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PAPER

The effect of the dietary supplement, Chitosan, on body weight: a randomised controlled trial in 250 overweight and obese adults

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CONTEXT: Chitosan, a deacetylated chitin, is a widely available dietary supplement purported to decrease body weight and serum lipids through gastrointestinal fat binding. Although evaluated in a number of trials, its efficacy remains in dispute.
OBJECTIVE: To evaluate the efficacy of chitosan for weight loss in overweight and obese adults.
DESIGN AND SETTING: A 24-week randomised, double-blind, placebo-controlled trial, conducted at the University of Auckland between November 2001 and December 2002.
PARTICIPANTS: A total of 250 participants (82% women; mean (s.d.) body mass index, 35.5 (5.1) kg/m^2; mean age, 48 (12) y)
INTERVENTIONS: Participants were randomly assigned to receive 3 g chitosan/day ($n=125$) or placebo ($n=125$). All participants received standardised dietary and lifestyle advice for weight loss. Adherence was monitored by capsule counts.
MAIN OUTCOME MEASURES: The primary outcome measure was change in body weight. Secondary outcomes included changes in body mass index, waist circumference, body fat percentage, blood pressure, serum lipids, plasma glucose, fat-soluble vitamins, faecal fat, and health-related quality of life.
RESULTS: In an intention-to-treat analysis with the last observation carried forward, the chitosan group lost more body weight than the placebo group (mean (s.e.), −0.4 (0.2) kg (0.4% loss) *vs* +0.2 (0.2) kg (0.2% gain), $P=0.03$) during the 24-week intervention, but effects were small. Similar small changes occurred in circulating total and LDL cholesterol, and glucose ($P<0.01$). There were no significant differences between groups for any of the other measured outcomes.
CONCLUSION: In this 24-week trial, chitosan treatment did not result in a clinically significant loss of body weight compared with placebo.
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Keywords: chitosan; body weight; serum lipids; randomised controlled trial

Introduction

Chitosan, a partially deacetylated polymer of N-acetyl glucosamine derived from the polysaccharide chitin, appears to bind to negatively charged lipids in animal trials, hence reducing their gastrointestinal uptake[1–3] and lowering serum cholesterol.[4,5] Some human trials have suggested that chitosan may decrease body weight and serum lipids,[6,7] and a meta-analysis[8] suggested a 3.3 kg greater weight loss in the intervention group compared with placebo. Other studies have found no effect of chitosan on clinical outcomes.[9,10] In order to resolve the uncertainty surrounding the effectiveness of this dietary supplement,[11,12] we conducted a large randomised controlled clinical trial of the effect of chitosan on body weight, lipids, and other health outcomes.

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Methods

The study was conducted at the University of Auckland, New Zealand, between November 2001 and December 2002. The study protocol and protocol-related documents were

approved by the Auckland Ethics Committee and the New Zealand Health Research Council's Standing Committee on Therapeutic Trials.

Study participants

Study participants were recruited using newspaper advertisements and were enrolled between November 2001 and July 2002. All participants provided written informed consent. Men and women aged over 18 y who wished to lose weight and had a BMI of between 28 and 50 kg/m^2 were included. The exclusion criteria were current treatment with chitosan-containing supplements; current or recent treatment with weight-loss medications; current or recent attendance at a commercial weight-loss clinic/programme; allergy to seafood; pregnancy or lactation; active gastrointestinal disease or obesity surgery; involvement in another clinical trial; and individuals judged to be unlikely to comply with study treatment and follow-up procedures.

Study design

The study was a 24-week, double-blind, placebo-controlled randomised trial. There was a 2-week single-blind pre-randomisation run-in phase on placebo. Only those participants who took greater than 85% of their study medication in the run-in phase (based upon capsule count) were eligible to take part in the double-blind 24-week randomised intervention phase.

Randomisation, medication dosing, and dispensing

Study participants were randomised in a 1 : 1 ratio to receive chitosan or placebo capsules. The study centre dispensed the study medication under blinded conditions using a randomisation sequence generated using a computerised random-number generator with mixed block sizes to prevent discovery. There was no stratification by sex or other demographic variables. Treatment assignment codes were not available to the investigators, research staff or data entry staff at any point during the study, and were held centrally by the study statistician.

The chitosan used in the study was β-chitosan derived from New Zealand squid pens, and independent analysis verified that the level of deacetylation was 75.5%, which conformed to prior specifications. The study medication was dispensed in identical capsules, each capsule containing either 250 mg chitosan or 250 mg placebo (maize cornflour). Participants were instructed to take four capsules with a glass of water three times daily before main meals such that a total of 12 capsules (3 g) per day of either chitosan or placebo were consumed. Treatment allocation was confirmed by independent assessment of capsule content in a subset of 25 participants during the first 4 weeks of the trial.

Visits and measurements

Participants were seen at eight scheduled clinic visits during the study. These were held at registration (−2 weeks), at baseline/randomisation (0 weeks), and at 4, 8, 12, 16, 20, and 24 weeks following randomisation. During each visit, the following assessments were performed: weight, waist circumference, blood pressure, capsule count, and adverse events. Body weight was measured on calibrated digital scales (Seca, Model 708, Germany) to the nearest 0.1 kg and was recorded twice at each visit. Participants were weighed lightly clad. Waist circumference was recorded to the nearest 0.1 cm midway between the last rib and the crest of the ileum at the natural point of waist narrowing using a nonstretch tape measure on lightly clad participants. Two blood pressure measurements were made on the non-dominant arm following 5 min sitting. A single-size cuff (Dinamap XL, 9300 series, USA) was used and two consecutive readings within 10 mmHg were required. At baseline, height was recorded using a wall-mounted stadiometer (Seca, model 222, Germany), and demographic information and a brief medical history were recorded. At baseline, 12 weeks, and 24 weeks, body fat percentage was assessed indirectly by multifrequency bioelectrical impedance analysis (SFB3 MFBIA, Impedimed, Australia).

At baseline, 12 weeks, and 24 weeks, blood samples were collected following a 12-h overnight fast. Serum lipids (total cholesterol (TC), HDL cholesterol (HDL-C), and triacylglycerol (TAG)) were measured using enzymatic colorimetric tests and LDL cholesterol (LDL-C) was calculated using the Friedwald equation. Plasma glucose was measured at baseline and 24 weeks using an enzymatic colorimetric assay. For determination of fat-soluble vitamins (vitamin A (retinol), beta-carotene, vitamin D, vitamin E (α-tocopherol), and prothrombin time (a surrogate measure of vitamin K)) at baseline and 24 weeks fasting, serum samples were centrifuged at room temperature and separated within 4 h of collection prior to analysis by high-performance liquid chromatography. Faecal samples were collected over a 3-day period at baseline and 24 weeks from a subsample of 51 participants. Analysis was carried out using a three-step process of saponification of fats, extraction of free fatty acids, and determination of total free fatty acids.

Study participants also completed a 24-h dietary recall, a physical activity questionnaire,[13] the SF-36 health-related quality of life questionnaire,[14] and the 12-item version of the Eating Attitudes Test (EAT-12).[15] All participants were given standardised low-fat dietary and prudent activity advice in the form of one-to-one sessions with investigators throughout the trial, and written information was also provided. No individualised advice was provided.

End points and measures of outcome

The primary study end point was change in body weight in kilograms from baseline to 24 weeks. Secondary outcome measures included changes in BMI, waist circumference, body fat percentage, systolic and diastolic blood pressure (SBP, DBP), serum lipids, plasma glucose, fat-soluble vitamins, faecal fat losses, and health-related quality of life (SF-36).

Power calculations and statistical analysis

Assuming a standard deviation of 6 kg, the sample size of 250 participants provided 90% power (with $P=0.05$) to detect a mean 2.5 kg greater weight loss in the intervention group.[16] All randomised participants were included in the primary analysis. Three analyses were conducted. In the first, the area under the curve summary measure[17] was employed to assess response profile over time with the last recorded observation carried forward (LOCF) for any missing data, based on an intention-to-treat (ITT) approach. The robustness of this analysis was assessed by performing two further analyses: a mixed-effects regression-modelling approach,[18] which handles missing data under the assumption that data are missing at random, and a per-protocol analysis. For secondary end points that were only measured at baseline and 24 weeks, analysis of covariance (ANCOVA), which adjusts for baseline values, was used for normally distributed data, and Mann–Whitney tests were used for non-normally distributed data. All analyses were carried out using SAS v8.0 (SAS Institute Inc, Cary, NC, USA) and $P=0.05$ was used to determine the statistical significance.

Results

Participant characteristics

Of the 432 individuals who registered to take part in the study, 182 withdrew or were excluded prior to randomisation (Figure 1). Nonrandomised individuals were similar to those randomised other than a lower mean (s.d.) age (42 (11.5) years *vs* 48 (11.7) y, $P<0.001$), a higher proportion of current smokers (19 *vs* 9%, $P=0.01$), and a mean capsule adherence of 81% at the end of the 2-week run-in period *vs* 97% in randomised individuals ($P=0.01$). In all, 250 individuals were randomised: 125 received chitosan and 125 received placebo. A total of 86 participants dropped out during the intervention period (42 in the chitosan group and

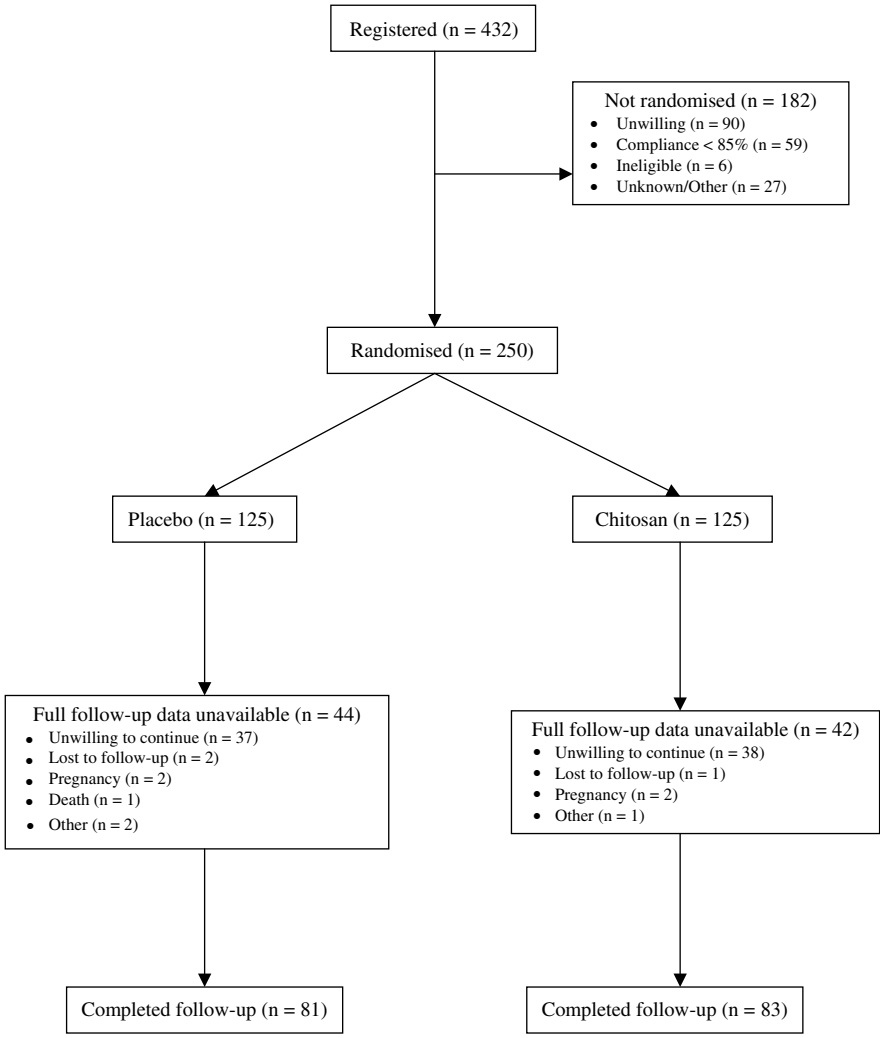

Figure 1 Flow chart describing progress of participants through trial.

Table 1 Baseline characteristics of study participants

Characteristic	*Chitosan group (n = 125)*	*Placebo group (n = 125)*
Age, mean (s.d.) (y)	47 (11.7)	48 (11.5)
Gender, N (%)		
Men	22 (17.6)	22 (17.6)
Women	103 (82.4)	103 (82.4)
Race, N (%)		
Caucasian	104 (83.2)	108 (86.4)
Indian	3 (2.4)	4 (3.2)
Polynesian	16 (12.8)	13 (10.4)
East Asian	1 (0.8)	0 (0)
African	1 (0.8)	0 (0)
Current cigarette smoker, *N* (%)	13 (10.4)	10 (8.0)
Current alcohol drinker, *N* (%)	63 (50.4)	59 (47.2)
Body weight, mean (s.d.) kg	95.9 (15.2)	98.9 (17.1)
Body mass index, mean (s.d.) kg/m^2	34.8 (5.1)	36.0 (5.1)
Waist circumference, mean (s.d.) cm	99.6 (11.9)	101.3 (13.7)
Body fat, mean (s.d.) %	37.8 (6.8)	38.9 (6.5)
Systolic blood pressure, mean (s.d.) (mmHg)	122.6 (17.7)	123.8 (18.9)
Diastolic blood pressure, mean (s.d.) (mmHg)	69.4 (9.4)	70.1 (9.7)
Total cholesterol, mean (s.d.) (mmol/l)	5.6 (1.0)	5.4 (0.9)
LDL cholesterol, mean (s.d.) (mmol/l)	3.6 (0.8)	3.3 (0.8)
HDL cholesterol, mean (s.d.) (mmol/l)	1.3 (0.3)	1.4 (0.4)
Total:HDL cholesterol ratio, mean (s.d.)	4.6 (1.2)	4.2 (1.2)
Triglycerides, mean (s.d.) (mmol/l)	1.6 (0.8)	1.5 (0.9)
Glucose, mean (s.d.) (mmol/l)	5.3 (1.3)	5.4 (1.4)
Vitamin A, mean (s.d.) (μmol/l)	2.0 (0.5)	1.9 (0.5)
Beta-carotene, mean (s.d.) (μmol/l)	0.7 (0.5)	0.6 (0.5)
25-OH Vitamin D, mean (s.d.) (nmol/l)	64.9 (25.2)	59.6 (19.5)
Vitamin E, mean (s.d.) (μg/l)	31.7 (8.5)	31.2 (8.1)
Prothrombin ratio, mean (s.d.)	1.0 (0.2)	1.0 (0.1)
Faecal fat, mean (s.d.) (mmol/day)	12.6 (8.0)	14.3 (6.8)
SF-36—physical component subscale (0–100)	47.9 (6.2)	47.6 (6.2)
SF-36—mental component subscale (0–100)	46.7 (7.2)	47.7 (7.2)

44 in the placebo group), and 164 (65.6%) completed the entire 24 weeks. There were no significant differences between the baseline characteristics of participants in each treatment group (Table 1).

Body weight

Changes in body weight over the 24-week intervention period for the chitosan and placebo groups are shown in Figure 2. In the last observation carried forward (LOCF) analysis for the ITT population, the chitosan group lost a mean (s.e.) of 0.39 (0.21) kg (0.4%) during the 24-week period *vs* a net gain of 0.17 (0.16) kg (0.2%) for the placebo group during the 24-week intervention. The mean (95% confidence interval (CI)) difference between treatment groups was therefore 0.56 (0.04, 1.08) kg ($P = 0.03$, Table 2).

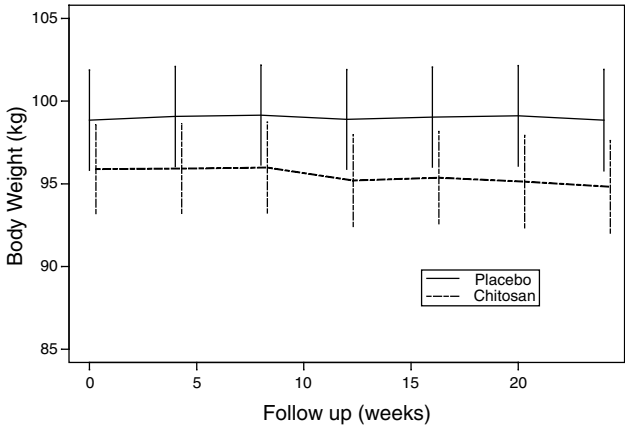

Figure 2 Change in body weight over 24 weeks. Intention-to-treat analysis (LOCF). Placebo = ——; chitosan = - - - - -.

Analyses restricted to the subset of individuals who attended all study visits ($n = 146$) and those who attended all visits and also maintained an average adherence rate of ≥85% throughout the trial ($n = 73$) indicated that the mean (95% CI) difference between groups remained small: 0.9 (0.1, 1.7) kg ($P = 0.03$) and 0.9 (−0.5, 2.2) kg ($P = 0.20$) respectively.

Other measures

Mean BMI, waist circumference and body fat percentage also decreased over the 24 weeks, although the difference between groups was not significant (Table 3). In addition, there were no significant differences between groups in SBP and DBP or fat-soluble vitamins. Changes in TC and LDL-C for the chitosan and placebo groups are shown in Figure 3. In the ITT analysis, TC levels decreased by a mean (s.e.) of 0.13 (0.03) mmol/l (2.3%) in the chitosan group during the 24-week period *vs* a net gain of 0.01 (0.03) mmol/l (0.2%) for the placebo group. The mean (95% CI) difference between treatment groups was therefore 0.14 (0.05, 0.22) mmol/l ($P < 0.01$). A similar pattern was seen for LDL-C (mean difference between groups: 0.12 (0.05, 0.20) mmol/l, $P < 0.01$) and glucose (mean difference between groups: 0.21 (0.08, 0.34) mmol/l, $P < 0.01$), but there were no significant differences between groups in HDL-C ($P = 0.5$) or TAG ($P = 0.2$). There were no significant differences in the mean faecal fat excretion between the chitosan group and the placebo group over the study period in both intention to treat analyses (mean difference between groups: 0.2 (−4.1, 4.5) mmol/day, $P = 0.9$, Table 3) and analyses involving only the 29 participants who provided both baseline and follow-up samples (mean difference between groups: 0.3 (−7.5, 8.2) mmol/day, $P = 0.9$).

No significant differences were seen between groups in the physical and mental component subscales of the SF-36 questionnaire throughout the period of the trial (mean (s.e.)) difference of 0.3 (0.8), $P = 0.7$; and 1.0 (0.9), $P = 0.3$,

Table 2 Change in body weight by analysis method and treatment group

	ITT (LOCF) analysis[a]				*Completers only analysis*[b]				*Per protocol analysis*[c]			
	Mean change (s.e.m.)				*Mean change (s.e.m.)*				*Mean change (s.e.m.)*			
Area under the curve	*Chitosan (n = 125)*	*Placebo (n = 125)*	*Treatment difference*	*P-value*	*Chitosan (n = 78)*	*Placebo (n = 68)*	*Treatment difference*	*P-value*	*Chitosan (n = 44)*	*Placebo (n = 29)*	*Treatment difference*	*P-value*
Weight (kg)	−0.39 (0.21)	0.17 (0.16)	0.56 (0.26)	0.03	−0.94 (0.29)	−0.05 (0.26)	0.90 (0.40)	0.03	−1.63 (0.44)	−0.74 (0.49)	0.88 (0.68)	0.20

[a]ITT = intention-to-treat analysis. Missing values are assigned the last value carried forward from the previous visit. [b]Includes only participants who attended all study visits. [c]Includes only participants who attended all study visits and maintained ≥85% compliance throughout, as measured by capsule counts.

respectively), or in the dieting (mean (s.e.) difference of 0.1 (0.24), $P=0.7$), bulimia (−0.37 (0.21), $P=0.1$) and oral control (0.01 (0.06), $P=0.9$) subscales of the EAT-12 questionnaire. Self-reported adherence as measured by capsule counts decreased only slightly over the 24-week study period (−4.5 (0.9)% in the chitosan group and −4.0 (0.8)% in the placebo group, $P=0.6$). There were no differences between the groups in physical activity or energy intake ($P=0.60$ and $P=0.79$, respectively).

There were a total of 10 serious adverse events (SAE) recorded over the study period: six in the placebo group and four in the chitosan group ($P=0.53$, Table 4). The SAE were defined as hospitalisations (three in the chitosan group, four in the placebo group, $P=0.71$), cancer incidence (one in the chitosan group, three in the placebo group, $P=0.34$) and one death (placebo group). Of the nonserious adverse events, 36 volunteers in the chitosan group and 19 in the placebo group reported noninfectious gastrointestinal side effects (defined as abdominal pain, bloating, constipation, indigestion, or non-infectious diarrhoea) ($P=0.02$). There were no significant differences between intervention groups in any other category of nonserious adverse events.

Comment

This randomised placebo-controlled trial demonstrated that treatment with chitosan combined with lifestyle and dietary advice produced marginally greater weight loss than advice alone in overweight and obese individuals. However, the mean difference between groups in weight loss of just over half a kilogram achieved over the 24-week study period cannot be considered to be of great clinical significance. Treatment with chitosan also led to improvements in some risk factors associated with obesity, including fasting TC, LDL-C and glucose levels, although these were also too small to be considered to be of clinical importance. In addition to our main analyses, a number of sensitivity analyses were performed, all of which gave similar results to the main analyses.

A number of previous trials investigating the effect of chitosan on body weight and lipids have been published, but results are conflicting. A meta-analysis of five Italian trials involving a total of 386 participants indicated a mean difference of 3.3 kg weight loss between the intervention and placebo group.[8] However, the trials included in the meta-analysis were not retrieved by searching electronic databases, but were obtained from a single manufacturer and published in a single journal over a 2-y period. They used a similar study design (a trial duration of 28 days and an energy-restricted diet), but it is unclear if intention-to-treat analyses were employed, and no description is given of the composition or dose of chitosan used. It is unclear if the individual patient populations may have overlapped.

Recent trials examining the effect of chitosan have produced more variable results. Some trials have reported a positive effect on body weight,[6,7,19] or lipid levels,[20,21] while

Table 3 Change in secondary outcomes by treatment group

	Chitosan			*Placebo*			*Treatment difference*		
Area under the curve (LOCF)[a]	*N*	*Mean change*	*s.e.m.*	*N*	*Mean change*	*s.e.m.*	*Mean*	*95% CI*	P-*value*
Body mass index (kg/m^2)	125	−0.17	(0.09)	125	0.05	(0.07)	0.21	−0.02, 0.44	0.07
Waist circumference (cm)	125	−0.57	(0.30)	125	0.07	(0.28)	0.64	−0.18, 1.46	0.13
Body fat (%)	121	−0.85	(0.27)	118	−0.61	(0.19)	0.24	−0.41, 0.89	0.46
Systolic blood pressure (mmHg)	125	−2.71	(0.92)	125	−1.55	(0.98)	1.16	−1.49, 3.81	0.39
Diastolic blood pressure (mmHg)	125	−2.70	(0.55)	125	−2.68	(0.49)	0.03	−1.43, 1.49	0.97
Glucose (mmol/l)	118	−0.14	(0.05)	116	0.06	(0.05)	0.21	0.07, 0.34	<0.01
Vitamin E, (μg/l)	120	−1.15	(0.50)	119	−0.08	(0.50)	1.07	−0.32, 2.47	0.13
Vitamin A (μmol/l)	120	−0.04	(0.02)	119	0.00	(0.02)	0.04	−0.03, 0.11	0.27
Beta-carotene (μmol/l)	120	−0.02	(0.03)	118	0.03	(0.03)	0.05	−0.03, 0.14	0.21
25-OH vitamin D (nmol/l)	122	−9.00	(1.81)	121	−8.64	(1.81)	0.36	−4.68, 5.40	0.89
Prothrombin ratio	117	0.01	(0.01)	115	0.03	(0.01)	0.02	−0.02, 0.05	0.31
Faecal fat (mmol/day)	25	−0.08	(1.53)	26	0.12	(1.50)	0.20	−4.11, 4.51	0.93

[a]AUC summary measure was used to assess the change for all end points measured at more than two time points. Change in end points that were only measured at baseline and 24 weeks (glucose, fat-soluble vitamins, faecal fat) was assessed using ANCOVA.

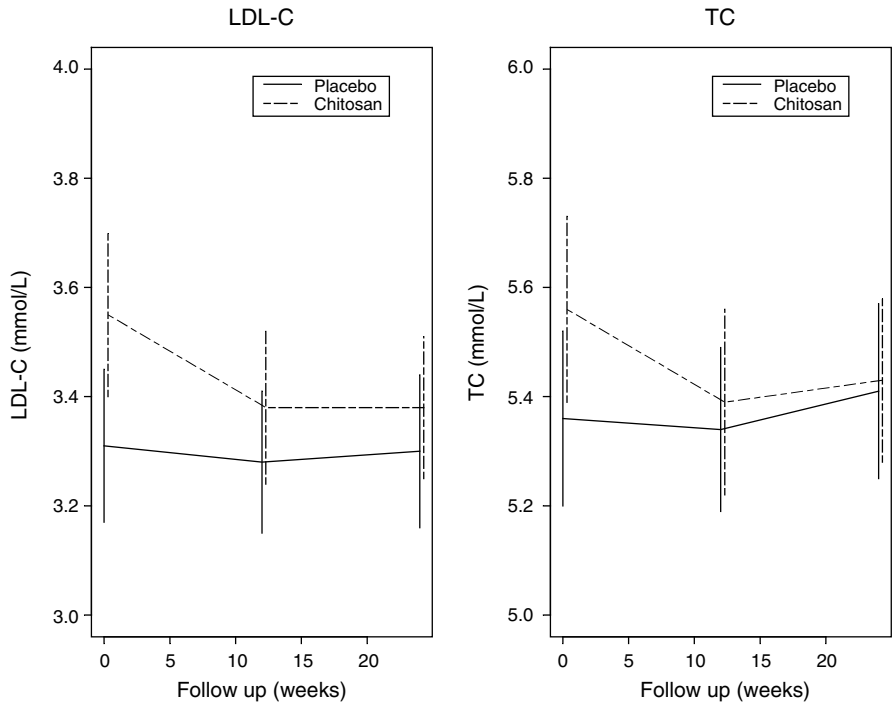

Figure 3 Change in TC and LDL-C over 24 weeks. Intention-to-treat analysis (LOCF). Placebo = ——; chitosan = - - - - -.

others have reported no effect on either outcome.[9,10] A Cochrane systematic review of the effect of chitosan on overweight and obesity is currently underway to synthesise the data from all available trials of chitosan to date.[22]

One possible explanation for the variability in results obtained in these trials of chitosan is that different types and compositions of chitosan have been used in the various studies. The composition of chitosan used has not been well described in many of the trials, but in the current study a β-chitosan derived from New Zealand squid pens was used, which was 75.5% deacetylated and had a molecular weight of 130 000. It is possible that different chemical compositions of chitosan could have variable effects on the binding of gastrointestinal lipids and thus weight loss. Few trials of dietary supplements and natural remedies are carried out according to pharmaceutical industry standards. However, this trial was conducted according to international Good Clinical Research Practice (GCRP) guidelines and was

Table 4 Adverse events by treatment group

Adverse event	*Chitosan N*[a]	*Placebo N*[a]	*Relative rate*	*95% Confidence interval*	P-*value*
Serious events	4	6	0.67	0.19, 2.36	0.53
Nonserious events[b]	109	108	1.01	0.77, 1.32	0.95
Gastrointestinal events—noninfectious					
Abdominal pain	6	4	1.50	0.42, 5.32	0.53
Bloating	10	3	3.33	0.92, 12.11	0.07
Constipation	17	8	2.13	0.92, 4.92	0.08
Indigestion	3	2	1.50	0.25, 8.98	0.66
Diarrhoea (presumed noninfectious)	3	3	1.00	0.20, 4.95	1.00
Other digestive disorder	7	2	3.50	0.73, 16.85	0.12
Total	36	19	1.89	1.09, 3.30	0.02
Gastrointestinal—infectious					
Diarrhoea (presumed infectious)	9	9	1.00	0.40, 2.52	1.00
Nausea/vomiting	12	10	1.2	0.52, 2.78	0.67
Total	17	18	0.94	0.49, 1.83	0.87
Other nonserious events	105	100	1.05	0.80, 1.38	0.73

[a]Denotes number of people who experienced one or more adverse events. [b]Analyses compared the number of people who experienced one or more adverse events. Participants may have reported more than one event and a total of 420 nonserious adverse events were reported in the chitosan group and 309 in the placebo group ($P<0.01$).

the largest trial of chitosan to date, with the largest number of follow-up visits and the most outcome measures. Importantly, intention-to-treat analyses and several sensitivity analyses were used, thus limiting the bias that inevitably results from restricting analysis to data from 'completers' only.

The lack of effect of chitosan on clinical outcomes in the current trial is supported by the results of the faecal fat substudy, which demonstrated that chitosan had no detectable effect on faecal fat excretion. Other trials that have examined the effect of chitosan on faecal fat excretion have also failed to find a significant effect of chitosan on faecal fat excretion.[6,23,24] Given the uniform lack of effect of chitosan on faecal fat excretion, it seems unlikely that it binds fat in the intestine of humans as claimed. It is possible that it might bind bile acids (which were not measured in any of these trials), thus explaining some effect on serum lipid levels, but it seems unlikely that the product could have a large effect on weight loss.

In conclusion, this trial demonstrates that chitosan does not have a clinically significant effect on weight loss or other measured outcomes in overweight and obese men and women taking a dose of 3 g/day. No increase in faecal fat excretion was observed to support the putative mechanism of action of chitosan, and treatment is associated with some minor gastrointestinal side effects. It therefore seems appropriate to focus public attention on the proven effective means of weight loss such as improved nutrition and increased physical activity.

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