Original Article

Reducing effect of calcium in combination with magnesium and lactulose on body fat mass in middle-aged Japanese women

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Background: It has been reported that adequate calcium intake decreases body fat and appropriate intakes of magnesium suppress the development of the metabolic syndrome. Furthermore, lactulose increases the absorption of calcium and magnesium. An optimal combination of calcium, magnesium and lactulose may therefore reduce body fat mass. Methods: An open-label randomized controlled trial was conducted to investigate the body fat-reducing effects of a test food containing 300 mg calcium, 150 mg magnesium, and 4.0 g lactulose. Body composition parameters and blood hormone and urine mineral concentrations were measured at baseline and at 6 and 12 months thereafter. Whole-body fat mass was measured with dual-energy x-ray absorptiometry. Results: Seventy-six middle-aged Japanese women (47.5±4.7 years) were randomized to the intake group (n=48) or the non-intake control group (n=28). At 12 months the difference in body fat mass change between the two groups (intake group – control group) was -0.8 kg (95% CI: -1.5 - 0.0 kg, p=0.046), although there were no differences in anthropometric data between the two groups. Body fat percentage at 12 months tended to be lower in the intake group, but the difference was not significant (p=0.09). Conclusions: These findings may suggest that calcium in combination with magnesium and lactulose can reduce body fat mass in middle-aged Japanese women. However, the contribution of magnesium and lactulose are unclear in this study. Further studies are needed to clarify these contributions.

Key Words: calcium, magnesium, lactulose, fat mass, Japanese women

INTRODUCTION

It has been reported that calcium intake induces a reduction in body fat mass and/or the percentage of body fat (reinforcement of the weight-loss effect).[1-4] However, there are also reports indicating that there are no (or only limited) favorable body composition changes induced by the intake of calcium.[5-7] Many interventional trials designed to evaluate the body fat-reducing effect of calcium alone or with dairy products have been conducted in Western countries.[7,8] These trials used dosages of 0.6-2.4 g/day. There have been no reports on the relationship between calcium intake and body fat in the Japanese population. The dietary habits of Western countries and Japan differ substantially, especially with regard to calcium intake. The average calcium intake in Japanese people is approximately 520 mg/day,[9] which is lower than that of people in Western countries. There is no guarantee that the body fat-reducing effect of calcium observed in Western populations can be reproduced in a Japanese population.

It is said that intracellular calcium ion plays a key role in regulating adipocyte lipid metabolism and triglyceride storage.[10] Magnesium is a calcium antagonist, and it is thought that magnesium deficiency raises intracellular calcium concentrations.[11] Lactulose is an oligosaccharide that is used globally as a drug to treat hepatic encephalopathy and constipation, and is a bifidus factor.[12,13] Both animal testing[14] and clinical trials[15,16] have shown that lactulose promotes the absorption of minerals such as calcium and magnesium. In a study using stable isotopes in adult men, we previously found that intake of 4 g of lactulose together with 300 mg of calcium and 150 mg of magnesium enhances calcium and magnesium absorption.[16] Thus, it is possible that lactulose promotes reduction in body fat by promoting calcium and magnesium absorption.

We conducted an open-label, randomized control trial in middle-aged Japanese women over a 12-month period

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to investigate the body fat-reducing effect of a test food containing 300 mg calcium, 150 mg magnesium, and 4 g lactulose.

MATERIALS AND METHODS

Ethics

This trial was performed in accordance with the Helsinki Declaration (2004, Tokyo revised version) and Ethical Guidelines for Epidemiological Research (June 17, 2002; Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare). The institutional review board of the Medical Ethics Committee of Kagawa Nutrition University approved this clinical trial. The trial protocol was explained to each subject, and all subjects provided written informed consent to participate in the study.

Subjects

This trial was conducted at Kagawa Nutrition University. The subjects were recruited from the mothers and other relatives of the students and staff at Kagawa Nutrition University. After the participants' consent was received, a screening inspection was implemented. All subjects were women aged 35-65 years. The following exclusion criteria were applied: 1) Serious liver, renal, cardiovascular, respiratory, endocrine, or metabolic disorders, or food allergies; 2) Bone metabolism disease or abnormal bone metabolism; 3) Abnormal blood calcium and/or magnesium levels; 4) Medical history of allergy to dairy products or diarrhea as a result of ingestion of dairy products. 5) Receiving treatment and/or taking a drug likely to influence body composition (ie female sex hormone, steroidal hormone, thyroid hormone, body fat-reducing drugs, antiepileptic drugs, osteoporosis drugs, vitamin D, or vitamin K); 6) Ingestion of calcium or magnesium supplements on a daily basis; 7) Ingestion of indigestible oligosaccharides on a daily basis; 8) Pregnancy or lactation; or 9) Other health concerns making a subject unsuitable for the trial, as judged by a doctor.

Randomization

The study design was a randomized non-treatment-control parallel group comparative trial. The randomization sequence was generated by stratified permutation-block method by pre- or post-menopause. Subjects were allocated to the intake or the control group according to that sequence. The allocation ratio was 2:1, on the assumption that the number of dropouts would be higher for the intake group than for the non-intake group as a result of lower compliance during the long-term study period.

Test food

The test food was a granulated powder made from lactulose crystals (containing more than 98% lactulose; MLC-97, Morinaga Milk Industry, Japan), a milk-based calcium (containing about 30% calcium, 1% magnesium, 14% phosphate, 7% protein, and 5% water; ALAMIN 998, NZNP, New Zealand) and magnesium oxide, by wet granulation with an ethanol binder. The granulated powder (2.7 g each) was placed into individual polyethylene bags covered with aluminum. Each package contained 150 mg calcium, 75 mg magnesium, and 2.0 g lactulose. The intake group ingested one package twice a day, with breakfast and supper. The control group did not ingest the test food.

Concomitant treatments, drugs, and supplements

During the study period, subjects were instructed to maintain their normal lifestyle, including dietary and exercise habits. They were prohibited from receiving treatment and taking any drug that would influence body composition and calcium metabolism (ie obesity remedies, antihyperlipidemic drugs, female hormones, steroid hormones, thyroid hormone, antiepilepsy drugs, osteoporosis drugs, vitamin D, vitamin K, calcium, magnesium, and indigestible oligosaccharides).

Outcome measures

At the beginning of the trial, and at 6 and 12 months thereafter, the outcomes were measured at the Metabolic Unit at the Sakado campus of Kagawa Nutrition University. After an overnight fast, body fat mass and anthropometry were measured and samples of blood and urine were collected.

Body fat and anthropometry

The primary endpoint was body fat mass at 12 months. The whole-body fat mass was measured with dual-energy x-ray absorptiometry (DXA) (PRODIGY, GE Healthcare, USA). The percentage of body fat was calculated by dividing body fat mass by weight, and multiplying by 100.

Weight was measured using the InBody 720 system (Biospace Japan, Tokyo, Japan).

Laboratory tests

Hematological tests (white blood cell count, red blood cell count, hemoglobin, hematocrit, and number of platelets), blood biochemical tests (total bilirubin, total protein, albumin, urea nitrogen, creatinine, uric acid, alkaline phosphatase, gamma glutamyl transpeptidase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, triglyceride, total cholesterol, high-density lipoprotein-cholesterol, fasting blood sugar, HbA1c, 1,25-dihydroxycholecalciferol - vitamin D_3, sodium, chlorine, potassium, calcium, magnesium, iron, and phosphorus), and urine tests (creatinine, calcium, magnesium, and phosphorus) were performed at SRL, Inc.

Hormone

Serum leptin, adiponectin, and insulin were measured by double-antibody radioimmunoassay, latex agglutination–turbidimetric immunoassay, and chemiluminescent enzyme immunoassay, respectively. Intact-PTH was measured by electrochemiluminescence immunoassay. All hormone tests were performed at SRL, Inc.

Diet survey

The intakes of energy, carbohydrates, protein, fat, and calcium were calculated from a food-intake-frequency questionnaire.[17] Diet surveys were performed at the beginning of the trial and at 6 and 12 months thereafter.

Self-report diary

The intake of the test food and of concomitant treatments,

drugs, supplements, and adverse events were monitored using a self-report diary.

Adverse events

Any adverse events were assessed by medical examination, laboratory testing, and evaluation of diary records. The degree and the causality of the symptom of the adverse event were evaluated according to NCI-CTCAE Version 3.0, adverse event common term standard Ver.3.0, the Japanese translation JCOG/JSCO version.

Statistical analysis

The number of patients was 80, which is the maximum number for enrollment at Kagawa Nutrition University. The following subjects were excluded from the analysis group: 1) Subjects with severe disease of any kind or disease associated with body fat or calcium metabolism; 2) Subjects taking prohibited concomitant treatments, drugs, or supplements; or 3) Subjects of the intake group for whom compliance was less than 67%.

Continuous data are expressed as mean±SD, and categorical data are given as the number of observations. Data that were assumed to have a log-normal distribution were transformed using common logarithms. For the baseline data, *P*-values were shown by *t*-test in the continuous data and by Pearson's chi-square test in the categorical data. Changes in body fat, body weight, BMI, and laboratory tests were analyzed using ANCOVA, which included 12- or 6-month change in data as the response variable, treatment effect as the explanatory variable, and baseline data as the covariate. Changes in 12- and 6-month data from baseline were tested by paired *t*-test. Pearson's chi-square test was used for the ratio of adverse events. All analyses of significance were two-sided and tested at the 5% level.

Analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Subjects

Seventy-six women were enrolled in the trial and allocated randomly to the intake group (n=48), and the control group (n=28; Figure 1). All of the subjects participated in the trial, but one subject in the intake group dropped out before the 12-month examination. Thus, 47 subjects in the intake group and 28 in the control group completed the test. The data of 23 subjects in the intake group and six subjects in the control group were excluded from analysis. Thus, the final analysis was conducted on the data of 25 subjects in the intake group and 22 subjects in the control group. The reasons for exclusion of data from the intake group were as follows: two subjects developed rheumatism and a gastric ulcer, 12 subjects used prohibited drugs, and nine subjects had a compliance of less than 67%. In the control group, two subjects developed transverse colon cancer and gastric ulcers, and four subjects used prohibited drugs. The subjects' baseline data are presented in Table 1. None of the measured parameters differed between the groups.

Compliance

The test food intake ratio (100×intake number/prescribed number) of the intake group was 88.3±8.5% (range: 67.8-99.5%, median: 88.7%).

Body fat and anthropometry

Body fat and anthropometric results are given in Table 2. The body fat mass change at 12 months differed significantly between the two groups (p=0.046), with an effect size (intake group – control group) of -0.8 kg (95% confidence interval: -1.5 - 0.0 kg). The difference between the two groups in body fat percentage change at 12 months showed a non-significant trend (p=0.09), with an effect size (intake group – control group) of -1.0%.

There was no difference in body weight change between the two groups. Waist circumference changes at 6

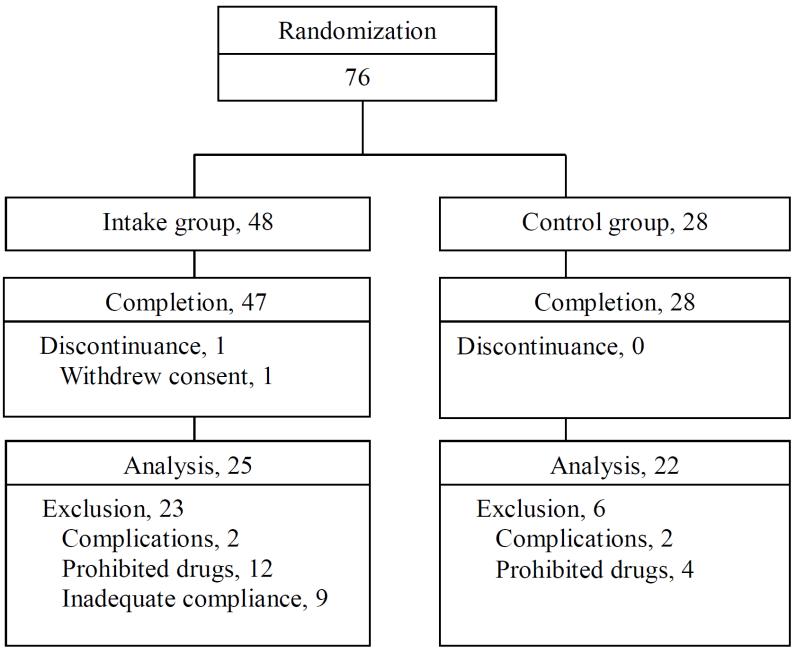

Figure 1. Flow of subjects through the study.

Table 1. Baseline characteristics of the subjects

Descriptors	Intake group (n=25)	Control group (n=22)	*p-value*[†]
Age (years)	48.8±2.7	46.2±6.0	0.056
Menopause (before:after)	19:6	17:5	0.918
Height (cm)	158±5.5	158±3.5	0.970
Weight (kg)	56.4±10.6	54.1±5.7	0.375
Body mass index (kg/m^2)	22.4±3.4	21.6±2.1	0.324
Waist (cm)	82.5±9.9	80.7±6.2	0.478
Body fat percentage (%)	31.0±8.3	30.5±5.4	0.810
Body fat mass (kg)	18.2±8.0	16.7±4.2	0.431
Calcium (mg/dL)	9.3±0.3	9.3±0.4	0.687
Magnesium (mg/dL)	2.3±0.1	2.3±0.2	0.324
Adiponectin (logarithmic transformation)	1.08±0.20	1.08±0.19	0.971
Leptin (logarithmic transformation)	0.82±0.32	0.78±0.24	0.571
Insulin (logarithmic transformation)	0.661±0.224	0.615±0.137	0.406
1,25-dihyroxycholecalciferol (pg/dL)	48.6±16.6	61.4±17.7	0.014
intact-PTH (logarithmic transformation)	1.6±0.1	1.6±0.1	0.744
Exercise habits (yes:no)	11:13	8:12	0.697

[†]For parametric data, *t*-tests; for categorical data, Pearson's chi-square test.

Table 2. Changes in body fat mass, body fat percentage and anthropometric data

		Intake Group	Control Group	*p-value*[†]
Body fat mass (kg)	6 months	-1.0±1.4 (25)	-0.8±0.8 (20)	0.726
	12 months	-1.3±1.5 (24)	-0.4±1.0 (20)	0.046
Body fat percentage (%)	6 months	-1.6±2.1 (25)	-1.5±2.0 (20)	0.887
	12 months	-1.9±2.0 (25)	-0.9±1.6 (20)	0.090
Weight (kg)	6 months	-0.1±1.5 (25)	0.1±1.5 (21)	0.554
	12 months	-0.1±1.4 (24)	0.2±1.1 (21)	0.583
Waist (cm)	6 months	-2.0±2.1 (25)	-1.8±3.2 (21)	0.803
	12 months	-2.5±2.4 (24)	-2.2±2.3 (21)	0.865

Data are expressed as means±SD (n)
[†]Between-group difference by ANCOVA

and 12 months were significantly decreased from baseline in both groups, with no significant difference between the groups.

Laboratory tests

Blood tests

The findings of the blood tests are given in Table 3. In the intake group, magnesium significantly increased from the baseline at 6 and 12 months. In the control group, calcium significantly decreased from the baseline at 6 months, and magnesium significantly increased from the baseline at 6 and 12 months. Serum 1,25-dihyroxycholecalciferol in the control group significantly decreased from baseline at 12 months. None of the measured parameters differed significantly between the groups.

Urine tests

The findings of the urine tests are given in Table 4. At 6 months, the calcium/creatinine ratio in the control group significantly reduced from baseline, and differed significantly between the two groups. These changes were no longer observed at 12 months. The magnesium/creatinine ratio of the intake group significantly increased from baseline at both 6 and 12 months, and was significantly higher than in the control group at both of these time points. There was neither a change from baseline nor a significant difference between the two groups in the phosphorus/creatinine ratio.

Hormone

The findings of the hormone tests are given in Table 3. Serum adiponectin in the control group significantly increased from baseline at 12 months. However, there was no difference between the two groups. Serum levels of both leptin and insulin did not change from baseline and did not differ significantly between the groups at 12 months. Serum intact-PTH significantly increased from baseline at 12 months in the intake group, and significantly increased from baseline at 6 months and 12 months in the control group. However, there was no difference between the two groups.

Frequency of food intake

Carbohydrate intake was significantly higher in the intake group than in the control group for all periods (221 vs 194 g/day, p=0.003; mean of the three periods). At 6 months, the total energy intake in the intake group was higher than that in the control group. No differences between the groups were found for the intake of any of the other measured parameters, such as fat, calcium, and vitamin D. At 6 months, vitamin K intake was lower than baseline in the control group. The mean calcium intake in

Table 3. Changes in biochemical variables from baseline

Item	Group	6 months	12 months
Calcium (mg/dL)	Intake	-0.1±0.4	0.0±0.4
	Control	-0.3±0.3**	0.0±0.4
Magnesium (mg/dL)	Intake	0.1±0.2**	0.2±0.2**
	Control	0.1±0.1**	0.1±0.1*
Adiponectin (logarithmic transformation)	Intake	0.00±0.12	0.04±0.10
	Control	0.02±0.08	0.04±0.08*
Leptin (logarithmic transformation)	Intake	0.01±0.12	-0.03±0.14
	Control	0.03±0.12	-0.03±0.18
Insulin (logarithmic transformation)	Intake	-0.030±0.176	-0.052±0.271
	Control	-0.063±0.180	0.031±0.153
1,25-dihyroxycholecalciferol (pg/mL)	Intake	0.9±16.1	-3.1±13.6
	Control	-1.6±16.9	-6.9±14.3*
intact-PTH (logarithmic transformation)	Intake	0.0±0.1	0.1±0.1**
	Control	0.1±0.1**	0.1±0.2**

Different from the baseline (paired *t*-test) at $p<0.05^{*}$ or $p<0.01^{**}$.
intact-PTH: intact-parathyroid hormone.

Table 4. Analysis of urine minerals

Item	Group	Baseline	6 months	12 months
Calcium/creatinine	Intake	0.118±0.060	0.123±0.070*	0.130±0.068
	Control	0.121±0.076	0.095±0.059#	0.120±0.074
Magnesium/creatinine	Intake	0.061±0.023	0.079±0.034*,##	0.086±0.032*,##
	Control	0.062±0.025	0.056±0.020	0.069±0.028
Phosphorus/creatinine	Intake	0.522±0.181	0.578±0.193	0.566±0.194
	Control	0.573±0.219	0.574±0.158	0.573±0.168

Different from the control group (ANCOVA) at $p<0.05$*.
Different from the baseline (paired *t*-test) at $p<0.05^{\#}$ or $p<0.01^{\#\#}$.

the intake group was 520 mg/day (excluding the test food), and that of the control group was 487 mg/day. Any other change in the periods weren't observed. No differences between the groups or changes in the periods were observed for the frequency of consumption of vegetables, tubers and staple food.

Safety

In the intake group, 362 adverse events were observed in 22 of 25 subjects during the trial period, giving an incidence ratio of 88%. In the control group, 358 adverse events were observed in 20 out of 22 subjects during the trial period (incidence ratio of 91%). The incidence ratio did not differ significantly between the two groups (Pearson's chi-square test, p=0.747). The major symptoms of the adverse events were cold-like symptoms (fever, chill, and pharyngeal pain), menstrual pain, headache, and digestive symptoms (stomach ache, abdominal pains, and diarrhea). There were no characteristic differences in symptoms between the two groups. There were no abnormal changes in laboratory test findings in individuals. In the intake group, adverse events that were undeniably caused by the test food were observed in only one subject. The symptoms were diarrhea and fatigue, and were of low intensity. In the control group, there were three subjects whose adverse events could be attributed directly to participation in the trial. The symptoms were headaches, and the intensity of the symptoms was low.

DISCUSSION

Fat-reducing effects

The present study evaluated the effects of calcium in combination with magnesium and lactulose on body fat mass in middle-aged Japanese women. At 12 months, the difference between groups was observed for body fat mass change. However there were no differences in anthropometric data between the two groups. Previous interventional trials on the effects of calcium on body fat mass have also reported changes in fat mass without changes in anthropometric data.[18-20] A clinical trial in post-menopausal women supplemented with calcium showed that the intake group had a significantly lower amount of abdominal fat and a greater amount of trunk lean mass than the placebo group, although there was no difference between the groups in the percentage change in BMI.[18] One report showed a significant zero-order correlation between calcium intake and percent body fat of –0.36 in post-menopausal women, but the correlation between calcium intake and BMI was non-significant.[19] Another report showed that calcium and vitamin D supplementation was only associated with reduced abdominal visceral adipose tissue, and the data showed no significant weight change or other changes in anthropometric variables.[20]

The amount of calcium

Calcium dosages of 0.6-2.4 g/day have been used in Western trials,[7,8] which may exceed the tolerable upper

intake level of calcium in a Japanese adult (2.3 g/day).[21] A significant finding of the present trial is that the body fat-reducing effect of calcium was induced by a relatively small calcium supplement (0.3 g/day with magnesium and lactulose), which maintained the total calcium intake below the tolerable upper intake level for Japanese. The average calcium intake in intake group was about 520 mg. Thus, the 300 mg of calcium of the test food added 58% to the average calcium intake.

Effects of magnesium and lactulose

The mechanism underlying the calcium-induced loss of body fat remains unclear. One of the proposed mechanisms is that a high-calcium diet suppresses the active form of vitamin D (1,25-dihydroxycholecalciferol), thereby reducing the intracellular concentration of calcium ions in adipocytes, which in turn would inhibit the production of fatty acid synthase and activate lipolysis, thus exerting an anti-obesity effect.[10] Unfortunately, the levels of serum 1,25-dihyroxycholecalciferol differed between the two groups at baseline. The test food intake did not affect the serum levels of either intact-PTH or 1,25-dihyroxycholecalciferol. No relationship between the change in the serum levels of both intact-PTH and 1,25-dihyroxycholecalciferol, and that of body fat mass was observed in this trial. However, an increase in magnesium in the blood might affect the intracellular concentration of calcium ions in adipocytes.

Because of their chemical similarity, magnesium and calcium may compete for intracellular binding sites. By eliminating this competition, the depletion of magnesium has been proposed to lead to higher intracellular calcium levels after stimuli.[11] This means that magnesium depletion may indirectly influence the effect of calcium on body fat by allowing intracellular calcium levels to increase. Therefore, the role of magnesium should be considered in the effect of calcium on body fat. Many reports have shown that lactulose promotes the absorption of minerals such as calcium and magnesium.[14-16] We have previously demonstrated that the intake of lactulose with calcium and magnesium, in the same composition as the test food in our present study, enhances calcium and magnesium absorption.[16] It is possible that magnesium and lactulose enhance the body fat-reducing effects of calcium. Some reports indicate that the effectiveness of calcium on the loss of body fat is enhanced by dairy products.[1,22] It is necessary to investigate the relation between calcium and other nutrients in combination with dairy products. The contribution of magnesium and lactulose on the body fat-reducing effects in this study is not known. Thus, the effects of magnesium and lactulose should be further investigated with adequate control foods without magnesium and/or lactulose.

Observation period

After 3 years of a 4-year clinical trial in post-menopausal women supplemented with calcium, it was found that the intake group had a significantly lower amount of abdominal fat than the placebo group.[18] In our trial, the test food-induced reduction in body fat was observed at the 12-month but not at the 6-month follow-up. It is thus possible that the fat-reducing effect of calcium may not be rapid and may increase after a longer supplementation period. Thus, the length of the observation period is important to fully determine the effect of calcium supplementation on body fat mass.

Limitations

This was an open-label trial, and as such it is possible that the conation and lifestyle habits of the subjects differed between the groups, thus biasing the test results. The exclusion rate in the treatment group was very high (48%). In this trial, the health condition and self-medication of the subjects were determined by a self-report diary. It may be that the actual information provided differed between the intake and control groups, because the descriptive quality of the diaries was lower in the control group than in the intake group. The subjects in the intake group had to record the intake of the test food every day, whereas those in the control group had no such obligation. It is therefore possible that subjects who used prohibited medicines were inadvertently included in the analysis of the control group. In addition, as the diet survey was not performed every day, the results of the diet survey might not rigorously reflect nutrition status.

The body fat-reducing effect of simultaneous supplementation with calcium, magnesium, and lactulose should be further investigated under double-blind conditions.

AUTHOR DISCLOSURES

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Original Article

Reducing effect of calcium in combination with magnesium and lactulose on body fat mass in middle-aged Japanese women

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日本中年女性攝取鈣質結合鎂及乳果糖對體脂肪量的降低效果

背景：關於足夠的鈣質攝取可降低體脂肪及適量的鎂攝取可阻斷代謝症候群的發展已有報告。此外，乳果糖可增加鈣及鎂的吸收。因此，鈣、鎂及乳果糖的最佳組合或可降低體脂肪量。方法：以開放式隨機控制實驗測試含 300 mg 鈣、150 mg 鎂及 4.0 g 乳果糖的食物對體脂肪降低的效果。在基線、6 個月及 12 個月後，分別測量體組成參數、血液中數種激素及尿中礦物質量。以雙能量 X 光吸收儀測量全身體脂肪量。結果：76 名中年日本女性(47.5±4.7 歲)被隨機分派為攝取組(n=48)或是非攝取控制組(n=28)。儘管兩組的體位測量值沒有差異，但在 12 個月後，兩組體脂肪改變量的差異(攝取組-控制組)為-0.8 公斤(95% CI：-1.5-0.0 公斤，p=0.046)。攝取組在 12 個月的體脂肪百分比傾向較低，但是這個差異不顯著(p=0.09)。結論：這些發現顯示鈣質結合鎂及乳果糖或可以降低日本中年女性的體脂肪量。然而，在這個研究中，鎂及乳果糖的貢獻並不清楚。需要更進一步的研究去釐清這些效益。

關鍵字：鈣、鎂、乳果糖、體脂肪量、日本女性