Lowering Serum LDL-Cholesterol in Mild Hypercholesterolemia Patients with Chitosan Capsules

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Synopsis

In the form of a clinical study, this study aimed to determine the efficacy and safety of chitosan in reducing LDL-cholesterol in patients having slightly above normal low-density lipoprotein cholesterol serum levels (LDL-cholesterol) who also were diagnosed with slightly high hypercholesterolemia. There were three groups of subjects in the randomized, double-blinded, placebo-controlled trial. Group 1 was provided with two chitosan capsules (580 mg/day). Group 2 was given four chitosan capsules (1,160 mg/day). Group 3 was given a placebo. The subjects began taking the chitosan capsules on a specified day, filled in the Intake Diary, and continued taking the capsules for 12 weeks. After beginning the chitosan capsule intake, the subjects came to the hospital after four weeks, eight weeks, and twelve weeks and were given blood tests and urine tests. Their body measurements were also taken and medical staff interviewed the subjects to confirm that they were continuing to take the chitosan supplements as prescribed. Results from the eighth week showed that the LDL-cholesterol of the men with more than 140 mg/dℓ of LDL-cholesterol at the baseline who took in 1,160 mg/day of chitosan was significantly reduced when compared to the LDL-cholesterol of the subjects who took the placebo ($p<0.05$). In addition, the chitosan supplements were effective in lowering levels of the LDL-cholesterol and no side effects were noticeable. The results suggest that chitosan supplements are effective and safe.

Key words : chitosan, LDL-cholesterol, Randomized Controlled Trial, humans

1 Introduction

Japanese people have had comparatively little arteriosclerosis disease such as coronary artery disease until around the 1970s or 1980s. However, since Japanese have adopted European and America lifestyles, there has been an increase in obesity, hyperlipemia and diabetes. The cholesterol levels of Japanese in their 40s and 50s have gradually risen from the 1960's to the 1990's. Those levels now approach the mean value of the cholesterol levels in the United States. There is now much concern about an increase in the frequency of arteriosclerosis-related disease in Japan in the coming years.

There are now a number of important clinical studies being conducted in Japan such as : the NIPPON DATA80, 90[1~3] of epidemiology investigation, MEGA[4] and JELIS[5,6]. The Atherosclerosis Society of Japan provided the arteriosclerosis disease prevention guideline for the purpose of preventing coronary artery disease and an atheroma cerebral infarction in 2007. However, this diagnostic standard does not show the standard when the medications were first prescribed or other risk factors. Since it has become necessary to emphasize improvements in lifestyles, researchers began to focus on patients who had the targeted values of LDL-cholesterol.

Chitosan is derived by the deacetylation of chitin, a major component of the shells of crustacea such as crabs and shrimps. The structure resembles cellulose[7,8]. Its functional group is the polycation of the amino group which has results in the various physiological functions of the chitosan[9,10]. Various researchers have found that chitosan has been effective in lowering blood cholesterol[11,12] in tests on animals and

humans. In this project, we produced capsules containing chitosan focusing on safety, convenience, and preservation. We then administered these capsules to adult males and females having had slightly high LDL-cholesterol over a long period of time and examined the effects on LDL-cholesterol using a double-blinded, placebo-controlled trial.

2 Materials and Methods

Study Design

This study was a parallel, placebo-controlled double-blind test.

A placebo control and chitosan capsules (Chitosan Food Industries Ltd, Miyazaki, Japan) were used. A chitosan capsule contained 290 mg of chitosan.

The study protocol was carried out with the approval (approval number 10) of the Effects Examination Diagnosis Committee of the hospital attached to the Medical School of Osaka City University based on the ethics guidelines of the Helsinki Declaration and Epidemiologic Study.

Subjects

An agreement was acquired from 150 volunteers aged 20 and above that passed the basis of selection of 120 mg/dℓ or more of LDL-cholesterol. 101 subjects were selected and were

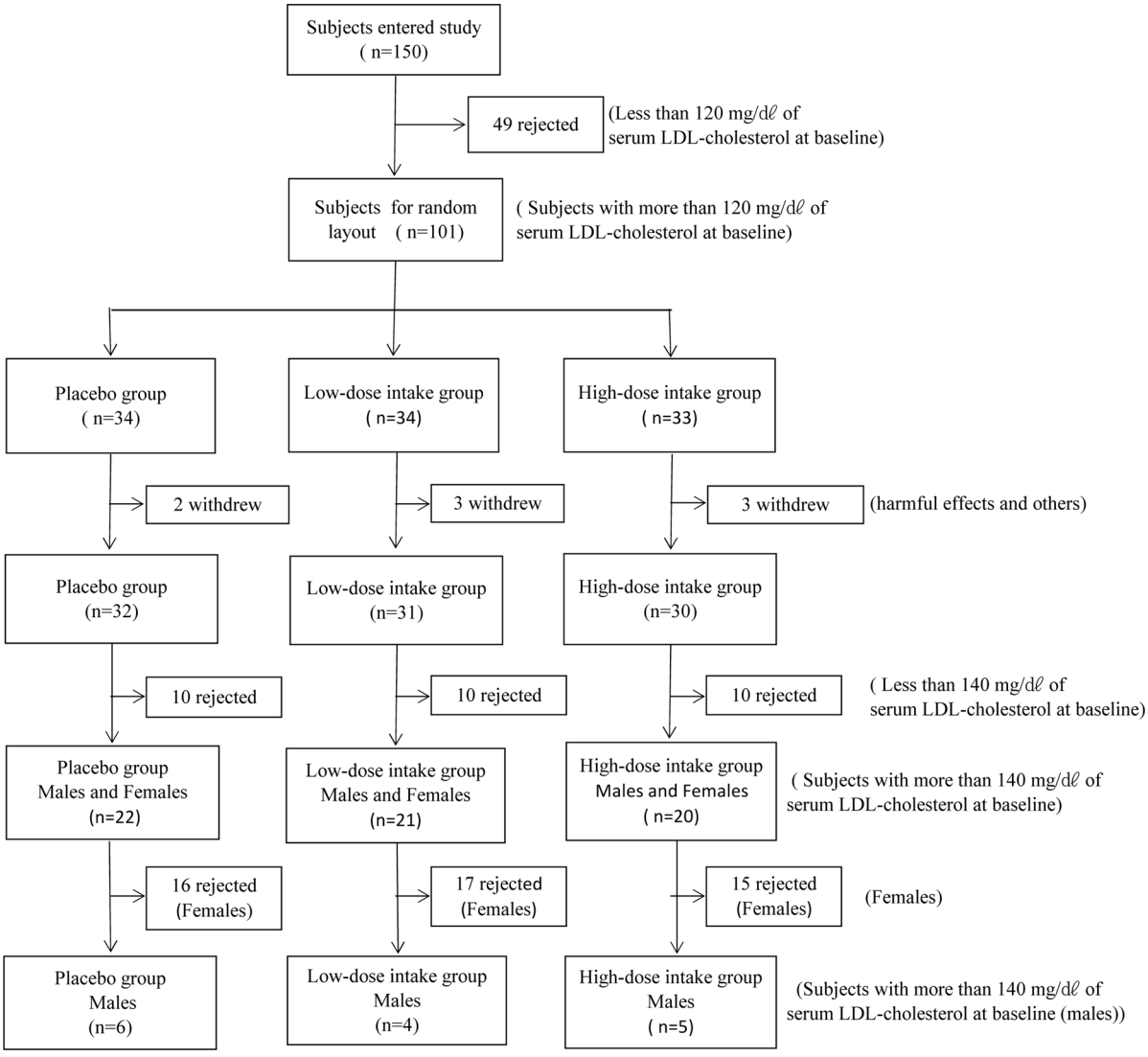

Fig. 1. Flow chart for the number of the subjects

Table 1. The characteristics and serum lipids of subjects with more than 120 mg/dℓ of serum LDL-cholesterol at baseline (males and females)

Parameter	Placebo	Low-dose intake	High-dose intake	*P*
Number of subjects	34	34	33	
Male : Female	10 : 24	10 : 24	10 : 23	
Age (y)	53 ± 12	53 ± 12	54 ± 11	0.90
Height (cm)	161.6 ± 9.1	159.5 ± 7.7	159.5 ± 7.9	0.50
Weight (kg)	61.7 ± 13.8	59.8 ± 11.6	61.4 ± 11.5	0.79
Body mass index (kg/m^2)	23.4 ± 3.5	23.4 ± 3.3	24.0 ± 3.4	0.68
Blood pressure (mmHg)				
Systolic	127 ± 17	127 ± 18	128 ± 23	0.93
Diastolic	80 ± 11	77 ± 18	77 ± 13	0.46
Pulse (n/min)	73 ± 10	72 ± 11	72 ± 10	0.85
Total cholesterol (mg/dℓ)	238 ± 27	238 ± 26	239 ± 25	0.71
HDL-cholesterol (mg/dℓ)	60 ± 12	66 ± 14	63 ± 14	0.39
LDL-cholesterol (mg/dℓ)	153 ± 21	153 ± 21	151 ± 21	0.58

Values are mean ± standard deviation.
P: *P*-value for comparison between groups

requested to come to the hospital. 49 subjects were found unsuitable. After obtaining all baseline data on their first visit to the hospital, they were assigned randomly to one of the three groups. Male and female were randomized separately. The subjects were given 0, 580 and 1,160 mg of chitosan per day in capsule form. They started chitosan capsules intake and entry in the diary on the appointed day. Intake was continued for 12 weeks (Fig. 1 and Table 1).

Test Products and Diet

Chitosan, which was supplied as a capsule, has a density of 72.5%, viscosity of 160 mPa s and extent deacetylation of 89.5%. The capsule used the standard of No. 1. The No. 1 capsule (400 mg capacity) containing 290 mg of chitosan was used. Placebo capsules contained 400 mg of Sweet potato starch. There was no difference between chitosan capsules and placebo capsules in the color, size and form. Subjects took four capsules at meal time with water daily.

Four capsules per day were placed inside a small bag. The quantity needed for four weeks were handed out to the subjects during every medical examination.

Table 2. The design of trial, and the schedule for evaluation

Observation item	Screening and baseline before 2 weeks of capsule intake	Capsule intake first day	After 4 weeks of capsule intake	After 8 weeks of capsule intake	After 12 weeks of capsule intake
	The-14th day	The 0th day	The 28th day	The 56th day	The 84th day
Capsule intake		←			→
Intake situation (Intake diary)		←			→
Medical examination by interview	○		○	○	○
Body measurement	○		○	○	○
Vital sign	○		○	○	○
Blood test	○		○	○	○
Examination of urine	○		○	○	○

Measurement Schedule and Methods of Measurements

The subjects came to the hospital after four weeks, eight weeks, and twelve weeks of intake and blood tests, urine tests, a body measurements were carried out. The subjects were interviewed about any changes in their behavior. The schedule of each evaluation item is shown in Table 2.

Each measuring method is shown below.

(1) Intake situation (intake diary)
  1) To ensure proper procedures, presence and the times of the intake are filled in.
  2) Test capsules were collected every four weeks and the intake schedule of the patient was confirmed.

(2) Body measurement: Height and weight (Only when coming to a hospital first time, the height was measured).

(3) Vital sign: Blood pressure (systolic pressure and diastolic pressure) and pulses

(4) Blood test (WBC: White blood cell, RBC: Red blood cell, Hb: Hemoglobin, Hct: Hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, Platelet) and Biochemical examination of blood (T-cholesterol, HDL-cholesterol, LDL- cholesterol, TG: Triglyceride, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, γ-GTP: gamma-Glutamyl transpeptidase, Albumin, Creatinine, BUN: Blood urea nitrogen, T-bilirubin, CK: Creatine kinase, and BS: Blood sugar)
  1) The quantity of drawing blood was 12 mℓ. It was divided for blood test, for the blood sugar determination and for biochemical examination of the blood. After it is left in the room temperature for 30 minutes, centrifuge (3,000 rpm, 10 min) is performed, and the serum is isolated, and it is frozen for preservation at −80°C until it was measured.
  2) It was measured using the automatic analyzer of the hospital center attached to the medical school of Osaka City University.

(5) Examination of urine: Sugar, Protein, Urobilinogen (It is measured by the paper method)

(6) Medical examination by interview

Statistical Analysis

Statistical analyses were performed with the SPSS Base and Advanced Models 10.1 statistics program.

The results are expressed as group means and standard deviation.

Changes in a group were analyzed using paired *t*-tests and comparisons between groups were analyzed using analysis of variance (ANOVA).

All statistical testing was two-sided with a significance level of 5%.

Contrasts with a *P*-value less than or equal to 0.05 were called statistically significant.

3 Results

The body weight and blood pressure remained stable during the trial period in every study group. There were no significant differences in blood test (WBC, RBC, Hb, Ht, MCV, MCH, MCHC, and Platelet) and biochemical examination of blood (TG, AST, ALT, and γ-GTP, Albumin, Creatinine, BUN, T-bilirubin, CK, and BS) among the study groups.

The change of serum lipids (T-cholesterol, HDL-cholesterol, LDL-cholesterol and Triglycerides) of each test group was shown in Table 3. No significant difference was recognized although analysis of variance of the LDL-cholesterol value was performed at four weeks, eight weeks and twelve weeks. Among all subjects (28) were under LDL-cholesterol 140 mg/dℓ, 22 subjects was equal to or less than T-cholesterol 220 mg/dℓ, and they were normal. The LDL-cholesterol of subjects of each group of more than 140 mg/dℓ at baseline was examined. The change of serum lipids of subjects of each group is shown in Table 4. The results of examination after each four-week period were analyzed using ANOVA. The significant difference was not recognized at

Table 3. Values of serum lipids of subjects with more than 120 mg/dℓ of serum LDL-cholesterol at baseline (males and females)

	Placebo (n=32)	Low-dose intake (n=31)	High-dose intake (n=30)
Total cholesterol			
Baseline	240.6±26.3	236.3±26.4	235.8±23.8
4 week	248.3±33.7	243.4±30.4	242.1±28.4
8 week	249.4±28.6	245.1±29.1	238.6±31.2
12 week	245.5±31.2	239.3±33.5	241.9±33.5
HDL-cholesterol			
Baseline	60.6±12.0	65.3±13.2	63.5±14.2
4 week	63.1±12.6	67.7±14.7	65.9±14.6
8 week	60.9±11.8	66.3±15.2	62.1±16.0
12 week	61.8±13.4	65.7±14.6	63.0±16.4
LDL-cholesterol			
Baseline	153.9±20.7	152.5±21.3	149.1±20.8
4 week	157.3±23.0	155.0±24.9	153.2±24.9
8 week	163.3±13.7	159.2±23.5	151.6±24.1
12 week	154.97±23.8	150.6±27.0	150.3±27.4
Triglycerides			
Baseline	132.5±68.7[a]	95.1±36.4[b]	126.1±57.4[ab]
4 week	134.4±102.8	97.5±36.3	111.6±49.0
8 week	120.3±64.2	99.3±38.8	121.9±52.5
12 week	122.3±75.4	97.5±35.7	128.3±66.3

Values are mean±standard deviation.
Means with different letter within a row are significantly defferent at $P<0.05$ (ANOVA).

Table 4. Values of serum lipids of subjects with more than 140 mg/dℓ of serum LDL-cholesterol at base line (male and female)

	Placebo (n=22)	Low-dose intake (n=21)	High-dose intake (n=20)
Total cholesterol			
Baseline	251.7±22.8	247.2±23.7	244.9±21.7
4 week	260.0±33.6	254.0±26.4	249.0±29.6
8 week	261.2±25.0	255.0±24.5	246.1±30.0
12 week	258.0±25.6	250.3±30.2	244.0±34.6
HDL-cholesterol			
Baseline	59.3±10.6 *	64.4±12.6	64.8±15.5 *
4 week	63.1±10.8 *	66.7±13.4	67.8±15.2 *
8 week	58.8±11.1	65.0±14.7	63.3±17.1
12 week	60.9±12.2	65.8±14.3	65.4±17.1
LDL-cholesterol			
Baseline	164.8±14.9	162.6±18.3	159.3±17.8
4 week	167.2±20.9	165.5±19.1	161.6±24.1
8 week	174.5±21.3	168.6±17.1	160.2±23.6
12 week	164.6±20.1	160.0±22.6	158.5±28.9
Triglycerids			
Baseline	145.6±66.2	99.9±40.9	147.6±55.7
4 week	140.2±83.5	94.9±35.9	127.3±45.6
8 week	145.6±66.2	102.6±43.4	138.0±47.3
12 week	140.2±83.5	92.0±33.7	123.2±39.8

Values are mean±standard deviation.
*: $P<0.05$ (ANOVA)

baseline, the fourth week and the twelfth week, but the different tendency ($F = 2.51$, $P = 0.089$) was recognized statistically by the eighth week. In the multiple comparison, the tendency ($P = 0.073$) for the LDL-cholesterol of the high-dose intake group to decrease at the eighth week as compared with the placebo group was recognized. The significant difference was not recognized between the placebo group and the low-dose intake group, or between the low-dose intake group and the high-dose intake group. Therefore, the LDL-cholesterol of the subjects of males with more than 140 mg/dℓ LDL-cholesterol at baseline was analyzed. The change of serum lipids of male subjects of more than 140 mg/dℓ LDL-cholesterol at baseline in each group is shown in Table 5. The effects of each examination were analyzed using ANOVA. The significant difference ($F = 4.70$, $P = 0.031$) was recognized statistically by the eighth week, though no significant difference were recognized at baseline, the fourth week or the twelfth week. In the multiple comparison, although the significant difference was not recognized at baseline, the fourth week and the twelfth week between each group, the significant decrease ($P = 0.036$) of the LDL-cholesterol was recognized statistically by the high-dose intake group at the eighth week as compared with the placebo group. Moreover, in the high-dose intake group, the significant tendency ($P = 0.082$) was recognized statistically in comparison with the low-dose intake group at the eighth week. The significant difference was not recognized between the placebo group and the low-dose intake group.

4 Discussions

The management goal of the LDL-cholesterol is in the primary prevention of coronary-artery disease. Patients with no main risk factors may be able to maintain LDL-cholesterol levels of less than 160 mg/dℓ (low risk group). Patients with one or two main risk factors may be able to

Table 5. Values of serum lipids of subjects with more than 140 mg/dℓ of serum LDL-cholesterol at base line (males)

	Placebo (n = 6)	Low-dose intake (n = 4)	High-dose intake (n = 5)	
Total cholesterol				
Baseline	248.3 ± 28.4	245.0 ± 32.5	251.6 ± 20.7	
4 week	260.8 ± 50.6	248.5 ± 29.1	226.6 ± 18.2	
8 week	247.0 ± 24.7	251.0 ± 13.4	237.0 ± 20.3	
12 week	244.2 ± 31.0	244.8 ± 19.7	221.0 ± 23.5	
HDL-cholesterol				
Baseline	51.2 ± 4.1	56.8 ± 13.4	57.4 ± 13.5	
4 week	55.3 ± 10.0	61.0 ± 15.9	60.6 ± 15.0	
8 week	49.7 ± 5.4	56.3 ± 13.1	54.6 ± 13.9	
12 week	48.8 ± 6.1	59.5 ± 15.2	52.8 ± 13.2	
LDL-cholesterol				
Baseline	166.8 ± 18.4	161.5 ± 16.9	159.0 ± 19.7	
4 week	165.0 ± 21.5	160.8 ± 25.0	141.0 ± 9.8	*
8 week	166.0 ± 13.7[a]	164.5 ± 5.3[a]	146.0 ± 12.0[b]	
12 week	156.7 ± 23.0	156.5 ± 14.7	145.6 ± 30.6	
Triglycerides				
Baseline	183.2 ± 93.4	109.0 ± 12.9	171.4 ± 88.2	
4 week	195.5 ± 120.4	105.0 ± 26.3	125.6 ± 64.3	
8 week	184.0 ± 92.4	134.3 ± 50.9	146.4 ± 63.0	
12 week	203.7 ± 89.8	116.5 ± 39.5	117.6 ± 43.5	

Values are mean ± standard deviation.
Means with different letter within a row are significantly defferent at $P < 0.05$ (ANOVA).
*: $P < 0.05$ (ANOVA)

maintain LDL-cholesterol levels of less than 140 mg/dℓ (intermediate risk group). However, when main risk factors are 3 or more, the LDL-cholesterol levels should be less than 120 mg/dℓ (high risk group). In addition, patients whose LDL-cholesterol is 140 mg/dℓ have a relative risk that is 1. 5 times that of 120 mg/dℓ LDL-cholesterol or a patient with 160 mg/dℓ LDL-cholesterol whose relative risk is about twice compared with LDL-cholesterol levels of 120 mg/dℓ should press for improvements in lifestyle. However, there are no safe areas in long-term prevention even if there is no risk factor. To prevent arteriosclerosis like this, the management of LDL-cholesterol and the improvement of the lifestyle are important, and it is especially important to improve eating habits. Therefore, the development of safe food that decreases LDL-cholesterol is important from the viewpoint of the primary prevention that prevents the occurrence of arteriosclerosis.

In this study, we investigated the lipid in blood before and after the chitosan ingestion by the subjects. The cholesterol in the blood was decreased by chitosan ingestion by being excreted through the cholic acid and chenodeoxycholic acid of the primary bile acid in feces. However, it is suggested that chitosan disturbed the circulation of liver bile acid to the intestines, decreased the cholesterol in the body cholesterol pools, and it reduced cholesterol in the blood[13,14]. In the guideline, arteriosclerosis is classified into the high risk groups and provides the management goal value of LDL-cholesterol 120 mg/dℓ. In this examination, when the subjects began to take the experimental supplements, the subjects were chosen who had LDL-cholesterol of 120 mg/dℓ or more. However, the decrease of the LDL-cholesterol of the chitosan intake group was not significant. Also in other reports[15], chitosan was shown to be effective on subjects, classified as seniors, who took chitosan with meals regularly. When diets were studied, chitosan was effective for those who ate regular meals three times a day with no snacks[16].

In this study, it is possible that the cause that a significant difference did not appear for about 30% of the subjects in each group was that they had between 140 mg/dℓ and 120 mg/dℓ of LDL-cholesterol.

Since chitosan capsules are considered to be natural medicine, it is consider to be the causes of having not appeared the significant difference in the effect of chitosan which receives influence in meal intake having pointed so that it might take in to either of three meals per day, having not directed to take a regular meal and having not investigated a meal ingestion situation, etc. However, even if there was no risk factor of arteriosclerosis, when considering long-term primary prevention, it is still not safe for subjects with LDL-cholesterol 140 mg/dℓ or more. The results were statistically significant different between each group at the eighth week.

By multiplex comparison, the decrease tendency of a LDL-cholesterol was documented at the eighth week by the high-dose intake group as compared with the placebo group. Moreover, when only the males of 140 mg/dℓ or more of LDL-cholesterol were tested, an analysis of variance was conducted. The significant difference was shown at the eighth week. By multiplex comparison, as compared with the placebo group, the LDL-cholesterol decreased significantly at the eighth week for the high-dose intake group. The decrease was similar to that of the low-dose intake group. According to the test result of Maezaki[13], it is reported that the value of the high T-cholesterol group was decreased by chitosan intake. In addition, there are some similar reports on the effectiveness of chitosan shown by people with a comparatively high T-cholesterol. It seems that chitosan showed the tendency to decrease LDL-cholesterol on subjects with a significant LDL-cholesterol of 140 mg/dℓ or more. The physiological change factor of the serum T-cholesterol value is reflecting the change of LDL-cholesterol. Moreover, sex difference, age difference, etc. are mentioned as change factors of

LDL-cholesterol, and LDL-cholesterol value of 40 year-olds is the highest in males. It may be related to the subjects being comparatively in the prime of life that LDL-cholesterol deceased significantly for males in this study. Moreover, chitosan had significantly decreased the LDL-cholesterol for the high dose intake group only at eight weeks in this study. This suggests that the medical treatment effect on serum lipid values by the chitosan intake is comparatively short term[17]. Although changes appeared in blood tests and scientific findings after taking in each all food intake groups, all had small changes within the standard value. The change patterns of chitosan food intake groups were the same pattern as the placebo group. Since a significant difference between groups was not observed, these changes are within the normal physiological limits. It is possible that the causal relationship with the chitosan food intake was low. Moreover, a few harmful effects such as constipation, stomachaches, upset stomach, and hives were observed within the examination period. Almost all examples were noticed after eating and were transient. And, they recovered completely during the examination period.

From the above-mentioned results, we believe that chitosan is safe and effective for a healthy person who has slightly higher LDL-cholesterol than normal and is not taking medication.

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境界域及び軽度コレステロール血症患者の血清 LDL-コレステロール値はキトサン入りカプセル摂取で減少する

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要　約

境界領域および軽度コレステロール血症患者の血清低密度リポタンパク質コレステロール値（LDL コレステロール）の人々に対するキトサン約 290 mg を含むカプセル摂取の影響および安全性を検討した。

2 個のキトサン・カプセル（580 mg/日）および 4 個のキトサン・カプセル（1,160 mg/日）の 2 用量を用いて、無作為化、2 重盲検化、プラセボ対照法で行なった。ボランティアの被験者は、医師による面接および身体測定、血液検査［血液生化学検査、一般的な血液検査］、尿検査および健康診断を行なった。これらのデータ（ベースライン）によって、被験者にキトサン・カプセルを割り付け配布した。被験者はキトサン・カプセル摂取を始めたときから摂取日記に書き入れ、12週間継続した。キトサン・カプセル摂取後の被験者は 4 週目、8 週目、12週目に血液検査、尿検査および身体測定が実行された。被験者はまた、面接によって、日常習慣に何か変化がなかったか確認した。1,160 mg/日のキトサンを摂取した被験者の LDL コレステロールは、8 週目に placebo を摂取した被験者の LDL コレステロールと比較して、減少傾向が見られた（$p<0.1$）。1,160 mg/日のキトサンを摂取したベースライン時に 140 mg/dℓ 以上の LDL コレステロール群の LDL コレステロールは、placebo を摂取した被験者の LDL コレステロールと比較すると、8 週目に著しく減少した（$p<0.05$）。

キトサン食品摂取は、医学上問題になる所見や因果関係を示す事実がなく、副作用に関してもほとんど問題となることはなかった。これらからキトサン食品の摂取は、血清 LDL-コレステロール値を低下させる補助食品となることが示唆された。