Effect of alginate supplementation on weight loss in obese subjects completing a 12-wk energy-restricted diet: a randomized controlled trial\textsuperscript{1–3}

Morten Georg Jensen, Mette Kristensen, and Arne Astrup

ABSTRACT

Background: Acute studies with alginate-based preloads suggested that these strong gelling fibers may induce increased feelings of satiety and reduce energy intakes. However, the long-term efficacy and safety of alginate supplementation on body weight regulation are lacking.

Objective: The primary aim of the study was to investigate the effects in subjects of alginate supplementation in conjunction with energy restriction (\(-300\) kcal/d) on loss of body weight and fat and, second, on metabolic risk markers in comparison with a placebo group.

Design: In a parallel, double-blind, placebo-controlled study, we randomly assigned 96 obese subjects to either an energy-restricted diet plus a placebo preload supplement or an energy-restricted diet plus an alginate-based preload supplement (15 g fiber). The preload was administered as a beverage 3 times/d before main meals for a period of 12 wk.

Results: No differences in loss of body weight and fat between groups were shown in the intention-to-treat (ITT) analysis (\(P > 0.1\)). However, in the completer analysis (\(n = 80\)), we showed a greater weight loss with alginate (6.78 \(\pm\) 3.67 kg) than with the placebo (5.04 \(\pm\) 3.40 kg) (\(P = 0.03\)), which was mainly attributed to a reduction in the percentage of body fat (\(P = 0.03\)). In the ITT analysis, a larger decrease in systolic and diastolic blood pressure was shown in the placebo group than in the alginate group (\(P < 0.05\)). Plasma concentrations of glucose, insulin, C-reactive protein, and ghrelin, HOMA-IR, and lipid metabolism did not differ between treatment groups in the ITT analysis (\(P > 0.1\)).

Conclusion: These results suggest that alginate supplementation as an adjunct to energy restriction may improve weight loss in obese subjects who complete a 12-wk dietary intervention. This trial was registered at clinicaltrials.gov as NCT01231178.


INTRODUCTION

The current obesity epidemic, with its associated metabolic consequences such as type 2 diabetes and cardiovascular disease (CVD)\textsuperscript{4}, requires new dietary tools for better control of hunger feelings, body weight, and obesity-related metabolic complications. One method to combat this growing health problem could be by increased dietary fiber consumption because an inverse association between fiber consumption and changes in body weight and fat has consistently been shown (1–4). To some extent, this finding has been supported by a number of intervention studies that examined the effect of high-fiber diets, or supplementation with fiber, on weight management (5–9). This relation has been well summarized by Howarth et al (10), whereby an increased dietary fiber consumption of 14 g/d was associated with a body weight loss of 1.9 kg over 3.8 mo and with greater effect in more obese subjects.

Alginate is a gelling polysaccharide and a structural component extracted from marine brown algae. The presence of alginate provides the mechanical strength and flexibility of seaweed, and the fiber is composed of mannuronic and guluronic acids, which influence its viscous physiologic properties. Sodium alginate is the most commonly used alginate, and for decades, the food industry has widely used alginates as additives because of their gelling, viscosifying, and stabilizing properties (11). Alginites have the ability to gel either in the presence of multivalent cations (ie, Ca\textsuperscript{2+}) or if the pH of the alginate-containing solution is lowered below the pKa value of the constituting acids (12). Furthermore, the gel strength is affected by the guluronic acid content. The ingestion of sodium alginate and subsequent gelation in the stomach have been shown to modulate human-appetite sensation in acute settings (13–19).

The proposed mechanisms for the effect of sodium alginate fibers in combination with calcium include changes in intrinsic physical properties such as gel formation and viscosity, and changes of gastric contents. This effect may cause decreased gastric emptying and nutrient absorption with blunting of postprandial glucose and insulin responses, all of which promote greater satiety (20). If some of these acute effects that have been observed are sustained with habitual consumption of alginate, it could potentially have beneficial effects on hunger management during weight-loss attempts. To our knowledge, the efficacy and tolerability of long-term consumption of sodium alginate fiber

\textsuperscript{1} From the Department of Human Nutrition, Faculty of Science, University of Copenhagen, Frederiksberg, Denmark.

\textsuperscript{2} Supported by grants from S-Biotek Holdings ApS and FOOD Research School/SCIENCE, University of Copenhagen.

\textsuperscript{3} Address correspondence to M Georg Jensen, Department of Human Nutrition, The Faculty of Science, University of Copenhagen, Rolighedsvej 30, DK-1958 Frederiksberg C, Denmark. E-mail: mmgj@life.ku.dk.

\textsuperscript{4} Abbreviations used: AE, adverse event; ComP, completer population; CVD, cardiovascular disease; ER, energy requirements; Hb A\textsubscript{1c}, hemoglobin A1C; ITT, intention-to-treat analysis; VAS, visual analogue scale.

exclusively on changes in body weight and fat still need to be investigated in a randomized controlled trial. Therefore, we investigated whether 12 wk of supplementation with a preload beverage on the basis of a guluronic acid–rich sodium alginate and calcium in combination with energy-restricted diets could enhance weight loss and decrease body fat mass in obese subjects compared with the consumption of an energy-restricted diet alone. Furthermore, we examined the effect on risk markers of CVD and type 2 diabetes.

SUBJECTS AND METHODS

Study design

The study was designed as a double-blinded, parallel-intervention study of 12-wk duration in which study participants were randomly assigned into 2 groups who consumed either an energy-restricted diet plus an alginate-based preload supplement or an energy-restricted diet plus a control preload supplement before each of the 3 main meals. The study was carried out at the Department of Human Nutrition, Faculty of Life Sciences, University of Copenhagen. Subjects gave their written consent after having received verbal and written information about the study. The Ethical Committee of the Capital Region of Denmark approved the study (journal H-2-2009-155) as being in accordance with the Helsinki II Declaration.

Subjects

Volunteers were recruited from areas around Copenhagen, Denmark, through advertising in local and national newspapers. The inclusion criteria were as follows: age of 20–55 y and with moderate to severe obesity [BMI (in kg/m²): 30–45]. Exclusion criteria were as follows: any known chronic illnesses (such as metabolic disease, liver and kidney disease, or CVD), hypertension (>160/100 mm Hg), elevated fasting total cholesterol (>6.5 mmol/L), diabetes or fasting glucose >7.0 mmol/L, a high level of physical activity (>10 h/wk), the use of dietary supplements, a regular use of medications (not including contraceptives), and smoking. A total of 120 men and women were assessed for eligibility and attended a screening visit at which body weight, height, waist circumference, blood pressure, and fasting biochemical markers for liver and kidney disease, diabetes, and CVD were measured. In addition, subjects were interviewed concerning general health, eating habits, dieting, food intolerances and dislikes, and work situations to assess eligibility for enrollment.

Test supplement

The sodium alginate used in the study (Protanal LFR 5/60; FMC Biopolymers) was a low-viscosity (particle size: 250 microns; molecular weight: ~50,000 kDa) and strong-gelling type with 65–75% guluronic acid extracted from the brown seaweeds Laminaria hyperborea and Laminaria digitata. The alginate supplement was administered as a powder mix (22 g in 7 × 10-cm foil packets) based on 3% alginate (15 g/500 mL H₂O) flavored with natural black current aroma (6 g) and sweetened with aspartame (0.08 mg) per preload dose. In addition, a calcium source (500 mg CaCO₃) was added for a sufficiently strong gel formation in the stomach. The control supplement (13 g in 7 × 10-cm foil packets) was matched with regard to energy content (~55 kcal), flavor, appearance, and calcium content and was based on a 1.2% combination of maltodextrin and sucrose per preload dose. The choice of maltodextrin was based on the fact that the organoleptic and physicochemical properties are important when selecting an adequate control, and digestible carbohydrates, such as maltodextrin, have been proposed as an acceptable control type (21–23).

All supplements administered were blinded to the subjects and investigation site. Both supplements were mixed and packed in small one-dose airtight aluminum foil sachets (by Dan Blends A/S) before the start of the study, packed in boxes of 50 doses each, and delivered to the Department of Human Nutrition and stored in a locker. Subjects were instructed to mix and shake one dose of test-supplement powder with 500 mL cold tap water and, after 15 min hydration, to consume the preload formulation 30 min before breakfast, lunch, and dinner.

Physicochemical properties of test supplements

Viscosities of the test supplements mixed with water were measured by using a Bohlin C-VOR rheometer (Malvern Instruments Ltd). The alginate or control drinks were transferred to the rheometer cup and left without shear for 5 min to achieve equilibrium before measurements were taken at a constant temperature of 20°C and at 15 different shear rates that ranged from 0.1 to 90 L/s. The viscosity measured was independent of the shear rate (ie, the liquid was Newtonian) and an average viscosity was reported.

Gelling properties of test supplements at acidic conditions similar to stomach pH were studied as well. The viscosity of non-Newtonian materials, such as these acid gels, is dependent on the applied shear rate during measurement. Therefore, oscillatory shear rheology was used to quantify mechanical properties [denoted gel strength (Pa)] of gels formed from the test supplement at pH 2.0. Oscillatory shear rheology was performed by using a Bohlin C-VOR rheometer at a frequency of 1 Hz. During oscillations, the stress amplitude was controlled and gradually increased from 1 to 500 Pa while the strain amplitude was recorded, and from this, the material constants, elastic modulus, and viscous modulus were obtained. The measured elastic modulus was almost constant at a wide range of applied amplitudes, as is commonly observed for many materials. Therefore, an average elastic modulus (Pa) was calculated and denoted as gel strength (Pa).

Weight-loss program

Apart from consuming test supplements, participants followed an energy-restricted diet with a free choice of food items to obtain a small weight loss (~0.5 kg/wk). The weight-loss program was based on an educational system that consisted of 4 color-coded isonenergetic interchangeable units (60 kcal) (24). Each color represented a different nutrient composition: blue counters for foods rich in protein, green counters for foods rich in complex carbohydrates and dietary fiber, yellow counters for foods rich in simple carbohydrates, and red counters for foods rich in fat. Subjects were requested to adhere to a diet of ≥5 counters less (~300 kcal/d) than their energy requirements (ERs) per day but no less than 20 counters/d (1200 kcal/d). ERs were assessed on the basis of age, sex, weight, and physical activity level (set to 1.3) as follows (25):
Analyzer (Diagnostic Products Corp); the intraassay CV was 2.5%.

with the use of an IMMULITE 1000 Automated Immunoassay assay (Immulite/immuliter 1000 insulin; Diagnostic Products Corp) analyzed by using an enzymatic colorimetric method performed in an Cue Hb 201+ analyzer. Blood glucose concentrations were analyzed by using a dry-chemistry photometric method with a COBAS MIRA Plus chemistry analyzer (Roche Diagnostic Systems Inc); intraassay CVs were 0.9% and 0.6%, respectively. HDL cholesterol was measured in serum by using a homogeneous enzymatic colorimetric test kit (Roche HDL-C Plus 2nd generation; Roche Diagnostics GmbH) on a COBAS MIRA Plus chemistry analyzer; the intraassay CV was 1.2%. LDL-cholesterol concentrations were calculated by using Friedewald’s equation (27) as follows:

\[
\text{LDL} = \text{total cholesterol} - \text{HDL} - (\text{triglycerides} \div 2.17)
\]

Ghrelin hormone concentrations were measured by using the enzyme-linked immunosorbent assay method on an SLT-Rainbow ELISA reader (SLT-LabInstruments Gmbh) with a Millipore Human Ghrelin Elisa kit (Millipore Corp); the intraassay CV was 2.0%. Serum high-sensitivity C-reactive protein was measured by using a solid-phase chemiluminescent immunometric assay with an IMMULITE 1000 Automated Immunnoassay Analyzer (Diagnostic Products Corp).

Gastrointestinal adverse events registration and palatability measurement

A visual analogue scale (VAS), which was 100 mm in length with words anchored at each end that expressed the most-positive and most-negative rating, was used to answer questions regarding subjective feelings of the following gastrointestinal symptoms after consumption of the test supplement: heartburn, reflux, nausea, distension, abdominal pain, constipation, increased gas production, and diarrhea. For example, a question was “Did you feel any nausea today after consuming the supplement?,” which was anchored at the low end with “none at all” and with the opposing term “extremely much” at the high end. Registrations were collected in the first week after randomization and in weeks 6 and 12 of the study period. In addition to the VAS registration, all subjects had the possibility to report spontaneous adverse events (AEs) on all visiting days at the Department of Human Nutrition, which took place every second week during the whole study. The staff documented and graded AEs as mild, moderate, or severe conditions.

The palatability of the test supplement was also recorded by using the VAS method as described by Flint et al (28) and was filled in after consumption of the supplement every day for the first week after randomization, week 6, and the last week of the study period. The question was “How did you find the supplement taste today?,” which was anchored at the low end with “very bad” and with the opposing term “very good” at the high end.

Compliance measurements

All subjects were instructed to return both opened and unopened supplement packaging on visiting days at the Department of Human Nutrition at every second week during the intervention. The returned packaging was counted for tracking the adherence of subjects to the study protocol and calculated as a percentage.

For women: ER (MJ/d) = 1/3 \times (0.0364 \times \text{weight} + 3.47) (1)

For men: ER (MJ/d) = 1/3 \times (0.0485 \times \text{weight} + 3.67) (2)

A maximum of one-third of the counters had to be red, and a minimum of 6 blue counters had to be consumed daily, which provided a minimum daily intake of 60 g protein. Participants were free to distribute the energy intake over the whole day, but they were encouraged not to eat during the evening and night. Participants met individually with a qualified dietitian 4 times during the study period and were instructed to keep a complete food diary throughout the study period.

Anthropometric measures

All measurements were performed at the Department of Human Nutrition in the morning after subjects had fasted for ≥10 h. Body weight was measured by using an electronic scale while the subjects were only underwear and no shoes. Body composition was measured by using dual-energy x-ray absorptiometry (Lunar Radiation Co, GE). Height was measured to the nearest 0.5 cm by using a wall-mounted stadiometer while the subjects were wearing no shoes. Waist circumference was measured to the nearest 0.5 cm at the narrowest point between the iliac crest and the lowest rib.

Laboratory measurements

Blood pressure was measured by using a fully automatic blood pressure monitor (Omron M4-I; Omron Healthcare Europe BV). A mean of 2 measurements was used. Each participant rested in a supine position with the head slightly elevated for 10 min before blood pressure measurements.

Blood samples were collected at baseline (week 0) and week 12 without stasis through an indwelling catheter after 10 min of rest in the supine position. Blood samples were kept on ice, centrifuged for 10 min at 2500 \( \times \) g at 4°C, separated into plasma and serum, and kept at −80°C until analyzed. Blood for glucose and ghrelin analysis was collected in iced tubes containing EDTA prepared with sodium fluoride. Blood for all other analyses was collected in plain tubes.

Biochemical procedures

Hemoglobin concentrations were analyzed by using a HemoCue Hb 201+ analyzer. Blood glucose concentrations were analyzed by using an enzymatic colorimetric method performed in an ABX Pentra (HORIBA ABX); the intraassay CV was 0.8%. Insulin was measured by using a solid-phase, 2-site chemiluminescent immunometric assay (Immulite/immuliter 1000 insulin; Diagnostic Products Corp) with the use of an IMMULITE 1000 Automated Immunoassay Analyzer (Diagnostic Products Corp); the intraassay CV was 2.5%. Hemoglobin A1C (Hb A1C) was measured by using an immunoturbidimetric assay with a Unimate Hb A1C test kit (Roche Diagnostics) on a COBAS MIRA Plus chemistry analyzer (Roche Diagnostic Systems Inc); the intraassay CV was 1.4%. HOMA-IR was calculated as

\[
\text{Insulin resistance} = \frac{\text{glucose (mmol/L)} \times \text{insulin (pmol/L)}}{135 (26)}
\]

Serum concentrations of total triacylglycerol and total cholesterol were assessed by using colorimetric test kits (Roche TG, Roche Diagnostics GmbH) on a COBAS MIRA Plus chemistry analyzer (Roche Diagnostic Systems Inc); intraassay CVs were 0.9% and 0.6%, respectively. HDL cholesterol was measured in serum by using a homogeneous enzymatic colorimetric test kit (Roche HDL-C Plus 2nd generation; Roche Diagnostics GmbH) on a COBAS MIRA Plus chemistry analyzer; the intraassay CV was 1.2%. LDL-cholesterol concentrations were calculated by using Friedewald’s equation (27) as follows:

\[
\text{LDL} = \text{total cholesterol} - \text{HDL} - (\text{triglycerides} \div 2.17)
\]

For men: ER (MJ/d) = 1/3 \times (0.0364 \times \text{weight} + 3.47) (1)

For women: ER (MJ/d) = 1/3 \times (0.0485 \times \text{weight} + 3.67) (2)

A maximum of one-third of the counters had to be red, and a minimum of 6 blue counters had to be consumed daily, which provided a minimum daily intake of 60 g protein. Participants were free to distribute the energy intake over the whole day, but they were encouraged not to eat during the evening and night. Participants met individually with a qualified dietitian 4 times during the study period and were instructed to keep a complete food diary throughout the study period.

Anthropometric measures

All measurements were performed at the Department of Human Nutrition in the morning after subjects had fasted for ≥10 h. Body weight was measured by using an electronic scale while the subjects were only underwear and no shoes. Body composition was measured by using dual-energy x-ray absorptiometry (Lunar Radiation Co, GE). Height was measured to the nearest 0.5 cm by using a wall-mounted stadiometer while the subjects were wearing no shoes. Waist circumference was measured to the nearest 0.5 cm at the narrowest point between the iliac crest and the lowest rib.

Laboratory measurements

Blood pressure was measured by using a fully automatic blood pressure monitor (Omron M4-I; Omron Healthcare Europe BV). A mean of 2 measurements was used. Each participant rested in a supine position with the head slightly elevated for 10 min before blood pressure measurements.

Blood samples were collected at baseline (week 0) and week 12 without stasis through an indwelling catheter after 10 min of rest in the supine position. Blood samples were kept on ice, centrifuged for 10 min at 2500 \( \times \) g at 4°C, separated into plasma and serum, and kept at −80°C until analyzed. Blood for glucose and ghrelin analysis was collected in iced tubes containing EDTA prepared with sodium fluoride. Blood for all other analyses was collected in plain tubes.

Biochemical procedures

Hemoglobin concentrations were analyzed by using a HemoCue Hb 201+ analyzer. Blood glucose concentrations were analyzed by using an enzymatic colorimetric method performed in an ABX Pentra (HORIBA ABX); the intraassay CV was 0.8%. Insulin was measured by using a solid-phase, 2-site chemiluminescent immunometric assay (Immulite/immuliter 1000 insulin; Diagnostic Products Corp) with the use of an IMMULITE 1000 Automated Immunoassay Analyzer (Diagnostic Products Corp); the intraassay CV was 2.5%. Hemoglobin A1C (Hb A1C) was measured by using an immunoturbidimetric assay with a Unimate Hb A1C test kit (Roche Diagnostics) on a COBAS MIRA Plus chemistry analyzer (Roche Diagnostic Systems Inc); the intraassay CV was 1.4%. HOMA-IR was calculated as

\[
\text{Insulin resistance} = \frac{\text{glucose (mmol/L)} \times \text{insulin (pmol/L)}}{135 (26)}
\]

Serum concentrations of total triacylglycerol and total cholesterol were assessed by using colorimetric test kits (Roche TG, Roche Diagnostics GmbH) on a COBAS MIRA Plus chemistry analyzer (Roche Diagnostic Systems Inc); intraassay CVs were 0.9% and 0.6%, respectively. HDL cholesterol was measured in serum by using a homogeneous enzymatic colorimetric test kit (Roche HDL-C Plus 2nd generation; Roche Diagnostics GmbH) on a COBAS MIRA Plus chemistry analyzer; the intraassay CV was 1.2%. LDL-cholesterol concentrations were calculated by using Friedewald’s equation (27) as follows:

\[
\text{LDL} = \text{total cholesterol} - \text{HDL} - (\text{triglycerides} \div 2.17)
\]
Statistical methods

The sample-size calculation was based on 80% power to detect a difference in weight loss of 1.5 kg with an estimated weighed SD of 1.5 (α = 0.05, β = 1–0.8). This calculation required 80 subjects to complete the intervention. Because we experienced a dropout rate of 20% from the previously conducted pilot study (29), 96 subjects were randomly assigned to allow for a similar dropout rate during the intervention period.

Subjects were randomly assigned to either 1 of 2 treatments by using a 4-block randomization. A validated computer program (Query Advisor, version 6.0; Statistical Solutions) was used to generate the random allocation sequence, which was performed by statistical staff outside the University of Copenhagen at the Universitetshospital Basel.

The statistical analysis was performed in the following 2 ways: 1) an intention-to-treat (ITT) analysis was performed on body weight, body composition, and metabolic risk factors in which all subjects were included (n = 96) with dropouts assigned an endpoint value as of baseline; the ITT analysis was also performed on AEs and blood pressure in relation to safety; and 2) a treatment efficacy analysis was performed on all subjects who completed the 12-wk intervention, which was defined as a completer population (ComP) and was independent of the degree of compliance.

All statistical analyses were performed with SAS System for Windows software (release 9.1, SAS institute Inc). All data are presented as means ± SEs unless otherwise indicated, and the statistical significance level was defined as P < 0.05. The homogeneity of variance and normal distribution were inspected by using residual plots and normal probability plots. At baseline, subject characteristics in the 2 treatment groups were compared by using unpaired t tests. An ANCOVA, with baseline body weight, lean body mass, and sex included as covariates, was used to assess the difference between treatment groups for all variables measured at weeks 0 and 12. For variables measured at weeks 0, 2, 4, 6, 8, 10, and 12, respectively, a mixed model of repeated measures ANCOVA, with baseline values and sex included as covariates, was applied to examine the effect of treatment and time and their interaction on changes in anthropometric and biochemical parameters. If the main effect of treatment was significant, post hoc comparisons were made by using Tukey-Kramer adjustment of P values.

The number of dropouts and number of subjects who experienced spontaneous AEs were compared between treatments by using Pearson’s chi-square test. In addition, the mean maximum experienced spontaneous AEs were compared between treatments by using unpaired t tests. An ANCOVA, with baseline body weight and sex included as covariates, was used to assess the difference between treatment groups for all variables measured at weeks 0, 2, 4, 6, 8, 10, and 12, respectively, a mixed model of repeated measures ANCOVA, with baseline values and sex included as covariates, was applied to examine the effect of treatment and time and their interaction on changes in anthropometric and biochemical parameters. If the main effect of treatment was significant, post hoc comparisons were made by using Tukey-Kramer adjustment of P values.

RESULTS

Physicochemical properties and palatability of test supplements

The viscosity of the supplement was measured to be 0.008 Pa·s for the control formulation and 0.026 Pa·s for the alginate-based formulation. After the acid gel formation of test supplements, the gel strength for the alginate-based formulation was measured to be ~1585 Pa. No gel was formed from the control formulation.

In the ITT analysis, we showed an effect of treatment (P < 0.0001) and time (P = 0.048) with a higher VAS score and, thereby, a better taste of the control supplement (63.7 ± 3.5 mm) than of alginate-based supplement (38.9 ± 3.7 mm) over the whole study period.

Subjects, compliance, and dietary intake

A total of 96 subjects were shown to be eligible to participate in the study, and 48 subjects were randomly assigned to each treatment group (Figure 1). A total of 80 subjects completed the whole intervention, and no differences in dropout rates between groups were shown [alginate group (n = 10) compared with control group (n = 6); P = 0.273]. Baseline characteristics of subjects who completed the 12-wk intervention are presented in Table 1. No differences in sex were observed at baseline, with 15 men and 23 women in the alginate group and 11 men and 31 women in the control group (P = 0.238). However, subject age was slightly greater in the alginate group (44.6 ± 7.6 y) than in the control group (41.2 ± 7.4 y) (P = 0.052). Similarly, subjects in the alginate group were taller (1.75 ± 0.08 m) than subjects in the control group (1.70 ± 0.08 m) (P = 0.020).

From the observed return rate of supplement packaging of the ComP, it was determined that a mean of 89.1% of alginate doses and 91.6% of control doses were consumed over the 12 wk (P = 0.24).

Of the 96 subjects who entered the study, only 50 subjects kept food diaries that were eligible for data analysis. The self-reported energy intake was numerically larger (~30 kcal/d) in the control group (1638 ± 48 kcal) than in the alginate group (1608 ± 48 kcal); however, the difference was not significant (P = 0.68).

Body weight and composition

In the ITT analysis, no difference in body weight between alginate (~5.87 ± 0.49 kg) and control (~4.68 ± 0.54 kg) groups was observed (P = 0.107). However, in the ComP analysis, we showed a significantly greater weight loss (~1.7 ± 0.5 kg) in the alginate group than in the control group after week 12 (P = 0.031).

![Figure 1. CONSORT diagram that shows the subject flow through the 12-wk intervention. Pearson’s chi-square test showed a trend for differences in noncompliant subjects between groups (P = 0.053). ComP, completer population; ITT, intention-to-treat population; PP, per-protocol population.](image-url)
A tendency toward a difference in baseline Hb A1c between alginate and control groups in the ITT analysis was observed (P = 0.058). Furthermore, there was a tendency toward a greater reduction in Hb A1c after alginate treatment (−0.07 ± 0.05%) than after control treatment (0.01 ± 0.04%) (P = 0.051) in the ITT analysis. In completers, the difference in baseline Hb A1c between alginate and control groups was significant (P = 0.035). However, after the 12-wk treatment, the reduction in Hb A1c was significantly greater in the alginate group than in the control group (P = 0.024; Table 1).

After the 12-wk intervention, fasting ghrelin values decreased in both groups, but no difference between the alginate-treatment group (−94.11 ± 30.11 pg/L) and control group (−50.02 ± 20.72 pg/L) was observed (P = 0.145) in the ComP analysis.

### Metabolic and endocrine responses

No difference in the reduction in fasting glucose between alginate (−0.10 ± 0.1 mmol/L) and control (−0.16 ± 0.1 mmol/L) groups or in HOMA-IR (−4.5 ± 1.1 and −3.22 ± 1.0, respectively) was observed in the ITT analysis (P > 0.1). Similarly, no differences in fasting glucose and HOMA-IR were shown in the ComP analysis (P > 0.1; Table 1).

No difference in decrease in fasting insulin between alginate (−23.29 ± 4.10 pmol/L) and control (−12.23 ± 4.13 pmol/L) treatments was observed in the ITT analysis (P > 0.1). In the ComP, we showed a tendency for differences in baseline values of fasting insulin between alginate and control groups (P = 0.09). Furthermore, a tendency to a larger decrease in baseline-adjusted insulin for the alginate compared with control treatments was observed (P = 0.06) (Table 1).

![FIGURE 2. Time course of mean (±SEE) changes in body-weight loss (kg) from baseline values during the 12-wk treatment (ComP; n = 80). Repeated-measures ANCOVA for ComP showed a treatment × time interaction (P = 0.011). *Post hoc comparison showed a treatment effect at week 12, P = 0.002. ComP, completer population.](image-url)
In the ITT population, we observed a larger decrease in systolic blood pressure in the control group (−5.5 ± 1.5 mm Hg) than in the alginate group (−1.2 ± 1.5 mm Hg) after the 12-wk intervention (P = 0.014). In addition, in the repeated-measurement ANCOVA, we showed an effect of treatment (P = 0.015) on changes in systolic blood pressure in the ITT population. When we analyzed the ComP, we also showed significant differences in changes in systolic blood pressure between the alginate (−1.6 ± 1.8 mm Hg) and control (−5.4 ± 1.6 mm Hg) groups after the 12-wk intervention (P = 0.035). The repeated-measurement ANCOVA also showed an effect of treatment (P = 0.018) on changes in systolic blood pressure (Figure 3).

There was no difference in the decline in diastolic blood pressure in the control group (−3.0 ± 1.0 mm Hg) compared with in the alginate group (−1.8 ± 1.4 mm Hg) after 12 wk in the ITT population (P = 0.203). However, in the repeated-measurement ANCOVA, we showed significant differences in changes in systolic blood pressure between groups for the ITT population (P = 0.025). For the ComP, no differences in changes in diastolic blood pressure between alginate and control groups after 12 wk were observed (P = 0.439). However, an effect of treatment (P = 0.020) on changes in diastolic blood pressure was shown in the repeated-measurement ANCOVA (Figure 3).

We observed a decrease in heart rate over time in both treatment groups, but the changes in heart rate were not different between alginate and control groups in the ITT (P > 0.1) or ComP (P > 0.1) analyses (Table 1).

In the ComP, the inflammation marker high-sensitivity C-reactive protein was higher at baseline in the control group than in the alginate group (P = 0.033). A decrease from baseline to week 12 was shown in both groups, with a nonsignificant but numerically larger decrease in the alginate group (−1.0 ± 0.5 mg/L) than in the control group (−0.4 ± 0.5 mg/L) (P = 0.341).

No differences were observed in changes in fasting values of triglycerides, total cholesterol, LDL cholesterol, or HDL cholesterol between the 2 treatment groups in the ITT (P > 0.1) or ComP (Table 1) analyses.

**Supplement tolerability**

In relation to study dropout, 5 subjects terminated study participation because of personal reasons, which were specified as a lack of time or work-related stress in the alginate group. An additional 5 subjects withdrew because of AEs such as being bloated; having abdominal pain, moderate nausea, or mild diarrhea; and experiencing an unpleasant taste of the test supplement. In comparison, in the control group, 4 subjects terminated participation because of personal reasons such as lack of time, and 2 subjects withdrew because of AEs such as mild diarrhea and difficulties handling the test supplement (ie, mixing the powder).

Reported AEs from the 12-wk supplementation were analyzed with data from the ITT population. Mild-to-moderate AEs (n = 147) were reported in 38 subjects in the alginate group compared with mild to moderate AEs (n = 91) reported in 33 subjects in the control group. Gastrointestinal symptoms dominated in both groups, and AEs were partly recorded repetitively by the same subjects. The number of subjects who reported AEs was not significantly different between treatment groups (P = 0.245).

VAS scores for abdominal pain and distension reported in the ITT population are shown in Figure 4. We observed a treatment effect for abdominal pain because mean values of maximum VAS scores during the first treatment week were higher in the alginate group (22.9 ± 4.1 mm) than in the control group (9.5 ± 2.4 mm) (P = 0.009). In week 6, mean values of maximum VAS scores continued to be higher in the alginate group (10.4 ± 2.7 mm) than in the control group (3.8 ± 1.4 mm) (P = 0.021). However, in week 12, no difference in abdominal pain was shown between the 2 treatment groups (P = 0.660). Furthermore, we showed a treatment effect for distension because mean values of maximum VAS scores during the first treatment week were higher in the alginate group (33.5 ± 4.1 mm) than in the control group (12.9 ± 2.8 mm) (P < 0.001). However, in weeks 6 (P = 0.291) and 12 (P = 0.468), no differences in distension were shown between the 2 treatment groups. For all other specific gastrointestinal AEs such as constipation, diarrhea, gas production, heartburn, nausea, eructation, or stomach rumbling, no significant differences between treatment groups were observed (P > 0.1) (data not shown).

**DISCUSSION**

We hypothesized that supplementation with a strong-gelling sodium alginate fiber as an adjuvant to a modestly energy-restricted diet could enhance weight loss and improve body composition in obese subjects. In an ITT analysis, no difference in weight loss or body composition was shown between alginate and control groups; however, in the 80 subjects who completed the study, body weight decreased significantly more in subjects who consumed the
correction for multiple testing showed a treatment effect at week 1 (**P = 0.009) and week 6 (*P = 0.021) for abdominal pain (A) and a treatment effect at week 1 (**P < 0.001) for distension (B). VAS, visual analogue scale.

FIGURE 4. Mean (±SEE) of VAS (0–100 mm) scores of the gastrointestinal adverse events abdominal pain (A) and distension (B) (intention-to-treat population; n = 96). The Mann-Whitney U test with Bonferroni correction for multiple testing showed a treatment effect at week 1 (**P = 0.009) and week 6 (*P = 0.021) for abdominal pain (A) and a treatment effect at week 1 (**P < 0.001) for distension (B). VAS, visual analogue scale.

Alginate-based preload beverage than in those who consumed the control beverage. Furthermore, a larger reduction in the percentage of body fat after the alginate supplementation was observed.

Previously, results on alginate supplementation have been derived from acute and short-term interventions with conflicting outcomes on appetite sensation and spontaneous food intake (15). One retrospective study with alginate in combinations with glucomannan and xanthan gum (PGX; Inovobiologic Inc) showed weight-reducing effects in overweight subjects (30). However, a weight-loss study showed that guar gum or guar gum and alginate combined with glucomannan did not stimulate additional weight loss compared with glucomannan alone (31). To our knowledge, this is the first randomized, double-blind, placebo-controlled trial to evaluate the effect of the single-fiber formulation of sodium alginate and calcium as part of a 12-wk weight-loss diet in obese subjects.

Generally, dietary fiber supplementation is thought to modulate appetite sensation and attenuate food intake through several mechanisms, including increased gastric distension, a decreased gastric emptying rate, and slow nutrient absorption (20). Although Torsdottir et al (32) showed a decreased gastric emptying rate, the effect of alginate fiber consumption on gastric emptying is still inconclusive (13, 15, 33). A previous MRI study showed that the addition of polysaccharides of different viscosities to a liquid meal increased fullness, and this effect was correlated with the gastric volume filled by the test meal (34), which attributed to the activation of mechanoreceptors in the stomach during distension. This form of gastric stimuli could have had an inhibitory effect on the food intake in the current study.

We previously showed that the alginate-based preload formulation used in this study induced greater feelings of satiety than did the control (33), which suggested that the obese subjects who consumed alginate in the current weight-loss study may also have experienced less hunger than did subjects who consumed the control preload. Previous fiber supplementation to a very low–caloric diet has been indicative of improved adherence by normalizing hunger during weight loss (35). Better hunger management during the hypocaloric diet regimen could be related to changes in gastrointestinal hormones such as ghrelin, cholecystokinin, glucagon-like peptide-1, and peptide YY, which all effect appetite regulation (36). The orexigenic hormone ghrelin is secreted to the bloodstream by the stomach and duodenum and increases food intake in humans (37). Cummings et al (38) reported that hypocaloric diet-induced weight loss often produced a coordinated decrease in plasma leptin and an increase in plasma ghrelin. We showed a nonsignificant but numerically larger suppression of active plasma ghrelin compared with in the control group. If such suppression of ghrelin secretion in the intraluminal environment is feasible by alginate preload consumption, this effect could result in a perception of less hunger before a main meal intake and support a better control of reduced energy intake.

To our knowledge, changes in body fat mass in humans after alginate intake have not been reported previously. Besides the effect of weight loss on a reduction in fat mass, it could also be hypothesized that the decreased percentage of body fat could have been because of a prebiotic effect. It has recently been suggested that the use of dietary fibers from seaweed as alginates can be considered a source of prebiotics (39). The prebiotic fiber inulin has been shown to decrease adipocyte size and adiposity by increased lipolysis in animal models (40) and to reduce fat mass in obese subjects (41). Such a prebiotic effect could act through gut fermentation and processes such as increased bifidobacteria growth and short-chain fatty acid production (42, 43), which have been proposed to be mechanistically involved in the modulation of adipose tissue (44). A potential prebiotic effect of alginate should be investigated further. Furthermore, an insoluble fiber as a control supplement could have isolated the importance of gelling in the stomach compared with effects in the colon on the outcome on the proposed mechanisms. Therefore, the choice of maltodextrin as a control could be regarded as a limitation of the intervention.

Our second hypothesis was that the intake of alginate fibers would lead to improvements in risk factors of type 2 diabetes and CVD, which have been proposed with similar viscous soluble fibers (45).

A number of soluble fibers exhibit a suppressive effect on the glycemic index of foods, which in turn has been proposed to influence body weight and obesity-related conditions (46). However, conflicting evidence on the hypoglycemic effects of alginate consumption in humans has been reported previously (33, 47, 48). Furthermore, in our current study, the related biomarkers of type 2 diabetes progressed to normalization over time, but no difference between treatments was observed. Although fasting Hb A1c decreased significantly in the ComP after alginate supplementation, this result was remote from being clinically relevant. Therefore, an additional investigation on the relation between alginate consumption and glycemic control and body fat accumulation is needed.

It has been previously stated that reductions in blood pressure can be achieved with even modest weight loss (49). However, the difference in blood pressure observed in our study could have
been a result of a larger consumption of sodium (1275 mg) from one dose of alginate formulation. Because of extraction processes of alginate from brown seaweed, the alginate is fixed to sodium. The additional amount of salt intake from the supplementation could have affected the plasma osmolality. Potentially, the renin-angiotensin-aldosterone mechanism could be stimulated, which would influence peripheral resistance by causing vasoconstriction and thereby raises the blood pressure (50). In our study, the renin-angiotensin-aldosterone mechanism may have potentially cancelled out the blood pressure–reducing effect of the larger weight loss in the alginate group. A study limitation could have been related to the use of automated blood pressure readings. In comparison with manual methods, the automated method may have lowered the precision and accuracy of reading. However, we ensured proper training of observers, identical positioning of subjects, and correct selection of cuffs sized to reduce these methodologic concerns.

No difference in fasting lipid concentrations was shown between treatment groups. Perhaps alginate displays a hypolipidemic effect only in combination with a high-fat diet.

Numerically more subjects dropped out from the study from the alginate group than from the control group. This result could have been because of the experience of gastrointestinal AEs and decreased palatability of the alginate-based preload beverage. The alginate group rated the beverage to have a less pleasant taste than did the control group. A decreased palatability of alginate formulations has also been previously reported (13, 14), which is a recurrent challenge when adding viscous fibers to beverages.

The greater proportion of subjects who dropped out in the alginate group should also be taken into consideration in the interpretation of the difference in weight-loss outcomes between the ITT and completer analyses. It is likely that subjects who reported fewer AEs and accepted the taste stayed in the study, whereas subjects who dropped out might have been individuals who exhibited, to a greater extent, a lower degree of tolerability to the alginate supplementation. Consequently, it remains a challenge to develop better-tasting alginate supplements, reduce sodium contents, and reduce gastrointestinal AEs.

In terms of AEs, abdominal pain and distension were more frequent with alginate consumption than with consumption of the control supplement, although these events were mostly transient during weeks 1 and 6. At the end of the study, no gastrointestinal AEs were shown, which indicated an adaptation of subjects to the alginate supplementation. Furthermore, all self-reported AEs were mild to moderate in nature and primarily related to the gastrointestinal tract for both groups. Therefore, the alginate supplementation was well tolerated by the majority of subjects, which was a result that was also in line with previous studies on the acceptability of alginate and gastrointestinal comfort (14, 16, 47, 48).

In conclusion, no effect of alginate supplementation was shown between groups in the ITT analysis. However, in obese subjects who completed the 12-wk supplementation by consuming the strong-gelling sodium alginate fiber as an adjuvant to a modest energy-restricted diet, enhanced weight loss and improved body composition were shown in comparison with control subjects. Furthermore, supplementation with alginate was acceptable for the majority of subjects. A normalization of obesity-associated risk factors was observed in both treatment groups. Special attention should be given to the sodium content and sensory property of the alginate formulation, which led to elevated blood pressure and lower palatability ratings in the group who received alginate compared with the control group. Overall, these results suggested that alginate may be a potential agent to achieve a clinically relevant reduction in body weight in obese subjects when consumed as prescribed as an adjuvant to an energy-restricted diet.

We express gratitude to all subjects who participated in the intervention and to the staff at the Department of Human Nutrition. We acknowledge F Larsen, S-Biotek Holding ApS, for constructive discussion of the study design. The authors’ responsibilities were as follows—MGJ: wrote the protocol and the manuscript and conducted the study; and all authors: planned the study, analyzed data, reviewed the manuscript, and approved the final manuscript. S-Biotek Holding ApS founded the study, MGI is supported by a research grant from S-Biotek Holding ApS, and AA is a member of the advisory board at S-Biotek Holding ApS. MK declared no conflict of interest.

REFERENCES


35. Quaade F, Vrist E, Astrup A. [Dietary fiber added to a very-low caloric diet reduces hunger and alleviates constipation] Ugenskr Laegor 1990; 152:95–8 (in Danish).