PAI kit from Biopool International (Ventura, CA) (22). The concentration of homocysteine was measured as S-adenosyl-L-methionine converted homocysteine with a competitive fluorescence polarization immunoassay using a monoclonal antibody from Abbott Laboratories (Abbott Park, IL) and a fluoresceinated tracer (reference interval 4.5–12.4 μmol/l). The protein concentration of von Willebrand factor was determined with an ELISA method using antibodies from DAKO (Glostrup, Denmark). Lipoprotein(a) [Lp(a)] was measured by a Mercodia Lp(a) radioimmunoassay kit (Uppsala, Sweden). Apolipoprotein (apo) B100 and apo A1 were measured on a Behring Nephelometer Analyzer II using antiserum and standard from Dade Behring (Marburg, Germany).

Statistical analysis

The incremental areas over the 240-min observation period were calculated geometrically as the incremental areas above fasting levels of glucose and insulin (23). Results are expressed as means ± SD. Mann-Whitney test was used to compare the height and age for the groups starting on Abalon (*n* = 12) and the control treatment (*n* = 8) at randomization, and Fischer's exact test was used to compare the distribution of sex between these two groups. Analysis of differences (within and between treatments) were performed using Wilcoxon's matched-pair signed-rank test regarding weight, waist, waist-to-hip ratio, 24-h BP, fasting values of the blood sample measurements, and urine determinations, whereas measures of glu-

Table 2—Composition of the diets of 20 type 2 diabetic subjects at the start of and after 6 weeks treatment

	Control		Abalon	
	Start	End	Start	End
Total energy (kcal/day)	2,021 ± 533	2,369 ± 550	2,040 ± 523	2,425 ± 547
Carbohydrate (% of energy)	48 ± 6	43 ± 7	47 ± 6	41 ± 6
Fat (% of energy)	30 ± 5	28 ± 5	30 ± 5	29 ± 5
Protein (% of energy)	19 ± 2	26 ± 4	19 ± 3	25 ± 3
Alcohol (% of energy)	4 ± 5	3 ± 4	4 ± 6	5 ± 5
Fiber (g/day)	27 ± 10	42 ± 11	26 ± 9	41 ± 10
Cholesterol (mg/day)	327 ± 106	319 ± 220	290 ± 109	363 ± 197

Data are means ± SD.

cose and insulin responses were made by analysis of variance with repeated measurements (SAS software, Cary, NC). *P* < 0.05 was considered statistically significant.

RESULTS— There were no significant differences in clinical characteristics before the Abalon and control treatments (Table 1). As seen, no difference occurred at the end of the two 6 weeks in weight, BMI, waist, WHR, BP, or pulse rate. On both treatments, the patients had a minor significant weight increase averaging 0.6 kg. Similar HbA_{1c}, fasting plasma glucose, and fasting plasma insulin levels were obtained as seen in Table 1. No statistically significant difference in 24-h urinary excretion of sodium, potassium, calcium, creatinine, or glucose was observed during the day the 24-h blood pressure was estimated (K.H., M.S., L.H., M.C., B.B., unpublished data).

Fasting blood lipids and other cardiovascular risk factors

Lipid profiles and other cardiovascular risk markers before and after 6 weeks of each dietary supplementation are summarized in Table 3. There were no significant differences at the beginning of each dietary supplementation (baseline) between plasma lipid concentrations, indicating that the wash-out period was sufficient. Abalon supplementation resulted in significantly lower levels of total cholesterol than placebo (5.11 ± 0.78 vs. 5.45 ± 0.88 mmol/l; *P* < 0.01), LDL cholesterol (3.01 ± 0.68 vs. 3.33 ± 0.72 mmol/l; *P* < 0.01), and apo B100 (0.86 ± 0.19 vs. 0.98 ± 0.25 g/l; *P* < 0.05), whereas similar HDL cholesterol (1.38 ± 0.35 vs. 1.33 ± 0.34 mmol/l; NS) and apo A1 (1.29 ± 0.06 vs. 1.36 ± 0.05 g/l; NS) were obtained. The percentage mean treatment difference between Abalon and

the control treatment assessed by Wilcoxon's test demonstrated significantly lower mean values after Abalon for LDL cholesterol (10 ± 15%; *P* < 0.05), triglycerides (22 ± 43%; *P* < 0.05), and apo B100 (30 ± 38%; *P* < 0.01), whereas total cholesterol did not reach statistical significance (8 ± 15%; *P* = 0.08). Also, the ratio of LDL cholesterol to HDL cholesterol was reduced by 12 ± 18% (*P* < 0.05), whereas the ratio between apo B100 and A1 was not significantly reduced (3 ± 11%; *P* = 0.07) by the soy supplementation.

As shown in Table 3, there was no change for the von Willebrand factor, factor VIIc, fibrinogen, or PAI-1. Interestingly, homocysteine was lower after Abalon compared with the control treatment both in absolute terms (11.6 ± 4.0 vs. 12.7 ± 4.7 μmol/l; *P* < 0.01) as well as in percentage treatment difference (14 ± 21%; *P* < 0.01), respectively.

Glucose and insulin responses

Glucose and insulin responses to Abalon compared with that from the control supplement (half-day dose) obtained during the test menu served the last day of the two 6-week periods showed similar response areas (above basal) during the 4-h observation periods for plasma glucose (533 ± 351 vs. 581 ± 333 mmol/l × 240 min) and serum insulin (51.2 ± 46.9 vs. 55.7 ± 45.8 nmol/l × 240 min).

CONCLUSIONS— In type 2 diabetic subjects, treatment with the soy-based dietary supplement Abalon for 6 weeks resulted in a significant (10%) reduction in LDL cholesterol, a 12% reduction in the LDL/HDL ratio, a nonsignificant (8%) reduction in total cholesterol, a 30% reduction in apo B100, and a 22% reduction in triglyceride levels; HDL cholesterol, how-

Table 3—Effects of a soy-based dietary supplement on cardiovascular risk markers in 20 type 2 diabetic subjects

	Control		Abalon		Abalon vs. control	Mean treatment difference (%)	
	Baseline	6 weeks*	Baseline	6 weeks†	P‡	(%)	P§
Cholesterol (mmol/l)							
Total	5.59 ± 0.81	5.45 ± 0.88	5.68 ± 0.84	5.11 ± 0.78	0.0041	-8 ± 15	0.0826
LDL	3.64 ± 0.80	3.33 ± 0.72	3.63 ± 0.78	3.01 ± 0.68	0.0044	-10 ± 16	0.0483
HDL	1.28 ± 0.29	1.33 ± 0.34	1.31 ± 0.22	1.38 ± 0.35	0.2024	0 ± 20	0.8517
Triglycerides (mmol/l)	1.70 ± 1.49	1.79 ± 1.17	1.70 ± 1.17	1.63 ± 0.97	0.3632	-22 ± 43	0.0400
Apo B100 (g/l)	0.95 ± 0.26	0.98 ± 0.25	1.09 ± 0.21	0.86 ± 0.19	0.0249	-30 ± 38	0.0027
Lp(a) (U/l)	32.3 ± 37.5	32.4 ± 39.8	29.5 ± 29.9	33.9 ± 37.7	0.3488	8 ± 34	0.1769
LDL/HDL ratio	2.95 ± 1.02	2.52 ± 0.62	2.82 ± 0.75	2.20 ± 0.61	0.0007	-12 ± 18	0.0120
Apo B100/apo A1 ratio	0.82 ± 0.17	0.73 ± 0.17	0.80 ± 0.17	0.68 ± 0.16	0.0056	-3 ± 11	0.0759
von Willebrand factor (%)	127 ± 31	124 ± 33	126 ± 27	124 ± 34	0.3251	-1 ± 23	0.6477
Factor VIIc (%)	105 ± 20	111 ± 20	104 ± 22	106 ± 18	0.0875	-3 ± 17	0.5958
Fibrinogen (μmol/l)	10.2 ± 2.6	10.0 ± 2.0	9.7 ± 1.8	9.8 ± 1.6	0.3632	-1 ± 21	1.0000
PAI-1 (ng/ml)	24 ± 15	23 ± 13	24 ± 13	21 ± 12	0.4973	-1 ± 63	0.6772
Homocysteine (μmol/l)	10.6 ± 2.6	12.7 ± 4.7	11.2 ± 3.9	11.6 ± 4.0	0.0040	-14 ± 21	0.0056

Data are means ± SD, unless otherwise indicated. *Treated with control supplement; †treated with Abalon; ‡significance of differences in Abalon and control treatments at week 6; §significance of mean treatment differences (%).

ever, remained unchanged. These results are fairly consistent with those in a recent meta-analysis with nondiabetic subjects (16). Thus, an average daily soy protein intake of 47 g induced a percentage reduction in total cholesterol of 9%, in LDL cholesterol of 13%, and in triglycerides of 11%. The initial serum cholesterol concentrations had a powerful effect on changes in total and LDL cholesterol concentrations in the group of subjects in the meta-analysis (16) of which many had moderate or severe hypercholesterolemia (>6.5 mmol/l). The lipid changes we observed included lower levels also of the ratio of LDL/HDL cholesterol and apo B100 after 6 weeks on Abalon. Such changes in lipid levels have been shown to be associated with less CAD (24–26). Because apo B is independently associated with cardiovascular disease and identifies high-risk phenotypes in normocholesterolemic type 2 diabetic patients (27), the 30% reduction induced by Abalon is noteworthy. It could be argued that the apparent difference in change in apo B100 versus the change in LDL cholesterol is enigmatic because there is one apo B molecule in the LDL particle. One explanation could be that the LDL particles have changed to larger less atherogenic particles during soy treatment. Another matter is that the LDL levels, in contrast to the apo B100 levels, are calculated not measured, which may have led to an underestimation in LDL cholesterol change and to some extent explain the apparent difference. Lp(a) is a cholesterol-carrying particle in the blood that is structurally sim-

ilar to LDL, with the addition of the apoprotein(a) moiety. Increasing evidence has indicated that Lp(a) is also an independent risk factor for coronary heart disease (28). Despite its resemblance to the LDL particle, Lp(a) levels in the blood are not responsive to most conventional diet approaches to lowering LDL cholesterol. In line with this, we did not show any significant impact of Abalon on Lp(a). Table 3 shows a few inconsistencies in statistical significance between the percentage mean treatment differences and the absolute values of which the percentage of mean differences is considered most relevant.

It is puzzling that the weight increase during the two study periods only accounts for 0.6 kg on average considering the extra energy intake recorded. The most likely explanation is that the subjects are less likely to underreport at the end rather than at the start of the study periods because of the tight weight control during the study periods. Concomitantly with an increased protein and energy intake with Abalon, patients should be encouraged to reduce dietary fat and protein in their habitual diet. It appears that the wash-out period between dietary supplement periods was adequate because our subjects had returned to their basal lipid levels and weights before the second 6-week period. Compliance with the dietary supplement was good in our study.

The mechanisms for the lipid-lowering effect of Abalon are not known. There is persuasive evidence to implicate soy protein in

the cholesterol-lowering effect. Thus, soy products provide a large amount of protein with high-quality amino acids, which seems to upregulate LDL receptors directly by 50% or more (29). The question of the mechanism involved is important, because selection of the protein source plays a critical role in the development of products with a greater or lesser likelihood of reducing serum cholesterol in humans. There is abundant evidence that both purified viscous soluble fiber and soluble fiber in foods reduce serum cholesterol levels (30). The action of soluble fiber seems to relate to an increase in fecal bile acid loss (31). That dietary soluble fiber in large amounts can result in a modest decrease in total and LDL cholesterol without changing HDL cholesterol also in people with diabetes has been demonstrated in several studies (32,33). Lo (34) reviewed data on soy fiber and reported that the addition of soy cotyledon fiber to diets of hypercholesterolemic individuals is effective in reducing total and LDL cholesterol. The combination of soy protein and cotyledon fiber therefore may be additive in cholesterol-lowering effects. The meta-analysis of Anderson et al. (16), however, indicated that a considerable proportion of the effect of soy products on serum cholesterol might be linked to the effects of isoflavones. The amount of isoflavones in Abalon is high (minimum 165 mg/ 50 g soy protein) because of the type of processing used to produce the product. Since isoflavones are compounds that have structure similar to estrogens and bind to estrogen receptors, it has been postulated

that this may be responsible for the effects soy protein has on serum lipids (35). Two proposed mechanisms for a hypocholesterolemic impact of isoflavones are the up-regulation of LDL receptors and/or inhibition of endogenous cholesterol synthesis. A reduction in total cholesterol has been observed after consumption of 45 mg isoflavones/day relative to levels during a control period with isoflavone-free products (35). However, in other studies, the cholesterol-lowering soy products were low in phyto-oestrogens, questioning this mechanism of action (28).

Whereas Abalon caused no change in the procoagulants fibrinogen, factor VIIc, and von Willebrand factor or in the fibrinolytic marker PAI-1 in the type 2 diabetic subjects, it is noteworthy that it reduced the level of homocysteinemia by 14% compared with control. Thus, many significant studies indicate an effect by elevated homocysteine on CAD occurrence, progression, and recurrence that is independent of traditional risk factors (7,8). Also in type 2 diabetic subjects, a strong correlation with CAD has been demonstrated (9,10). This differential effect on homocysteinemia observed may at least in part be ascribed to the higher methionine content in casein compared with isolated soy protein (3.0 vs. 1.0 g/100-g product).

A very modest improvement in blood glucose attributed to fiber intake from soy beans has been reported in type 2 diabetic subjects both in some acute (17) and some more long-term experiments (36), while this was not seen in other studies (37). No change in insulin levels occurred (17,38). In the present study, similar results were obtained both regarding fasting blood glucose and insulin levels as well as in response to test meal with Abalon.

In conclusion, these results indicate beneficial effects of dietary supplementation with Abalon on cardiovascular risk markers in type 2 diabetic subjects. This improvement is seen even in individuals with near-normal lipid values. Ingestion of soy products has been shown to further improve the effectiveness of low-fat diets in nondiabetic subjects (38–40). Thus, a dietary supplementation with Abalon in type 2 diabetic patients may provide an acceptable and effective option for blood lipid control, thereby postponing the requirement for drug therapy for these patients.

Acknowledgments — This study was supported by grants from Aarhus University and

Nutri Pharma ASA, Oslo, Norway, which also provided the Abalon and placebo.

We thank Tove Skrumsager and Kirsten Eriksen for excellent technical assistance and Eva Pedersen, RD, for diet preparation and monitoring and calculating the food records.

References

- Kannel WB, D'Agostino RB, Wilson PW, Belanger AJ, Gagnon DR: Diabetes, fibrinogen, and risk of cardiovascular disease: the Framingham experience. *Am Heart J* 120: 672–676, 1990
- Laakso M, Ronnema T, Lehto S, Puukka P, Kallio V, Pyorala K: Does NIDDM increase the risk of coronary heart disease similarly in both low- and high-risk populations? *Diabetologia* 38:487–493, 1995
- Kannel WB, McGee DL: Diabetes and cardiovascular disease: the Framingham Study. *JAMA* 241:2035–2038, 1979
- Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
- Bierman EL: George Lyman Duff Memorial Lecture: atherogenesis in diabetes. *Arterioscler Thromb* 12:647–656, 1992
- Reaven GM, Lithell H, Landsberg L: Hypertension and associated metabolic abnormalities: the role of insulin resistance and the sympathetic-adrenal system. *N Engl J Med* 334:374–381, 1996
- Robinson K, Mayer EL, Miller DP, Green R, van Lente F, Gupta A, Kottke-Marchant K, Savon SR, Selhub J, Nissen SE, Kutner M, Topol EJ, Jacobsen DW: Hyperhomocysteinemia and low pyridoxal phosphate: common and independent reversible risk factors for coronary artery disease. *Circulation* 92:2825–2830, 1995
- Nygård O, Nordrehaug JE, Refsum H, Ueland PM, Farstad M, Vollset SE: Plasma homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med* 337:230–236, 1997
- Okada E, Oida K, Tada H, Asazuma K, Eguchi K, Tohda G, Kosak S, Takahashi S, Miyamori I: Hyperhomocysteinemia is a risk factor for coronary arteriosclerosis in Japanese patients with type 2 diabetes. *Diabetes Care* 22:484–490, 1999
- Hoogeveen EK, Kostense PJ, Beks PJ, Mackaay AJ, Jakobs C, Bouter LM, Heine RJ, Stehouwer CD: Hyperhomocysteinemia is associated with an increased risk of cardiovascular disease, especially in non-insulin-dependent diabetes mellitus: a population-based study. *Arterioscler Thromb Vasc Biol* 18:133–138, 1998
- Lichtenstein AH, Kennedy E, Barrier P, Danford D, Ernst ND, Grundy SM, Leveille GA, Van Horn L, Williams WC, Booth SL: Dietary fat consumption and health. *Nutr Rev* 56:S3–S19, 1998
- Salmeron J, Ascheiro A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL, Willett WC: Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care* 20:545–550, 1997
- Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC: Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *JAMA* 277:472–477, 1997
- Ha TKK, Lean MEJ: Recommendations for the nutritional management of patients with diabetes mellitus. *Eur J Clin Nutr* 52: 467–481, 1998
- Potter SM: Soy protein and cardiovascular disease: the impact of bioactive components in soy. *Nutr Rev* 56:231–235, 1998
- Anderson JW, Johnstone BM, Cook-Newell ME: Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med* 333:276–282, 1995
- Tsai AC, Vinik AI, Lasichak L, Lo GS: Effects of soy polysaccharide on postprandial plasma glucose, insulin, glucagon, pancreatic polypeptide, somatostatin, and triglyceride in obese diabetic patients. *Am J Clin Nutr* 45:596–601, 1987
- The Danish Veterinary and Food Administration: *The Composition of Foods*. 4th ed. Copenhagen, Denmark, Danish Veterinary and Food Administration, 1996
- Andersen L, Dinesen B, Jørgensen PN, Poulsen F, Røder M: Enzyme immunoassay for intact human insulin in serum or plasma. *Clin Chem* 39:578–582, 1993
- Bladbjerg EM, Marckmann P, Sandstrøm B, Jespersen J: Non-fasting factor VII coagulant activity (FVII:C) increased by high-fat diet. *Thromb Haemost* 71:755–758, 1994
- Jespersen J, Sidelmann J: A study of the conditions and accuracy of the thrombin time assay of plasma fibrinogen. *Acta Haematol* 67:2–7, 1982
- Declerck PJ, Moreau H, Jespersen J, Gram J, Klufft C: Multicenter evaluation of commercially available methods for the immunological determination of plasminogen activator inhibitor-1 (PAI-1). *Thromb Haemost* 70:858–863, 1993
- Jenkins DJA, Wolever TMS, Taylor RH, Barker HM, Fielden H, Baldwin JM, Bowling AC: Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr* 34:362–366, 1981
- Kannel WB, Castelli WP, Gordon T: Cholesterol in the prediction of atherosclerotic disease: new perspectives based on the Framingham Study. *Ann Intern Med* 90:85–91, 1979
- Arntzenius AC, Kromhout D, Barth JD, Reiber JH, Brusckhe AV, Buis B, van Gent CM, Kempen-Voogd N, Strikwerda S, van der Velde EA: Diet, lipoproteins, and the progression of coronary atherosclerosis: the

- Leiden Intervention Trial. *N Engl J Med* 312: 805–811, 1985
26. Lamarche B, Moorjani S, Lupien PJ, Catin B, Bernard PM, Dagenais GR, Despres JP: Apolipoprotein A-1 and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Quebec cardiovascular study. *Circulation* 94:273–278, 1996
 27. Wagner AM, Perez A, Calvo F, Bonet R, Castellvi A, Ordóñez J: Apolipoprotein(B) identifies dyslipidemic phenotypes associated with cardiovascular risk in normocholesterolemic type 2 diabetic patients. *Diabetes Care* 22:812–817, 1999
 28. Scanu AM: Lipoprotein(a): a genetic risk factor for premature coronary heart disease. *JAMA* 267:3326–3329, 1992
 29. Sirtori CR, Lovati MR, Manzoni C, Gianazza E, Bondioli A, Staels B, Auwerx J: Reductions of serum cholesterol by soy proteins: clinical experience and potential molecular mechanisms. *Nutr Metab Cardiovasc Dis* 8:334–340, 1998
 30. Anderson JW, Garrity TF, Wood CL, Whitis SE, Smith BM, Oeltgen PR: Prospective, randomized, controlled comparisons of the effects of low-fat and low-fat plus high-fiber diets on serum lipid concentrations. *Am J Clin Nutr* 56:887–894, 1992
 31. Lia A, Hallmans G, Sandberg AS, Sundberg B, Aman P, Anderson H: Oat beta-glucan increases bile acid excretion and a fiber-rich barley fraction increases cholesterol excretion in ileostomy subjects. *Am J Clin Nutr* 62:1245–1251, 1995
 32. Uusitupa M, Siitonen O, Savolainen K, Silvasti M, Penttilä I, Parviainen M: Metabolic and nutritional effects of long-term use of guar in the treatment of noninsulin-dependent diabetes of poor metabolic control. *Am J Clin Nutr* 49:345–351, 1989
 33. Nuttall FQ: Dietary fiber in the management of diabetes. *Diabetes* 42:503–508, 1993
 34. Lo GS: Physiological effects of physicochemical properties of soy cotyledon fiber. In *New Developments in Dietary Fiber*. Gurda I, Brine CJ, Eds. New York, Plenum, 1990, p. 49–66
 35. Tham DM, Gardner CD, Haskell WL: Potential health benefits of dietary phytoestrogens: a review of the clinical, epidemiological, and mechanistic evidence. *J Clin Endocrinol Metab* 83:2223–2235, 1998
 36. Mahalko JR, Sandstead HH, Johnson LK, Inman LF, Milne DB, Warner RC, Haunz EA: Effect of consuming fiber from corn bran, soy hulls, or apple powder on glucose tolerance and plasma lipids in type II diabetes. *Am J Clin Nutr* 39:25–34, 1984
 37. Thomas BL, Laine DC, Goetz FC: Glucose and insulin response in diabetic subjects: acute effects of carbohydrate level and the addition of soy polysaccharides in defined-formula diets. *Am J Clin Nutr* 48:1048–1052, 1988
 38. Wong WW, Smith EO, Stuff JE, Hachey DL, Heird WC, Pownell HJ: Cholesterol-lowering effect of soy protein in normocholesterolemic and hypercholesterolemic men. *Am J Clin Nutr* 68 (Suppl. 6):1385S–1389S, 1998
 39. Jenkins DJA, Kendall CWC, Mehling CC, Parker T, Rao V, Agarwal S, Novokmet R, Jones PJH, Raeini M, Story JA, Furumoto E, Vidgen E, Griffin LC, Cunnane SC, Ryan MA, Connelly PW: Combined effect of vegetable protein (soy) and soluble fiber added to a standard cholesterol-lowering diet. *Metabolism* 48:809–816, 1999
 40. Jenkins DJA, Kendall CWC, Vidgen E, Mehling CC, Parker T, Seyler H, Faulkner D, Garsetti M, Griffin LC, Agarwal S, Rao V, Cunnane SC, Ryan MA, Connelly PW, Leiter LA, Vuksan V, Josse R: The effect on serum lipids and oxidized low-density lipoprotein of supplementing self-selected low-fat diet with soluble-fiber, soy, and vegetable protein foods. *Metabolism* 49:67–72, 2000