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In the Absence of Dietary Surveillance, Chitosan does not Reduce Plasma Lipids or Obesity in Hypercholesterolaemic Obese Asian Subjects

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ABSTRACT

Objective: To investigate the effects of Absorbitol on body weight, anthropometry, body composition, blood pressures and lipid profiles in obese, hypercholesterolaemic subjects without dietary restriction.

Design: A randomised, double blind. Placebo-controlled study.

Subjects: Normal volunteers with no history of chronic illnesses (n=88) who were obese (body fat percentage > 20% in males and > 30% in females) and hypercholesterolaemic (total cholesterol > 5.20mmol/L). Sixty-eight (72.3%) subjects completed the study.

Intervention: After a 4 week run in phase, 4 placebo/ Absorbitol (250 mg) capsules were prescribed 3 times a day before meals. Subjects received written information on healthy lifestyle but there was no dietary restriction or monitoring.

Main outcome measures: Weight, body mass index, lean body mass, waist, hip, blood pressure, fasting lipids and insulin levels were taken at baseline, 4th and 16th week of the study.

Statistical analysis performed: Analyses were on an intention-to-treat basis. Comparisons between groups were made using Student's t and Mann-Whitney tests for parametric and non-parametric data respectively.

Results: There was no significant change in the measured parameters in Absorbitol treated subjects compared to those on placebo, with exception of HDL-cholesterol which increased in the absorbitol group and decreased in the placebo group (p=0.048). The side effects of Absorbitol were also comparable to that of placebo.

Conclusions: In the absence of dietary surveillance, Absorbitol does not bring about improvement in weight, anthropometry, body composition, blood pressure or lipid profile.

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INTRODUCTION

Chitosan, an non-acetylated or partially deacetylated chitin (a linear homopolymer of β (1-4) linked N-acetylglucosamine) can be found in the fungal cell wall and the exoskeletons of various arthropods such as crabs and shrimps[1]. It dissolves in the stomach to form an emulsion with intra-gastric oil droplets, which then precipitate in the small intestine at pH 6.0-6.5[2,3]. It inhibits fat digestion by binding to the dietary lipid present in the microemulsion and micelles present in the small intestine[4]. Its ability to inhibit fat digestion and absorption had been shown to be as effective as cholestyramine in rats[5].

Experiments in broiler chickens and rats fed chitosan achieved a significant reduction in weight and cholesterol levels[6-9]. Human studies had also shown that chitosan produced significant decrease of weight and cholesterol levels whist subjects were on a hypocaloric diet of ~ 1000 kcal a[10,11]. Maezaki et al demonstrated a cholesterol lowering effects of chitosan on 8 male adults on 2549-2623 kcal a day diet[12].

In Singapore, Absorbitol, a salt of chitosan, (MinusFat, Ocean Healthcare Pte. Ltd.) is marketed as a weight reducing agent and frequently used by the general public without prior dietetic counselling. In contrast to previous human studies that subjected test individuals to hypocaloric diet, people taking this compound in Singapore are not under strict supervision and thus they have a more liberal caloric intake. We undertook this study to investigate the effects of Absorbitol on body weight, anthropometric measurements, body composition, blood pressures and lipid profiles in obese, hypercholesterolemic Asian subjects while not on dietary surveillance.

METHODS

This was a randomised, double blind, placebo controlled study. The ethics committee of Singapore

General Hospital approved the study protocol. The purpose of the study was explained and informed consent was obtained from each subject. He/she was allowed to withdraw from the trial at any point in time.

Normal volunteers were recruited from the general public by advertisement. Only normoglycemic obese individuals, defined as percentage body fat > 20% in males and > 30% in females[13], with total cholesterol of > 5.20 mmol/L were enrolled in the study. Individuals with seafood allergy, history of alcohol and drug usage, chronic illnesses such as diabetes mellitus, hypertension, ischemic heart disease, stroke, and chronic liver or renal dysfunction were excluded.

The study spanned 16 weeks and subjects were required to make 3 visits: at baseline, after 4 weeks and at the end of 16 weeks. Each subject received brief information from the physician and an educational booklet regarding a healthy lifestyle and healthy diet at the beginning of the study. During the run-in phase comprising the first 4 weeks, all subjects were prescribed placebo (450 mg cornstarch) identical to Absorbitol capsules and instructed to take 4 capsules 3 times a day. This period was introduced to allow the stabilization of any changes in the metabolic parameters that occurred with lifestyle and dietary modification. At the end of 4 weeks, subjects who met the entry criteria were randomised to receive either placebo or 4 capsules of absorbitol (257 mg Shellfish L112 Absorbitol, 175 mg corn starch, 10 mg calcium carbonate, 5 mg magnesium stearate) 3 times a day for further 12 weeks.

For each visit, subjects were asked to attend an out patient clinic after a 10-hour fast. They were advised not to take any beverages containing alcohol or caffeine, to abstain from exercising vigorously and drinking excessive amount of water in the 12 hours prior to attendance at the clinic.

Anthropometric measurements were taken with the subjects in light clothing and without shoes. Height was measured with a wall-mounted stadiometer to the nearest 0.1 cm and weight was measured to the nearest 0.1 kg on a digital scale (SECA). Body mass index (kg/m^2) was calculated by dividing weight over $height^2$. Waist and hip circumferences were taken with a non-elastic tape measure. The waist was defined as the narrowest circumference between the costal margin and the iliac crests and the hip as the widest circumference between the waist and the thighs[14,15].

Blood pressure was evaluated in the left arm in a sitting position after a 5-minute rest. Two readings were taken for each subject and the mean value used in the analysis. Korotkov phase V was taken as the diastolic blood pressure.

Bioelectric impedance analysis was performed with a SEAC Bioimpedance meter (UniQuest Ltd., model SFB3). This meter measures bioimpedance over the frequency range of 4-1024 kHz using a tetrapolar method. Fat free mass was calculated according to the formula described by Lukaski et al[16]. Percentage body fat was then derived from (weight - fat free mass) / weight based on a 2-compartment model.

Any adverse reactions were determined by history taking and compliance to treatment was monitored by pill counting.

Venesection was performed at the end of each visit for measuring lipid profile and fasting insulin. Plasma glucose was assayed at the first visit to exclude those with diabetes mellitus. The serum total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol and glucose were assayed by dry chemistry with Kodak Ektachem Clinical Chemistry Slides and read on the Kodak Ektachem 700 analyser in the Biochemistry Department of the Singapore General Hospital. Methods used were glucose oxidase, O2 electrode for glucose; cholesterol oxidase for total cholesterol; dextran sulphate and cholesterol oxidase for HDL and lipase/glycerol kinase calorimetric method without glycerol correction for measurement of triglyceride, respectively. Insulin was assayed by microparticle enzyme immunoassay (Abbot Imx, Chicago, III).

Statistical Methods

Data were tested for normal distribution using the Kolmogorov-Smirnov test. Comparisons between groups were done using the Student's T test for normally distributed data and the Mann Whitney rank sum test for non-parametric data. Results were analysed on an intention-to-treat basis. All analyses were 2-tailed with p-value of < 0.05 considered statistically significant. All values were expressed as mean $\pm$ standard deviation unless otherwise stated. Statistical analysis was performed using SPSS version 7.5 for Windows (SPSS Inc, Chicago, III).

RESULTS

A total of 88 subjects were enrolled in the study, of which 85 (96.6% of the cohort enrolled) returned for their 2^{nd} visit and analyses of results were performed with the final 68 subjects (72.3% of cohort enrolled) who completed the entire project. Among the 31 females, 15 subjects were assigned to placebo and 16 were given Asorbitol treatment. In the male group, 17 subjects received placebo and 20 received Asorbitol.

Baseline characteristics of treatment and placebo groups at the beginning of the study are shown in table I. In the female cohort, the Asorbitol treated

Table I. Baseline characteristics of subjects in treatment and placebo groups.

Parameters Mean ± SD	Female		Male	
	Absorbitol	Placebo	Absorbitol	Placebo
Age (year)	42.8 ± 6.0	44.3 ± 8.1	42.4 ± 7.3	42.5 ± 7.5
Weight (kg)	63.9 ± 9.0	60.0 ± 9.5	75.1 ± 11.2	77.1 ± 11.1
BMI (kg/m^2)	25.6 ± 2.6	24.6 ± 3.3	25.7 ± 3.6	27.0 ± 3.4
Lean mass (kg)	41.1 ± 7.1	38.4 ± 4.4	55.7 ± 8.2	54.4 ± 7.8
Fat mass (kg)	22.8 ± 4.1	21.6 ± 6.3	19.4 ± 5.0	22.8 ± 6.5
Fat percentage	35.8 ± 4.4	35.5 ± 5.2	25.7 ± 4.4	29.3 ± 5.8*
Waist (cm)	80.6 ± 6.9	76.4 ± 8.3	87.9 ± 8.2	90.6 ± 8.0
Hip (cm)	99.6 ± 6.2	98.8 ± 6.7	99.7 ± 6.5	102.0 ± 6.2
Waist-hip ratio	0.81 ± 0.05	0.77 ± 00.5*	0.88 ± 0.03	0.89 ± 0.05
Systolic BP (mmHg)	109.9 ± 18.6	109.0 ± 14.3	117.5 ± 16.0	118.2 ± 13.1
Diastolic BP (mmHg)	74.0 ± 6.9	74.0 ± 6.1	83.5 ± 11.4	80.4 ± 11.4
Total cholesterol (mmol/L)	6.22 ± 0.87	6.37 ± 0.77	6.02 ± 0.58	6.56 ± 1.77
HDL-cholesterol (mmol/L)	1.30 ± 0.29	1.44 ± 0.49	1.21 ± 0.29	1.11 ± 0.35
LDL-cholesterol (mmol/L)	4.22 ± 0.86	4.13 ± 0.82	3.92 ± 0.60	4.18 ± 0.84
Triglyceride (mmol/L)	1.53 ± 0.72	2.14 ± 2.83	2.07 ± 0.87	2.58 ± 1.54
Fasting insulin (mU/L)	10.9 ± 6.7	9.0 ± 4.7	10.1 ± 6.5	11.8 ± 4.4

BMI body mass index
BP blood pressure
HDL high density lipoprotein
LDL low density lipoprotein
* p<0.05 Student's test

group had significantly higher waist-hip ratios than the placebo treated group (p=0.046) whereas in the male cohort, the Asorbitol treated group had a lower percentage body fat compared to the placebo group at the start of the trial (p=0.044).

Table II shows the change in measured variables during the treatment period. The change in each parameter was obtained by subtracting results of the 2nd visit from the 3rd visit. The change was positive if there had been a rise and negative if there had been decline in the measure parameter. The change in HDL-cholesterol in male subjects in placebo and absorbitol groups were significantly different (p=0.048). This difference was due to a small increase (0.07) In HDL-cholesterol in men on absorbitol and a small decrease in HDL-cholesterol level (0.04 mmol/1) in those on placebo. When each group is taken on its own, there is no significant change in HDL-cholesterol from the baseline. A similar pattern in women but this did not reach statistical significance.

Compliance with the prescribed therapy was generally good with no significant difference between the placebo and absorbitol groups. Percentage of drug consumed was 70.4% ± 7.5 and 82.6% ± 3.3 among males taking placebo and absorbitol respectively. The equivalent figures for females were 78.6% ± 6.4 and 78.6% ± 4.7.

Out of 85 subjects who returned for the second visit, data on side effects were available from 76 individuals. 13 (17.1%) subjects reported adverse effects from the treatment prescribed. The most frequent complaints were gastro-intestinal (5 receiving placebo and 7 receiving absorbitol) and included epigastric discomfort, constipation, diarrhoea, nausea and dryness of throat. 1 placebo treated subject reported the occurrence of a non-specific macular rash. The prevalence of side effects reported were not significantly different between the groups (p=0.53).

12 female and 8 male subjects defaulted follow up. Their baseline characteristics (data not shown) were similar to subjects in the placebo and Asorbitol groups except for age. Those that defaulted were younger (age 36.8 ± 8.5.p = 0.003).

DISCUSSION

While animal experiments have shown weight reducing and hypocholesterolemic effects of chitosan[6-9], most human studies demonstrated similar success only in individuals given a hypocaloric diet of about 1000 kcal[10,11]. Maezaki et al reported cholesterol-lowering effect of chitosan in 8 adult males with daily intake of 2549-2623 kcal[12]. Hitherto, no study has involved free-living

Table II. Changes in the parameters of subjects during the treatment phase.

	Female			Male		
Parameters Mean ± SD	Absorbitol	Placebo	P	Absorbitol	Placebo	P
Weight (kg)	0.03 ± 1.54	0.26 ± 1.21	NS	-0.51 ± 1.79	-0.44 ± 0.99	NS
BMI (kg/m^2)	0.00 ± 0.63	0.11 ± 0.49	NS	-0.18 ± 0.64	-0.15 ± 0.34	NS
Lean mass (kg)	0.60 ±1.75	-0.02 ± 1.16	NS♦	-0.42 ± 2.17	-0.63 ± 2.58	NS♦
Fat mass (kg)	-0.57 ± 1.76	0.27 ±1.43	NS	-0.08 ± 1.76	0.19 ± 2.21	NS
Fat percentage	-0.95 ± 2.43	0.24 ± 2.13	NS♦	-0.07 ± 2.19	0.34 ± 2.91	NS♦
Waist (cm)	0.84 ± 1.49	0.24 ± 2.19	NS♦	0.15 ± 1.85	-0.01 ± 1.95	NS♦
Hip (cm)	0.03 ± 2.59	-0.09 ± 2.96	NS♦	0.01 ± 2.07	-0.58 ± 1.88	NS♦
Waist-hip ratio	0.009 ± 0.018	0.002 ± 0.027	NS	0.001 ± 0.019	0.005 ± 0.023	NS
Systolic BP (mmHg)	2.4 ± 11.5	2.4 ± 14.7	NS♦	-0.6 ± 9.5	1.3 ± 11.3	NS
Diastolic BP (mmHg)	0.2 ± 10.2	-0.5 ± 8.0	NS	-1.0 ± 11.0	-1.2 ± 12.2	NS
Total cholesterol (mmol/L)	-0.12 ± 0.58	-0.20 ± 0.35	NS	0.14 ± 0.51	-0.08 ± 0.50	NS
HDL-cholesterol (mmol/L)	0.06 ± 0.29	-0.12 ± 0.32	NS♦	0.07 ± 0.22	-0.04 ± 0.09	P<0.05
LDL-cholesterol (mmol/L)	-0.11 ± 0.45	-0.06 ± 0.44	NS	-0.05 ± 0.10	-0.02 ± 0.44	NS
Triglyceride (mmol/L)	-0.01 ± 1.09	0.15 ± 0.68	NS	-0.11 ± 1.03	0.14 ± 0.73	NS
Insulin (mU/L)	0.44 ± 5.36	-0.65 ± 3.37	NS	2.70 ± 11.59	1.48 ± 2.77	NS

Unless otherwise indicated, Student's test was used
♦ Mann Whitney test
NS not significant

males and females. While the authors recognise the importance of diet in the modulation of body weight and lipid profile, this product is often purchased by individuals over the counter without a medical prescription for purpose of weight reduction without prior dietary counselling or subsequent monitoring. In light of this, we only counselled the subjects on healthy lifestyle and diet once and deliberately omitted nutritional surveillance throughout the study period to reflect the actual circumstances in which these products are used. The cohort of subjects in our study were more obese and had higher lipid profiles than national average (National Health Survey 1992, data unpublished). It was thus very likely that their daily calorie and fat intake exceeded the national average (1673 kcal and 56 g fat for women and 2283 kcal and 78 g fat for men - National Health Survey 1992).

This study did not show any significant change in weight, anthropometric measurement, body composition, blood composition, blood pressure, lipid profile or fasting insulin levels in subjects treated with Asorbitol compared to the placebo treated group. We believe that subjects could have inadvertently increased their calorie intake under the false belief that chitosan would bind all fat that was consumed. Any beneficial effects of chitosan would then be masked by the dietary indiscretion. The fall in HDL-cholesterol among men taking placebo and the improvement in those on absorbitol is consistent with this hypothesis.

Non-compliance to therapy might also have contributed to the results shown. Compliance was monitored by the percentage of capsules consumed. In the Asorbitol group, compliance was 82.6% in females and 78.6% in males during the treatment period of 12 weeks. This reflected an average dose of 2.48 g and 2.36 g Asorbitol a day in females and males respectively. The study reported by Maezaki et al had used 3-6 g of chitosan a day to demonstrate beneficial effects on the metabolic parameters. Our group of patients in contrast, had received a smaller dose that might be sub-therapeutic and therefore accounted for the drug failure.

While Asorbitol might not have brought about metabolic improvements in the subjects, the treatment was well tolerated and the incidences of side effects were similar between placebo and treated group.

CONCLUSIONS

To achieve weight loss and cholesterol reduction, dietary restriction remains a cornerstone of therapy. While we believe that there may be some benefit of chitosan in achieving weight loss and cholesterol lowering, our study demonstrates that, in the absence of dietary surveillance, chitosan does not bring about improvements in weight, body composition or lipid profile.

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