Effect of chitosan on weight loss in overweight and obese individuals: a systematic review of randomized controlled trials

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Summary

This article aims to determine whether chitosan, a popular, over-the-counter, weight loss supplement, is an effective treatment for overweight and obesity. It is designed as a systematic review of randomized controlled trials. The data sources include the electronic databases Medline, EMBASE, Biosis, CINAHL and Cochrane Central Register of Controlled Trials (CCTR); the specialized websites Controlled Trials, International Bibliographic Information on Dietary Supplements (IBIDS), System for Information on Grey Literature in Europe (SIGLE), Reuter's Health Service, Natural Alternatives International and Pharmanutrients; and bibliographies of relevant journal articles. Included were randomized controlled trials of chitosan with a minimum duration of 4 weeks in adults who were overweight or obese and/or had hypercholesterolaemia at baseline. Fourteen trials involving a total of 1071 participants were included in the review. Analyses involving all trials indicated that chitosan preparations result in a small but statistically significant greater reduction in body weight (weighted mean difference −1.7 kg; 95% confidence interval −2.1, −1.3 kg, $P < 0.00001$) compared with placebo. Analyses restricted to high-quality studies showed that reductions in weight [−0.6 (−1.2, 0.1) kg, $P = 0.11$] were less than in lower quality studies [−2.3 (−2.7, −1.8) kg, $P < 0.00001$]. Results obtained from high-quality trials indicate that the effect of chitosan on body weight is minimal and unlikely to be of clinical significance.

Keywords: Chitosan, dietary supplement, obesity, systematic review.

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Introduction

Overweight and obesity are increasingly prevalent (1–3) and are important contributors to cardiovascular disease (4–6), type II diabetes mellitus (7,8) and several common cancers (9,10). Excess body weight also leads to impairment in health-related quality of life (11). Estimations of the global burden of disease attributable to excess body weight indicate that high body mass index (BMI) is a leading cause of loss of healthy life causing two and a half millions deaths and over 30 million lost years of healthy life in 2000 (12).

The dietary supplement, chitosan, is derived from the polysaccharide chitin (a by-product of crustaceans) and in animal trials appears to bind to negatively charged lipids thus reducing their gastrointestinal uptake (13,14) and lowering serum cholesterol (15). A previous meta-analysis of trials of chitosan in humans suggested greater weight loss with chitosan compared with placebo (16). However, more recent studies have found no effect of chitosan on body weight (17,18). Thus there is ongoing debate about the role and effectiveness of chitosan as a weight loss treatment (19–21). We conducted a systematic review to determine

The following search strategy was run across Medline (1966 to January week 5 2004) using the Ovid interface and was adapted for EMBASE, Biosis and CINAHL:

1 chitin/
2 (chitin or chitosan or poliglusam).mp.
3 or/1–2
4 Clinical trial.pt
5 random$.mp
6 ((single or double) adj (blind$ or mask$)).mp
7 placebo$.mp
8 or/4–7
9 3 and 8

whether chitosan is an effective treatment for overweight and obesity (22).

Methods

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CCTR) (Cochrane Library Issue 1, 2004), Medline (1966 to January 2004), EMBASE (1980 to January 2004), Biological Abstracts (Biosis) (1980 to January 2004) and CINAHL (1982 to January 2004) for all reports of randomized trials (Box).

We searched the following websites using the phrase 'chitin or chitosan or poliglusam': Controlled Trials (February 2004); International Bibliographic Information on Dietary Supplements (IBIDS) database from the National Institutes of Health Office of Dietary Supplements (February 2004); System for Information on Grey Literature in Europe (SIGLE) (February 2004); Reuter's Health Service (February 2004); Natural Alternatives International (February 2004); and Pharmanutrients (February 2004). We also hand searched reference lists of relevant trials and reviews.

Study selection and data extraction

Studies were eligible for inclusion in the review if they were randomized controlled trials with minimum treatment duration of 4 weeks in adults who were overweight or obese and/or had hypercholesterolaemia at baseline. Criteria for defining overweight or obesity were at the authors' discretion and varied according to study, for example, some studies used BMI cut-points, which varied from study to study, while others used a defined percentage excess weight compared with ideal weight/height tables. Studies including children, pregnant women, or patients with serious medical conditions were excluded. Published and unpublished studies in any language were eligible for inclusion.

Two authors (C.D.M., C.N.M.) reviewed relevant studies independently and completed a standardized data extraction form. Differences in opinion were resolved by consulting a third party (A.R.). All trial investigators were contacted for additional information or data, which was obtained for a total three trials involving 404 participants. For studies written in languages other than English or German translations of papers were obtained.

Statistical analysis

Data were expressed as weighted mean differences (WMD) and standard deviations (SD). The weight given to each study was the inverse of its variance (1/(se(WMD)^2)), that is, more precise estimates (usually from larger studies with more events) were given more weight (23). Where studies did not report mean difference and SD additional analyses were undertaken to calculate these variables from the available data. Most eligible studies reported mean and SD values at baseline and at follow-up but did not report the mean difference or SD of the difference over time. Therefore baseline and follow-up values were used to calculate mean and SD over time. One study provided individual participant data but no group mean data so these were calculated (24). Another study reported percentage change over time rather than absolute values so calculations were necessary to transform this to absolute values over time (25).

Where there was no evidence of statistical heterogeneity the results were pooled statistically using a fixed effects approach. The pooled effect size was computed by using the inverse variance weighted method. A random effects approach was also used as a sensitivity analysis. Statistical heterogeneity was tested for using the Q statistic devised by Cochran with significance being set at $P < 0.10$. Possible sources of clinical heterogeneity were assessed by the following sensitivity analyses: study quality (allocation concealment); use of a treatment preparation comprising agents other than just chitosan; study duration. The process of concealing randomized study assignments is known as allocation concealment and when studies do not report any concealment approach, adequacy is considered unclear (26). Studies reporting appropriate methods of allocation

concealment are considered 'A grade' trials. Studies where the method of allocation concealment is unclear are considered 'B grade'. Other aspects of study quality including blinding, completeness of follow-up and use of intention-to-treat analyses were also noted but were not used as a sensitivity analysis. The existence of small study bias was checked using the funnel plot. Analyses were carried out using Review Manager 4.2 (27) and STATA 8.0 (28).

Results

Thirty-six potentially eligible studies were retrieved and 14 randomized controlled trials were included (Fig. 1). Two other trials also met the inclusion criteria but did not provide data in a form suitable for inclusion in the review (29,30). Attempts to contact these authors for additional data were unsuccessful.

Table 1 shows the main characteristics of the 14 included randomized controlled trials. One thousand and seventy-one participants were randomized in total with 538 participants allocated to the chitosan intervention group and 533 allocated to the placebo group. The mean trial duration was 8.6 weeks (range 4–24 weeks) and mean study size was 77 participants (range 24–250). The dose of chitosan used in studies ranged from 1.0 g day^{-1} to 15 g day^{-1} (mean 3.8 g day^{-1}) and five studies (25,31–34) used treatment preparations that contained other weight loss ingredients in addition to chitosan.

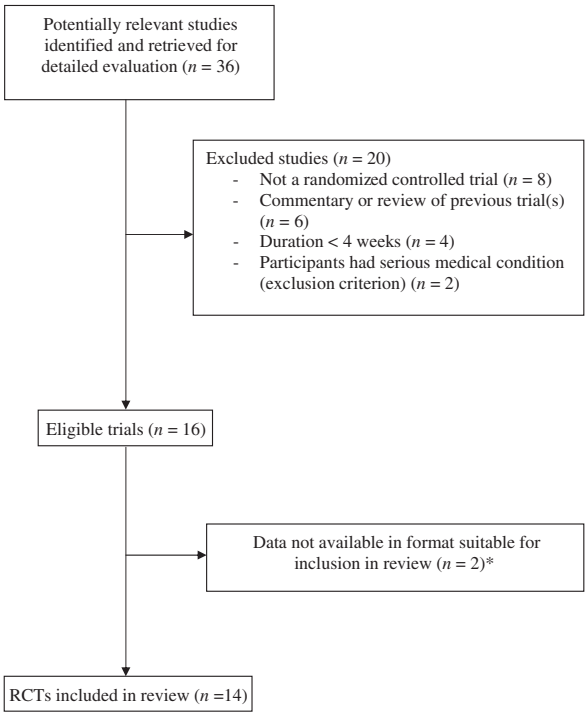

Figure 1 Identification and screening of studies. *One study (29) only provided results as percentage change over time so a standard deviation could not be calculated, and another (30) was described in an abstract but did not provide any results. Repeated attempts were made to contact both authors but were unsuccessful.

Studies varied in quality and/or reporting of methods. It is recommended that use of appropriate methods for preventing foreknowledge of treatment assignment (allocation concealment) be used as a key method of measuring study quality (26). Although all studies included in the review were described as randomized the method of allocation concealment was unclear for all but four 'A grade' studies (17,35–37).

Body weight

Combining trials that provided data on body weight (17,18,24,25,31–39) using a fixed effects model produced a WMD in body weight of –1.7 (–2.1, –1.3) kg in favour of chitosan vs. placebo ($P < 0.00001$) (Fig. 2). The use of a random effects model in a sensitivity analysis did not substantially alter this estimate [–2.1 (–3.2, –1.0) kg, $P = 0.0002$].

Limiting trials to those that met the allocation concealment quality criteria (A grade) (17,35–37) resulted in an estimated weight loss of –0.6 (–1.2, 0.1) kg, $P = 0.11$, vs. an estimated WMD of –2.3 (–2.7, –1.8) kg, $P < 0.00001$ in remaining trials (Fig. 3) (18,24,25,31–34,38,39). The I^2 statistic indicated no heterogeneity in the A grade trials [$Chi^2 = 0.5$, d.f. = 3 ($P = 0.9$), $I^2 = 0\%$] but significant heterogeneity in the B grade (allocation concealment unclear) trials [$Chi^2 = 29.5$, d.f. = 8 ($P = 0.0003$), $I^2 = 72.9\%$].

Similarly, limiting included trials to those that used chitosan alone as the intervention (without additional weight loss agents) (17,18,24,35–37,39) reduced estimated weight loss to –0.9 (–1.4, –0.4) kg, $P = 0.001$, compared with a WMD of –2.7 (–3.3, –2.2) kg, $P = 0.0008$ in trials where the intervention included agents other than just chitosan (25,31–34,38). The I^2 statistic indicated no heterogeneity in the chitosan only trials [$Chi^2 = 3.0$, d.f. = 6 ($P = 0.8$), $I^2 = 0\%$] but significant heterogeneity in trials where other ingredients were in the intervention [$Chi^2 = 21.1$, d.f. = 5 ($P = 0.0008$), $I^2 = 76.3\%$].

Trials that exceeded 4 weeks in duration (18,34–39) produced a lower WMD of –0.8 (–1.3, –0.3) kg, $P = 0.004$, compared with a WMD of –2.7 (–3.3, –2.1) kg, $P = 0.0008$ in trials that only lasted 4 weeks (17,24,25,31–33). Once again, the I^2 statistic indicated no heterogeneity in trials exceeding 4 weeks in duration ($I^2 = 0\%$) but significant heterogeneity in the trials where other agents were used in the intervention ($I^2 = 76.2\%$).

Other outcomes

Combining trials that provided data on total cholesterol (17,18,24,31,33,35,36,39,40) produced a WMD in total

Table 1 Characteristics of randomized controlled trials of chitosan vs. placebo for overweight and obesity

	Participants* and setting	Interventions	Outcomes	Duration	Quality†
Bokura 2003 (35)	90 females aged 34–70 years with mild to moderate hypercholesterolaemia. Japan	Three capsules of chitosan (200 mg) twice daily vs. three capsules placebo (300 mg lactose). Normal diet	Body weight, BMI, blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides	8 weeks	A
Colombo 1996 (31)	86 ambulatory males and females aged 20–70 years with mild obesity (overweight by 10% to 25% compared with ideal weight/height tables) and hyperlipoproteinaemia. Italy	Two capsules twice daily (dose not stated) of chitosan preparation (chitosan, guar's meal, ascorbic acid and other micronutrients) vs. two capsules placebo (dose and composition not stated). Low calorie diet	Body weight, % overweight, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, side-effects, quality of life, compliance, appearance of faeces, haematological and blood chemistry, fat-soluble vitamins	4 weeks	B
Giustina 1995 (32)	100 ambulatory males and females aged 20–70 years with mild obesity (overweight by 10% to 25% compared with ideal weight/height tables) and mild hypertension. Italy	Two tablets twice daily (dose not stated) of chitosan preparation (mixture of chitosan, guar's meals, ascorbic acid and other micronutrients) vs. two tablets placebo twice daily (dose and composition not stated). Low calorie diet	Body weight, % overweight, blood pressure, heart, respiratory rate, side-effects, quality of life, compliance, appearance of faeces (7, 14, 21 and 28 days) Haematological and blood chemistry (28 days only)	4 weeks	B
Ho 2001 (18)	85 normoglycaemic obese males and females (body fat > 20% in males and >30% in females) who were hypercholesterolaemic and had no history of chronic illnesses. Singapore	Four capsules of chitosan (257 mg) three times daily vs. placebo (no details given). Normal diet	Body weight, BMI, waist and hip circumferences, blood pressure, fat free mass, % body fat, total cholesterol, triglyceride, HDL cholesterol, fasting insulin, adverse events	12 weeks	B
Macchi 1996 (24)	30 obese males and females aged 30 and 80 years old, with 25% excess body weight. Italy	Four tablets chitosan (250 mg) daily vs. four tablets placebo (composition not stated). Low calorie diet	Body weight, BMI, % body fat, iron, electrolytes, transaminase, total cholesterol, HDL cholesterol, triglycerides, glucose, urea nitrogen and creatinine, side-effects, well-being and appetite	4 weeks	B
Ni Mhurchu 2004 (36)	250 overweight or obese (BMI 28–50 kg m^{-2}) males and females aged ≥18 years. New Zealand	Four capsules of chitosan (250 mg) three times daily vs. four capsules of placebo (maize cornflour) (250 mg). Standardized dietary and lifestyle advice	Body weight, BMI, waist circumference, % fat, blood pressure, glucose, total cholesterol, LDL and HDL cholesterol, triglycerides, fat-soluble vitamins, health-related quality of life, adverse events, adherence to treatment, faecal fat	24 weeks	A
Pittler 1999 (17)	34 overweight male and female volunteers (BMI 23.9–28.5 kg m^{-2} for women, 25.0–29.9 kg m^{-2} for men), aged 18–60 years. UK	Four capsules of chitosan (250 mg) daily vs. four capsules placebo (no details of composition). Normal diet	Body weight, blood pressure, quality of life, total cholesterol, triglycerides, fat-soluble vitamins, adverse effects, compliance	4 weeks	A

Table 1 *Continued*

	Participants* and setting	Interventions	Outcomes	Duration	Quality†
Schiller 2001 (37)	69 overweight and mildly obese (BMI 27–40) females aged 21–55 years, with stable weight history and history of daily fat consumption ≥ 30% of calories. USA	Three capsules of chitosan (500 mg) twice daily vs. three capsules of placebo (maltodextrin-semolina flour) (500 mg) Normal diet	Body weight, BMI, waist-to-hip ratio, % body fat, % lean body mass, fasting serum lipid levels, fecal fat, Beck depression inventory, health-related quality of life, diet, gastrointestinal and elimination symptoms	8 weeks	A
Sciutto 1995 (25)	90 ambulatory males and females aged 20–70 years with mild obesity (overweight by 10% to 25% compared with ideal weight/height tables), mild hypertension and hyperlipoproteinaemia. Italy	Two tablets chitosan preparation twice daily (mixture of chitosan, guar's meals, ascorbic acid and other micronutrients) vs. two tablets placebo (dose and composition not stated). Low calorie diet	Body weight, % overweight, blood pressure, side-effects, quality of life, compliance, appearance of faeces (7, 14, 21 and 28 days). Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides (0, 7 and 28 days). Haematological and blood chemistry (0 and 28 days)	4 weeks	B
Veneroni 1996 (33)	80 males and females aged 20–70 years with mild obesity (overweight by 10% to 25% compared with ideal weight/height tables) and hyperlipidaemia. Italy	Two tablets chitosan preparation twice daily (mixture of chitosan, guar's meals, ascorbic acid and other micronutrients) vs. two tablets placebo (dose and composition not stated). Low calorie diet	Body weight, % overweight, diet, compliance, appearance of faeces, adverse events, quality of life (0, 7, 14, 21 and 28 days). Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, haematological and blood chemistry (0 and 28 days)	4 weeks	B
Williams 1998 (38)	32 adult overweight male and female volunteers aged 23–57 years, meeting standard inclusion criteria for Phase I clinical trials. UK	5 g RW94 powder stirred into a glass of fruit squash three times daily vs. 5 g placebo (maize starch). Normal diet	Body weight, state of health, adverse events, compliance	6 weeks	B
Woodgate 2003 (34)	24 obese (BMI ≥ 30) male and female volunteers aged 20–50 years. Canada	Two capsules of chitosan preparation (1395 mg) three times daily (proprietary blend of glucomannan, chitosan, fenugreek, G sylvestre and vitamin C) vs. two capsules of placebo (rice flour). Normal diet	Body weight, % body fat, fat mass, lean body mass, BMI, blood pressure, resting heart rate, upper abdominal circumference, waist and hip circumferences	6 weeks	B
Wuolijoki 1999 (40)	51 healthy women with a BMI of 28–34.99 and employed at Tampere University Hospital. Finland	Three capsules of chitosan (400 mg) twice daily vs. three capsules of placebo (starch). Normal diet	Body weight, adverse events, compliance (4, 6, and 8 weeks). Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides (baseline, 4, and 8 weeks). Haematological parameters and fat-soluble vitamins (baseline and 8 weeks)	8 weeks	B
Zahorska-Markiewicz 2002 (39)	50 obese (BMI > 30) but otherwise healthy females aged between 22 and 59 years. Poland	Two tablets of chitosan (750 mg) three times daily vs. placebo (dose and composition unknown). Low calorie diet (1000 kcal day^{-1}), physical activity and intensive behaviour modification	Body weight, BMI, body fat, fat free mass, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose, blood pressure	24 weeks	B

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Numbers of participants reported are those that were randomized into the study and may be more than the total analysed (Fig. 1).

†This grading system is based on that recommended by the Cochrane Collaboration (;26). A grade = allocation concealment (concealment of randomization assignment) adequate, B grade = allocation concealment unclear.

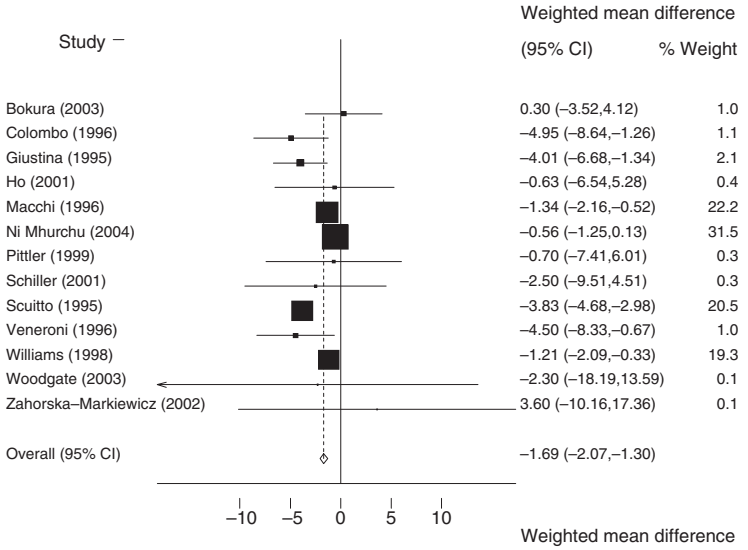

Figure 2 Analysis of change in body weight – all trials.

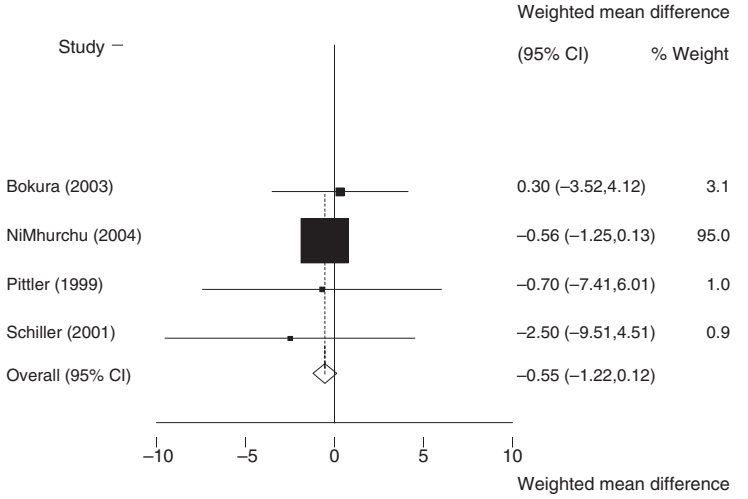

Figure 3 Analysis of change in body weight – A grade trials. This grading system is based on that recommended by the Cochrane Collaboration (26). A grade = allocation concealment (concealment of randomization assignment) adequate, B grade = allocation concealment unclear.

cholesterol of –0.2 (–0.3, –0.1) mmol L^{-1} in favour of chitosan vs. placebo ($P < 0.00001$). A grade trials (17,35,36) produced an estimated reduction in cholesterol of –0.2 (–0.2, –0.1) mmol L^{-1}, $P = 0.0002$, vs. an estimated WMD of –0.5 (–0.7, –0.3) kg, $P < 0.00001$ in the B grade trials (18,24,31,33,39,40). The I^2 statistic indicated little heterogeneity in the A grade trials ($I^2 = 23.2\%$) but significant heterogeneity in the B grade trials ($I^2 = 78.7\%$).

Combining data from trials that provided data on numbers of adverse events (17,18,24,25,31–36,38–40) showed that there were no clear differences between intervention and control groups in terms of frequency of adverse events: odds ratio of 1.2 (0.8, 1.8), $P = 0.5$.

Only two included trials measured the effect of chitosan on faecal fat excretion (36,37), and both used different measures. Ni Mhurchu *et al.* (36) measured faecal fat excretion in a subsample of 51 study participants and found a reduction in faecal fat excreted by the treatment group [–0.08 (1.53) mmol day^{-1}, or –0.6%] vs. the placebo group [+0.12 (1.50) mmol day^{-1}, or +0.8%], $P = 0.9$. Schiller *et al.* (37) measured faecal fat excretion in a subsample of seven study participants and although there was an increase in faecal fat excreted by the treatment group [+6.0 (5.0) g day^{-1}, or +204%] vs. the placebo group [–2.3 (2.6) g day^{-1}, or –39%] the sample size was too small to draw any conclusions about statistical significance.

No evidence of publication bias was found using the Egger regression method in STATA (metabias command) (28) ($P = 0.62$).

Discussion

This systematic review indicates that chitosan may have a small effect on body weight. However, this finding should be interpreted with caution because the results were sensitive to study quality, study duration, and the inclusion of

weight loss agents other than chitosan. Data from high-quality trials suggest an estimated mean weight difference of only –0.6 (–1.2, 0.1) kg between people taking chitosan vs. people taking placebo. This difference of approximately half a kilogram achieved over trial periods ranging from 4 weeks to 6 months is minimal and therefore unlikely to be of clinical significance. The effect of chitosan on total cholesterol levels was similarly reduced in high-quality studies [–0.2 (–0.2, –0.1) mmol L^{-1}] but remained statistically significant ($P = 0.0002$) although its clinical significance is also questionable.

Several small studies reported surprisingly small SD associated with changes in outcomes. Three studies in particular had sample sizes of only 20 (24), 27 (38) and 88 (25) and yet reported SD for change in body weight that were less than those reported in a trial involving 250 participants (36). This unusual finding suggests either remarkably homogeneous sample populations or a data error. As the weight is inversely proportional to the precision these small studies (with apparent high precision) have been given more weight and thus have a large influence on the combined estimate.

A previous meta-analysis of chitosan as a treatment for body weight reduction (16) found a mean difference in terms of weight reduction between chitosan and placebo groups of 3.3 (1.5, 5.1) kg, which is considerably greater than that found in this review. However, the meta-analysis by Ernst and Pittler (16) was based on only five Italian studies published in 1995 and 1996 (24,25,31–33) and since then many additional studies of chitosan have been published that have been included in this updated review. Concerns were expressed about the possibility of a systematic bias in the five studies included in the previous meta-analysis because they were all supplied by one manufacturer, were similar in design, and appeared in the same Italian journal. It is worth noting that these five studies consistently demonstrated the greatest effects in this review, did not meet the allocation concealment criteria, were all of short duration, and four of them also included other weight loss agents in addition to chitosan. As a result, these studies were excluded from many of the sensitivity analyses, thus partly explaining the smaller effects seen in the restricted analyses. Correspondence with the authors of these studies was unsuccessful and therefore these issues, together with the possibility of duplicate publication, remain unresolved.

The use of non-prescription is weight loss products is common the USA, particularly amongst young obese women, of whom over a quarter (28%) report using such products (41). Although comparable data are not available for the UK it has been estimated that almost one-fifth (19.8%) of the population purchased over-the-counter herbal remedies in 1997–98 (42). Under current regulations in most countries manufacturers of dietary supplements are not required to provide evidence of efficacy or safety before marketing a product. However, there have been recent calls to regulate these products for both safety and efficacy (43,44). The costs of relying on ineffective dietary supplements as a means of controlling weight rather than employing more effective weight loss methods are difficult to quantify but are unlikely to be trivial.

In conclusion, this systematic review of randomized controlled trials of chitosan suggests a small effect of approximately 1.7 kg weight loss in short-term treatment of overweight and obesity. However, results obtained from high-quality and long-term trials indicate that the effect of chitosan on body weight is substantially less and unlikely to be of clinical significance.

Acknowledgements

This paper is based on a Cochrane review, which is expected to be published in full in the Cochrane Library in 2005. For the complete review, the Cochrane Library should be consulted: http://www.update-software.com/clibng/cliblogon.htm. We are grateful to Maree Hackett and Andrew Jull for their advice and help with this review. Funding: Health Research Council of New Zealand. This research was designed and conducted independent of the funding received. Potential conflicts of interest: The authors designed and conducted one of the trials included in the review (36).

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