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# Visceral Fat-Reducing Effect and Safety of Continuous Consumption of Beverage Containing Resistant Maltodextrin: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Clinical Trial

Machiko KITAGAWA[1], Shinsuke NAKAGAWA[2], Takuto SUZUKI[3], Yuka KISHIMOTO[1], Sumiko KANAHORI[1], Yoshitaka HATAKEYAMA[4], Shimpei TOMITA[4] and Ikuo FUKUHARA[5]

[1] *Matsutani Chemical Industry Co., Ltd., 5–3 Kita-Itami, Itami, Hyogo 664–8508, Japan*
[2] *Coca-Cola (Japan) Co., Ltd., 6–3 Shibuya 4-chome, Shibuya-ku, Tokyo 150–0002, Japan*
[3] *Coca-Cola Tokyo Research & Development Co., Ltd., 4–4–14 Aomi, Koto-ku, Tokyo 135–0064, Japan*
[4] *New Drug Research Center Inc., 452–1 Toiso, Eniwa, Hokkaido 061–1405, Japan*
[5] *Fukuhara Clinic, 1–15 Shimamatsuhigashimachi 3-chome, Eniwa, Hokkaido 061–1351, Japan*

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***Summary*** Obesity is regarded as a global concern with increasing prevalence, most notably in developed countries. Metabolic syndrome is a predictor of cardiovascular disease and type 2 diabetes mellitus and is defined as the accumulation of multiple risk factors caused by abdominal visceral obesity. Resistant maltodextrin (RMD) is a soluble dietary fiber that has been shown to reduce visceral fat in long-term clinical trials when continuously administered at 10 g, three times daily. Herein, we evaluated the effects of long-term consumption of 5 g RMD three times daily. A total of 140 healthy adults were randomly assigned to two intervention groups for a 12-wk randomized, double-blind, placebo-controlled, parallel-group trial. Participants ingested a test beverage containing 5 g RMD or a placebo beverage without RMD. Interviews, anthropometric measurements, physiological examination, blood tests, and urinalyses were conducted at baseline and every 4 wk during the trial. Computed tomography scans were performed at baseline and at the end of week 8 and 12. Results showed that abdominal visceral fat area (VFA) significantly decreased in the test group from 105.33±26.83 $cm^2$ at baseline to 101.15±24.33 $cm^2$ at week 12. Further, a significant difference was observed in the VFA between the test and control groups ($p<0.05$), confirming the function of continuous RMD consumption in reducing abdominal visceral fat. Furthermore, neither serious adverse events nor adverse clinical findings were observed in the blood or urine tests following consumption of RMD, suggesting that continuous consumption of RMD containing beverages is safe.

***Key Words*** obesity, soluble dietary fiber, indigestible dextrin, long-term human study, insulin resistance, healthy adult, free life

Obesity is defined as excessive accumulation of adipose tissue. In particular, it has been established that excessive accumulation of visceral fat is closely associated with complications of obesity such as glucose and lipid metabolism disorders, and cardiovascular diseases (*1*). Furthermore, it has been reported that patients with increased visceral fat are likely to develop these complications even when their body weight is within a normal range (*2*, *3*). As such, the accumulation of multiple risk factors to health consequent to abdominal visceral obesity has been defined as metabolic syndrome (*4*).

Obesity is considered to constitute a global health concern, with the prevalence of obesity steadily increasing mainly in developed countries. In particular, the prevalence of obesity in the United States rose from 30.5% in 1999–2000 to 39.6% in 2015–2016, and just over 70% of Americans are considered to be either overweight or obese (*5*). In Japan, according to the results of the National Health and Nutrition Survey conducted in 2017, the prevalence of obese people over the age of 20 y with body mass index (BMI)≥25 $kg/m^2$ was 30.7% among men and 21.9% among women (*6*). Although no significant increase or decrease has occurred over the past ten years, the prevalence of individuals with obesity remains high, and its prevention and reduction are considered to be important goals. Lifestyle improvement is of the utmost importance in the prevention of obesity; notably dietary habits have demonstrated considerable influence. In recent years, certain food components such as tea catechin, black oolong tea polymerized polyphenols, and manno-oligosaccharides from coffee beans have been reported to reduce body fat (*7*–*9*), while a low-carbohydrate diet restricts available carbohydrates showing favorable effects on improving blood lipid profiles and reducing

E-mail: machiko-kitagawa@matsutani.co.jp

body weight (*10*). These food components and dietary restrictions are thus, garnering attention as they can be expected to prevent metabolic syndrome and help lose excess body weight.

Resistant maltodextrin (RMD), also known as indigestible dextrin, is a type of non-viscous water-soluble dietary fiber. It is used as an active food component of many foods for specified health uses (FOSHU) and foods with function claims in Japan. Physiologically, it has been reported to have functions to attenuate postprandial elevation of blood glucose and triglyceride levels when ingested with each meal (*11*, *12*). Furthermore, reduced visceral fat owing to the recurrence of these beneficial effects was confirmed in long-term studies in which RMD was continuously consumed with each meal (*13*–*15*). However, the number of studies is limited as were the numbers of participants per group in each study. Moreover, the results were obtained by consuming 10 g of RMD 3 times daily, a total of 30 g/d over the duration of the studies. Therefore, in the present study we conducted a randomized, double-blind, placebo-controlled, parallel-group clinical trial to evaluate the effects on visceral fat accumulation following long-term consumption of half the reported RMD dosage (5 g as dietary fiber) with each meal, as an effective dose that has been confirmed to attenuate postprandial elevation of blood glucose and triglyceride levels.

## MATERIALS AND METHODS

*Participants.* Participants were screened according to the inclusion and exclusion criteria specified in the protocol of this clinical trial. The inclusion criteria were set to include healthy men and women, at least 20 but below 65 y of age, with BMI of at least 23 but below 30 kg/m$^2$, which corresponds to the target population indicated in the notice on FOSHU (*16*). Exclusion criteria included: 1) expected receipt of medication or surgery owing to a serious illness or injury within 1 mo from the start of the clinical trial; 2) serious medical condition such as disease of the heart, liver, kidney, or digestive system in past medical history or in the history of present illness; 3) regular receipt of medication or consumption of FOSHU to improve e.g., glucose metabolism, lipid metabolism, or blood pressure; 4) women who were or might become pregnant, or breastfeeding mothers; 5) excessive alcohol consumption; 6) donation of 400 mL blood within the last 12 wk or 200 mL within the last 4 wk prior to initiating beverage consumption in the trial; 7) constipation; 8) shift work; 9) allergies to the food items used in the trial; 10) metallic objects inserted (e.g., via surgery) in the area to be scanned by computed tomography (CT); 11) regular consumption of two or fewer meals per day; 12) current or scheduled participation in another clinical trial; or 13) being deemed inappropriate to participate by the principal doctor in charge of the clinical trial.

The participants comprised paid volunteers recruited by Shinyaku Research Center (Eniwa City, Hokkaido, Japan). The volunteers were provided full explanation on matters such as the purpose, content, and methods of the clinical trial along with expected side effects. The clinical trial was conducted after obtaining written informed consent from the participants. Through evaluation of previous studies to set a target number of participants, we identified several clinical trials in which human subjects received high doses of RMD (9 g) (*13*–*15*). Significant reduction of visceral fat area (VFA) was reported in each trial, although the dose administered differed from that used in the current trial. In particular, considering that a clinical trial that reported a reduction in body fat from apple polyphenols owing to a similar mechanism of action included 138 human participants (*17*), we set the target number of participants at 140 (70 participants per group), taking into account the possibility of participants being withdrawn or dropping out. Following the approval of the IRB of Miyawaki Orthopedic Clinic (research protocol No. 17105; date of approval: February 7, 2018), the clinical trial was conducted at Shinyaku Research Center in accordance with the ethics code of the Declaration of Helsinki (revised in October 2013), the "Ethical Guidelines for Medical Research on Human Subjects" (Ministry of Education, Culture, Sports, Science and Technology (MEXT); Ministry of Health, Labor and Welfare (MHLW); partially revised on February 28, 2017), and the "Ethical Guidelines for Medical Research on Human Subjects—Guidance—" (MEXT; MHLW; partially revised on May 29, 2017). This clinical trial was registered with the UMIN Clinical Trial Registry (UMIN-CTR) (UMIN000032508) prior to the initiation of the trial.

Table 1. Nutritional compositions of the study beverage (per 350 mL).

| | Test beverage | Placebo beverage |
|---|---|---|
| Energy (kcal) | 0 | 0 |
| Protein (g) | 0 | 0 |
| Fat (g) | 0 | 0 |
| Carbohydrate (g) | 5 | 0 |
| Available carbohydrate (g) | 0 | 0 |
| Dietary fiber (g) | 5 | 0 |
| Sodium chloride (g) | 0.1 | 0.1 |
| Resistant maltodextrin (As dietary fiber) (g) | 5 | 0 |

*Study beverages used in this trial.* A tea beverage (composed primarily of roasted green tea, oolong tea, and black tea) containing 5 g of RMD was used as a test beverage in this trial. The RMD used was produced by Matsutani Chemical Industry Co., Ltd. (Itami, Japan; trade name: Fibersol-2). The placebo tea beverage did not contain RMD. RMD has low sweetness, and its texture does not change even when dissolved in water. Both beverages were manufactured with the same volume in 350-mL plastic bottles and the beverages could not be distinguished in terms of appearance or flavor. The nutritional information of the study beverage mate-

rials used in this trial is shown in Table 1.

*Clinical trial methods.* This study was a randomized, double-blind, placebo-controlled, parallel-group clinical trial in which participants consumed either a test or placebo beverage for 12 wk followed by a 5-wk observation period. The individual in charge of statistical analysis stratified the participants by age, gender, and visceral fat area into dichotomous data, and the participants were randomly assigned to two groups using block randomization; in addition, the individual responsible for allocation assigned each study beverage by using random numbers. Blinding was maintained by sealing the allocation table and keeping it secure until unsealing following locking of the database. Blinding was applied to the participants, investigators, and everyone involved in planning or conducting the clinical trial. The individual in charge of allocation was a third party (Head of the Higashi Shinjuku Clinic) who was not involved in the planning, conducting, or analysis of the clinical trial.

During the trial, the participants ingested the assigned study beverage three times daily with food (breakfast, lunch, and dinner). When the entire portion was not completely consumed with the meal, the remaining beverage was ingested immediately after. The participants were instructed not to make major changes in lifestyle habits such as dietary or exercise habits, sleeping rhythm, or smoking or alcohol drinking habits from those prior to taking part in this trial. Additionally, intake of medication or functional foods that may have affected the trial was prohibited. Interviews, anthropometric measurements, physiological examination, blood tests, and urinalyzes were conducted prior to initiating beverage ingestion (week 0 as baseline), at the end of week 4, 8, and 12 of the intervention period, and at the end of the 5-wk follow-up observation period. CT scans were conducted at baseline and at the end of week 8 and 12 of the intervention period. During routine hospital visits for medical checkups, the participants were asked to submit food logs and daily life journals.

*Measurement items.* Abdominal VFA was regarded as the primary outcome in the efficacy evaluation, whereas abdominal subcutaneous fat area (SFA), total abdominal fat area (TFA), body weight, BMI, waist circumference, blood lipids (total cholesterol (TC), high (HDL-C) and low (LDL-C) -density lipoprotein cholesterol, triglycerides (TG)), and parameters related to glucose metabolism (i.e., fasting blood glucose, insulin, glycoalbumin, and 1,5-anhydroglucitol (1,5-AG)) were regarded as the secondary outcomes. The parameters for the safety assessment were the incidence rates of side effects and adverse events, and physiological and clinical examination items, excluding those measured for efficacy evaluation.

Anthropometric measurements and physical examination: Body height was measured once during preliminary health checkup for screening. Body weight, BMI, waist circumference, body temperature, blood pressure, and pulse rate were measured on every medical examination day during the trial.

Blood tests and urinalysis: Blood tests included measurements of white blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), hematocrit (Ht), and platelet count (Plt). The biochemical analysis of blood included measurements of total protein (TP), albumin (Alb), total bilirubin (T-Bil), aspartate aminotransferase (AST or GOT), alanine aminotransferase (ALT or GPT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), $\gamma$-glutamyl transpeptidase ($\gamma$-GTP), creatine phosphokinase (CPK), uric acid (UA), urea nitrogen (UN), creatinine (Cre), sodium (Na), chloride (Cl), potassium (K), calcium (Ca), inorganic phosphorus, magnesium (Mg), serum iron, TC, LDL-C, HDL-C, TG, HbA1c (only during screening), fasting blood glucose, insulin, glycoalbumin (GA), and 1.5-AG. Urinalysis included a qualitative analysis of proteins, glucose, urobilinogen, and bilirubin. Urine pH, specific gravity, ketone bodies, and occult blood reaction were also analyzed and measured. The measurement of each item was entrusted to SRL, Inc. (Tokyo, Japan).

Abdominal fat areas: Using a CT Scanner (ROBUSTO-Ei, full-body X-Ray scanner; Hitachi, Ltd., Tokyo, Japan), abdominal tomography was performed by a skilled CT technologist. CT images were analyzed using Fat Scan™ Ver. 3.0 software (East Japan Institute of Technology Co., Ltd., Ibaraki, Japan) to calculate VFA, SFA, and TFA.

Survey of food logs, exercise logs, daily life journals, and interviews with doctors: Survey of food intake and exercise was conducted 3 d prior to the hospital visit for medical examination. Participants were instructed to keep food logs and take photos of their food, and a nutritionist used a computer program for nutritional analysis (Excel Eiyo-kun ver. 8; Kenpakusha Co., Ltd., Tokyo, Japan) to calculate daily intake of total energy, proteins, fats, and carbohydrates. The number of steps taken per day was measured using a pedometer (Omron Health Counter, Omron Healthcare, Lake Forest, IL, USA). Throughout the clinical trial, participants recorded daily intake of study beverages, alcohol consumption, exercise and dietary habits, intake of medications and/or functional foods, and subjective symptoms. Interviews with doctors were conducted on every medical examination day to evaluate any subjective symptoms or objective findings.

*Statistical analysis.* All the measured values are expressed as the means±standard deviation. The qualitative values of urinalysis are shown by grade and number of cases. For intragroup comparison, repeated measures ANOVA was performed and Dunnett's test was performed to determine the significant differences. *F*-test for the equality of variances was conducted for intergroup comparison of measured values and changes from baseline ($\Delta$). In the case of equal variance, the Student's *t*-test was performed, and in the case of unequal variance, the Aspin-Welch *t*-test was performed. With regard to the qualitative values of urinalysis, the Wilcoxon signed-rank test was used for intragroup comparison, and the Wilcoxon rank-sum test with multiplicity correction was used for intergroup

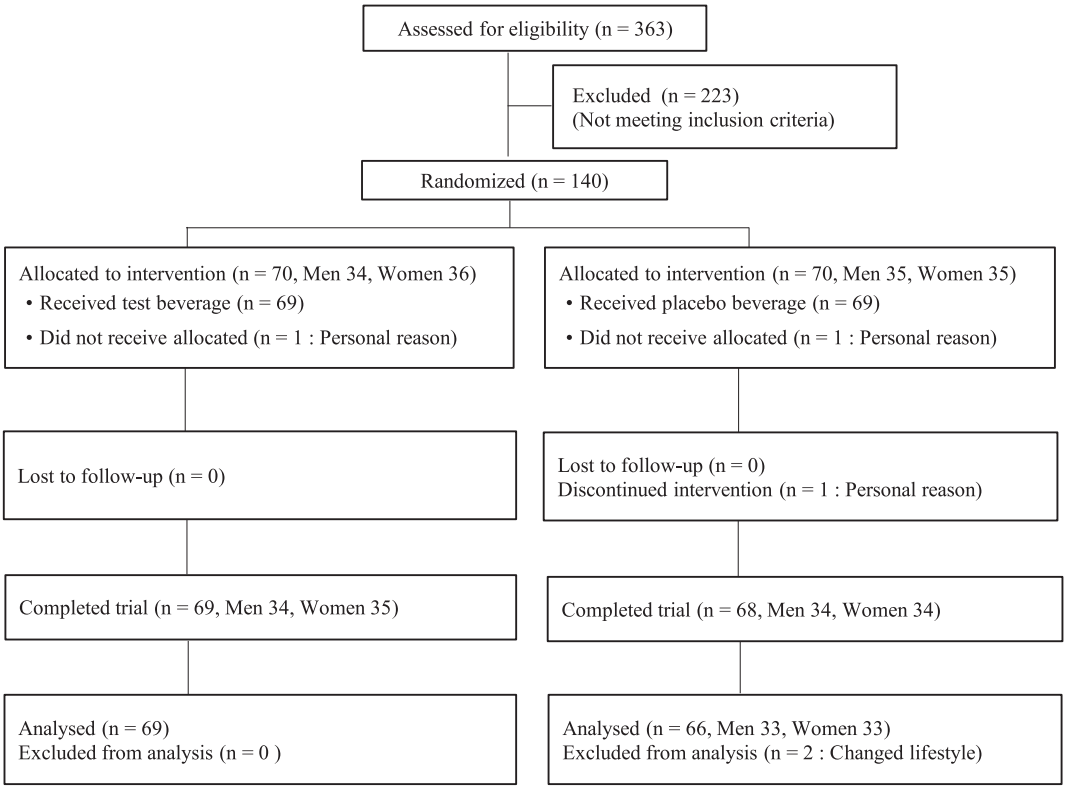


Fig. 1. Flow diagram of the progress stages of this randomized, pracebo-controlled, parallel study.

comparison of measured values. The statistical significance level was set to 5% by a two-tailed test and SAS 9.3 (SAS Institute Inc.) software was used for the statistical analysis.

## RESULTS

*Participants analyzed*

Figure 1 shows the flow diagram from enrollment of participants to analysis in the clinical trial. Among 363 volunteers who granted their consent to participate in the trial and joined the screening test twice, a total of 140 participants who met the inclusion criteria and none of exclusion criteria and showed no significant changes between two screening tests were randomly allocated to two intervention groups (70 participants per group) (intention to treat: ITT); one group to ingest a test beverage and the other group to ingest a placebo beverage. No statistically significant differences were detected with respect to age, sex, and abdominal visceral fat area between two intervention groups at baseline. As one participant from each group (two in total) withdrew prior to the start of the trial for personal reasons, we began the trial with 138 participants (full analysis set: FAS). Following the medical examination at week 8 of intake, one participant from the control group declined to continue participation for personal reasons. Thus, the trial was completed with 137 participants. From the daily life journals submitted by the participants, two participants were noted to have changed daily life habits (substantial changes in the amount of exercise consequent to the start of a night shift at work and to job change) and were subsequently removed from the analysis based on exclusion criteria. Thus, a total of 135 participants (mean age: 47.1±8.9 y; mean BMI: 26.5±1.9 kg/m$^2$; VFA: 106.9±31.0 cm$^2$) were included in the analysis (per protocol set: PPS). Based on the study protocol, the PPS (66 in the control group and 69 in the test group) was included in the efficacy evaluation, while the FAS (69 in the control group and 69 in the test group) was included in the safety evaluation. No significant intergroup differences were observed in participant initial characteristics with regard to any of the items or in compliance, as the beverage intake rate was 99.5±1.3% in the control group and 99.6±1.0% in the test group.

*Efficacy evaluation*

*Abdominal fat areas.* Results of VFA, SFA, and TFA are shown in Table 2. In the test group, the measured values of VFA (the primary outcome) decreased significantly at week 12 of intervention compared to baseline ($p$=0.026). The change of VFA at week 8 from baseline was −0.48±12.82 cm$^2$ in the control group and −2.86±13.57 cm$^2$ in the test group. At week 12, the changes were 1.47±14.89 and −4.18±15.44 cm$^2$ for the control and test groups, respectively and the test group exhibited significantly lower values compared to the control group ($p$=0.032). The SFA values, which was a secondary outcome, significantly decreased at week 8 in the control group compared to baseline ($p$=0.005). The TFA values, secondary outcome, significantly decreased at week 8 in the test group compared to baseline ($p$=0.031). No significant difference was

Table 2. Efficacy evaluation (The primary and secondary outcomes of the study).

| Parameter | Unit | Group | Ingestion period | | | | Follow-up period |
|---|---|---|---|---|---|---|---|
| | | | 0 wk | 4 wk | 8 wk | 12 wk | 5 wk |
| VFA | $cm^2$ | C | 106.60±34.08 | — | 106.12±34.12 | 108.07±34.21 | — |
| | | T | 105.33±26.83 | — | 102.47±26.42 | 101.15±24.33* | — |
| SFA | $cm^2$ | C | 226.73±65.22 | — | 220.52±66.31** | 225.53±67.99 | — |
| | | T | 230.69±69.40 | — | 225.79±73.42 | 228.80±75.04 | — |
| TFA | $cm^2$ | C | 333.33±70.56 | — | 326.64±72.98 | 333.60±76.42 | — |
| | | T | 336.01±70.53 | — | 328.27±77.69* | 329.95±78.75 | — |
| Body weight | kg | C | 70.15±8.24 | 70.14±8.13 | 70.06±8.47 | 70.03±8.53 | 70.11±8.48 |
| | | T | 71.12±8.78 | 71.32±8.84 | 71.30±8.79 | 71.31±8.81 | 71.39±9.05 |
| BMI | $kg/m^2$ | C | 26.12±1.97 | 26.12±1.98 | 26.08±2.04 | 26.06±2.08 | 26.10±2.10 |
| | | T | 26.47±1.81 | 26.54±1.88 | 26.55±1.88 | 26.55±1.93 | 26.57±2.03 |
| Waist circumference | cm | C | 91.98±5.56 | 91.68±5.49 | 91.01±5.67** | 90.41±5.99** | 89.78±6.55** |
| | | T | 92.85±5.92 | 92.47±5.88 | 91.79±5.54** | 91.02±5.51** | 90.66±5.95** |
| TC | mg/dL | C | 212.1±29.0 | 212.8±30.4 | 214.1±31.7 | 215.8±33.6 | 216.8±32.3 |
| | | T | 215.5±36.5 | 222.4±34.4* | 222.0±38.0* | 220.6±39.4 | 220.9±36.4 |
| HDL-C | mg/dL | C | 52.7±14.8 | 56.0±14.4** | 55.0±15.3** | 57.4±16.1** | 54.0±13.5 |
| | | T | 55.0±14.2 | 56.9±14.0** | 56.4±14.3 | 57.3±13.2** | 54.2±12.7 |
| LDL-C | mg/dL | C | 137.3±25.2 | 140.5±29.5 | 139.4±28.4 | 140.5±29.5 | 143.8±29.9** |
| | | T | 139.4±33.2 | 147.0±33.1** | 145.7±37.6* | 143.0±37.7 | 143.6±34.4 |
| TG | mg/dL | C | 124.7±65.6 | 125.0±62.9 | 125.7±57.3 | 127.0±51.9 | 125.7±52.2 |
| | | T | 118.7±62.5 | 124.3±61.0 | 124.9±59.5 | 131.6±75.6 | 145.9±84.8** |
| Fasting blood glucose | mg/dL | C | 94.0±11.6 | 94.0±10.2 | 92.9±10.2 | 97.8±14.3* | 92.7±9.4 |
| | | T | 91.0±10.9 | 91.3±8.8 | 89.8±7.1# | 92.3±9.1## | 89.4±7.3# |
| Insulin | μIU/mL | C | 7.132±4.167 | 6.774±3.921 | 7.203±4.522 | 7.037±5.845 | 8.325±11.207 |
| | | T | 7.175±4.696 | 6.960±3.286 | 7.612±3.815 | 6.203±2.481 | 6.498±3.655 |
| Glycoalbumin | % | C | 12.74±1.04 | 12.89±1.02** | 12.90±1.04** | 13.05±1.01** | 13.22±1.09** |
| | | T | 12.77±1.04 | 12.96±1.11** | 13.00±1.09** | 13.06±1.14** | 13.22±1.15** |
| 1,5-AG | μg/mL | C | 23.62±6.77 | 23.76±6.91 | 24.14±6.84* | 24.27±6.83** | 23.72±6.53 |
| | | T | 23.64±6.24 | 24.87±6.05** | 25.51±6.53** | 25.58±6.71** | 23.95±5.90 |

Data are expressed as the means±SD.
C, Control group ($n$=66); T, Test group ($n$=69).
* $p<0.05$, ** $p<0.01$, vs. 0 wk (by Dunnett's test).
# $p<0.05$, ## $p<0.01$, vs. Control group (by $F/t$-test).

observed in SFA and TFA between the groups or in terms of change over time.

*Anthropometric measurements and physical examination.* Results are shown in Table 2. Although no significant change was observed in body weight or BMI in either group, waist circumference significantly decreased after 8 wk of intervention. With regard to parameters related to blood lipid, TC levels at week 4 and 8 in the test group, HDL-C levels at week 4, 8, and 12 in the control group and at week 4 and 12 in the test group, LDL-C levels at the end of the follow-up period in the control group and at week 4 and 8 in the test group, and TG levels at the end of the follow-up period in the test group, were significantly higher than those at baseline. Regarding parameters related to glucose metabolism, fasting blood glucose levels in the control group at week 12, glycoalbumin levels in both groups after week 4, and 1,5-AG levels in the control group at week 8 and 12 as well as in the test group at week 4, 8, and 12 were significantly higher than those at baseline. In comparison between groups, fasting blood glucose levels of the test group were significantly lower than those of the control group at week 8 and 12 and at the end of the follow-up period. The test group exhibited significantly lower changes in HDL-C at week 12 and at the end of follow-up and significantly higher changes in TG at the end of follow-up compared to the controls. The test group exhibited significantly higher changes in 1,5-AG at week 4, 8, and 12 than those of the controls. There were no other differences observed between groups.

*Safety evaluation*

*Incidence rates of side effects and adverse events.* Table 3 shows adverse events for each group that were observed during the trial. A total of 34 incidents of adverse events among 69 participants in the control

Table 3. Safety evaluation (Adverse events observed during the study).

| Adverse event | Test group | | Control group | | Adverse event | Test group | | Control group | |
|---|---|---|---|---|---|---|---|---|---|
| | Number of incidents | (%) | Number of incidents | (%) | | Number of incidents | (%) | Number of incidents | (%) |
| Cold symptoms | 9 | (13.0%) | 9 | (13.0%) | Dermatitis | 1 | (1.4%) | 0 | (0.0%) |
| Dental caries | 3 | (4.3%) | 1 | (1.4%) | Hemorrhoids | 1 | (1.4%) | 0 | (0.0%) |
| Low back pain | 2 | (2.9%) | 3 | (4.3%) | Abnormal changes in γ-GT | 0 | (0.0%) | 1 | (1.4%) |
| Muscle pain | 1 | (1.4%) | 2 | (2.9%) | | | | | |
| Headache | 1 | (1.4%) | 1 | (1.4%) | Stomachache | 0 | (0.0%) | 1 | (1.4%) |
| Diarrhea | 1 | (1.4%) | 1 | (1.4%) | Stomach discomfort | 0 | (0.0%) | 1 | (1.4%) |
| Toothache | 2 | (2.9%) | 0 | (0.0%) | Acute gastroenteritis | 0 | (0.0%) | 1 | (1.4%) |
| Joint pain | 0 | (0.0%) | 3 | (4.3%) | Bone fracture | 0 | (0.0%) | 1 | (1.4%) |
| Atopic dermatitis | 1 | (1.4%) | 0 | (0.0%) | Anorexia | 0 | (0.0%) | 1 | (1.4%) |
| Sore throat | 1 | (1.4%) | 0 | (0.0%) | Cough | 0 | (0.0%) | 1 | (1.4%) |
| Shoulder pain | 1 | (1.4%) | 0 | (0.0%) | Hyperthermia | 0 | (0.0%) | 1 | (1.4%) |
| Hay fever | 1 | (1.4%) | 0 | (0.0%) | Sprain | 0 | (0.0%) | 1 | (1.4%) |
| Abnormal changes in liver function items | 1 | (1.4%) | 0 | (0.0%) | Abnormal changes in white blood cell count | 0 | (0.0%) | 1 | (1.4%) |
| Eczema | 1 | (1.4%) | 0 | (0.0%) | Runny nose | 0 | (0.0%) | 1 | (1.4%) |
| Abnormal changes in uric acid | 1 | (1.4%) | 0 | (0.0%) | Fatigue | 0 | (0.0%) | 1 | (1.4%) |
| | | | | | Abdominal pain | 0 | (0.0%) | 1 | (1.4%) |
| Swelling of gums | 1 | (1.4%) | 0 | (0.0%) | Stye | 0 | (0.0%) | 1 | (1.4%) |

Control group ($n$=69); Test group ($n$=69).

Table 4. Safety evaluation (Result of physiological examination and blood tests).

| Parameter | Unit | Group | Ingestion period | | | | Follow-up period |
|---|---|---|---|---|---|---|---|
| | | | 0 wk | 4 wk | 8 wk | 12 wk | 5 wk |
| Body temperature | ˚C | C | 36.43±0.36 | 36.47±0.24 | 36.40±0.33 | 36.46±0.31 | 36.44±0.28 |
| | | T | 36.38±0.35 | 36.40±0.35 | 36.39±0.35 | 36.41±0.30 | 36.47±0.29 |
| Systolic blood pressure | mmHg | C | 125.1±14.4 | 123.6±13.5 | 126.3±15.0 | 121.1±14.6** | 120.1±14.6** |
| | | T | 128.8±15.9 | 127.4±16.1 | 128.5±15.5 | 124.6±14.4** | 123.2±15.8** |
| Diastolic blood pressure | mmHg | C | 77.4±10.3 | 75.9±9.4 | 77.0±9.6 | 74.4±10.3** | 74.6±10.4** |
| | | T | 78.8±11.5 | 77.4±11.9 | 78.7±12.4 | 75.1±11.3** | 74.7±11.7** |
| Pulse rate | beats/min | C | 69.3±9.8 | 69.2±9.0 | 68.4±9.2 | 70.0±10.3 | 71.6±10.2* |
| | | T | 68.1±8.6 | 69.0±9.5 | 67.7±8.8 | 68.4±8.8 | 69.1±8.7 |
| WBC | /μL | C | 6,403±2,062 | 6,097±1,224 | 6,059±1,413 | 5,968±1,623 | 6,063±1,743 |
| | | T | 5,975±1,684 | 6,322±1,843 | 6,157±1,749 | 6,055±1,491 | 6,110±1,601 |
| RBC | $\times 10^4$/μL | C | 487.2±36.3 | 491.1±34.6 | 491.0±34.6 | 492.0±33.2 | 486.3±34.8 |
| | | T | 479.6±33.6 | 487.7±34.1** | 484.8±32.4* | 485.4±31.0* | 481.2±35.0 |
| Hb | g/dL | C | 14.37±1.40 | 14.50±1.33 | 14.45±1.31 | 14.41±1.27 | 14.28±1.38 |
| | | T | 14.40±1.19 | 14.72±1.29** | 14.60±1.16** | 14.50±1.16 | 14.39±1.34 |
| Ht | % | C | 43.78±3.61 | 44.98±3.41** | 44.00±3.45 | 44.56±3.29** | 43.88±3.66 |
| | | T | 43.61±3.07 | 45.44±3.30** | 44.13±3.08* | 44.68±2.95** | 44.09±3.48* |
| Plt | $\times 10^4$/μL | C | 27.26±4.73 | 27.67±4.86 | 27.30±5.17 | 26.66±4.91 | 26.14±4.52** |
| | | T | 26.63±4.81 | 27.14±4.92 | 26.92±4.79 | 26.40±4.81 | 25.77±4.35** |

Data are expressed as the means±SD.
C, Control group ($n$=69); T, Test group ($n$=69).
*$p$<0.05, **$p$<0.01, vs. 0 wk (by Dunnett's test).

group and 29 incidents among 69 participants in the test group were observed, although no serious adverse events were reported and the doctors in charge of the trial found no causal relationship with the study beverages used in the trial.

The incidence rate of adverse events was 48.3% in the control group and 41.3% in the test group; no significant intergroup differences were observed. Furthermore, no major abnormalities in the subjective symptoms or objective findings were observed during interviews with doctors and in the daily life journals of participant.

Table 5. Safety evaluation (Result of blood biochemical analysis).

| Parameter | Unit | Group | Ingestion period | | | | Follow-up period |
|---|---|---|---|---|---|---|---|
| | | | 0 wk | 4 wk | 8 wk | 12 wk | 5 wk |
| TP | g/dL | C | 7.39±0.36 | 7.41±0.32 | 7.41±0.34 | 7.40±0.35 | 7.34±0.37 |
| | | T | 7.29±0.36 | 7.42±0.35** | 7.36±0.31 | 7.28±0.29# | 7.24±0.30 |
| Alb | g/dL | C | 4.44±0.31 | 4.52±0.25** | 4.43±0.27 | 4.59±0.25** | 4.49±0.26 |
| | | T | 4.42±0.33 | 4.55±0.29** | 4.46±0.26 | 4.56±0.23** | 4.48±0.28* |
| T-Bil | mg/dL | C | 0.72±0.28 | 0.72±0.27 | 0.75±0.25 | 0.76±0.32 | 0.72±0.25 |
| | | T | 0.73±0.27 | 0.76±0.29 | 0.76±0.32 | 0.75±0.27 | 0.77±0.29 |
| AST (GOT) | U/L | C | 21.7±6.3 | 20.8±5.2 | 22.4±5.4 | 22.4±5.6 | 22.5±6.1 |
| | | T | 20.6±5.5 | 21.0±5.8 | 21.4±5.1 | 21.6±5.5 | 22.1±6.1* |
| ALT (GPT) | U/L | C | 27.5±14.0 | 25.4±13.4 | 27.1±12.9 | 25.6±13.0 | 29.0±15.6 |
| | | T | 24.8±11.0 | 25.5±12.8 | 25.9±11.8 | 24.2±11.5 | 27.8±15.1* |
| LDH | U/L | C | 172.2±33.6 | 175.9±31.8 | 176.1±33.8 | 181.7±32.4** | 180.9±31.7** |
| | | T | 173.7±33.5 | 182.2±31.5** | 179.5±34.8* | 187.2±40.7** | 185.3±32.3** |
| ALP | U/L | C | 213.4±68.7 | 218.5±72.7 | 217.1±72.3 | 212.4±71.9 | 209.4±69.4 |
| | | T | 208.2±52.2 | 213.9±54.7 | 214.2±55.4* | 202.9±50.0 | 205.7±48.3 |
| γ-GTP | U/L | C | 33.8±19.5 | 35.6±20.5 | 35.3±19.7 | 35.1±20.0 | 39.1±26.4** |
| | | T | 29.8±18.8 | 33.1±20.4* | 33.9±23.5** | 30.8±17.3 | 32.4±21.0 |
| CPK | U/L | C | 127.7±103.9 | 126.6±94.1 | 136.5±115.1 | 135.1±103.8 | 117.5±80.9 |
| | | T | 115.1±57.4 | 125.4±70.0 | 117.7±60.1 | 122.7±66.8 | 117.8±57.8 |
| UA | mg/dL | C | 5.62±1.30 | 5.93±1.39** | 5.92±1.36** | 5.88±1.28** | 5.76±1.38 |
| | | T | 5.67±1.35 | 5.84±1.32 | 6.03±1.42** | 5.88±1.34* | 5.88±1.40* |
| UN | mg/dL | C | 12.94±3.10 | 12.09±2.96* | 11.99±2.79** | 12.42±2.95 | 13.25±3.28 |
| | | T | 12.36±2.92 | 11.89±2.71 | 12.04±2.63 | 11.91±2.64 | 12.99±2.81 |
| Cre | mg/dL | C | 0.710±0.147 | 0.738±0.144** | 0.742±0.138** | 0.761±0.142** | 0.712±0.131 |
| | | T | 0.713±0.152 | 0.744±0.154** | 0.759±0.151** | 0.754±0.149** | 0.718±0.146 |
| Na | mEq/L | C | 140.6±1.6 | 140.7±1.6 | 140.1±1.4* | 140.2±1.8* | 139.5±1.7** |
| | | T | 140.8±1.5 | 140.7±1.4 | 140.5±1.4 | 140.1±1.5** | 139.8±1.4** |
| Cl | mEq/L | C | 105.9±2.1 | 105.6±1.8 | 105.3±1.7** | 105.5±1.8 | 105.2±1.5** |
| | | T | 106.4±1.7 | 105.8±1.6** | 105.8±1.5#** | 106.0±1.5* | 105.8±1.7#** |
| K | mEq/L | C | 4.28±0.34 | 4.21±0.30 | 4.16±0.26** | 4.19±0.35 | 4.22±0.31 |
| | | T | 4.30±0.28 | 4.26±0.29 | 4.24±0.31 | 4.19±0.24** | 4.25±0.28 |
| Ca | mg/dL | C | 8.94±0.29 | 9.19±0.28** | 9.13±0.32** | 9.04±0.32** | 8.99±0.32 |
| | | T | 8.95±0.28 | 9.22±0.28** | 9.19±0.30** | 9.01±0.26 | 8.96±0.29 |
| Inorganic phosphorus | mg/dL | C | 3.27±0.38 | 3.29±0.48 | 3.20±0.44 | 3.26±0.49 | 3.25±0.51 |
| | | T | 3.26±0.33 | 3.32±0.45 | 3.26±0.44 | 3.21±0.44 | 3.17±0.40 |
| Mg | mg/dL | C | 2.23±0.17 | 2.26±0.18 | 2.28±0.15** | 2.31±0.15** | 2.29±0.16** |
| | | T | 2.25±0.14 | 2.27±0.16 | 2.28±0.13 | 2.31±0.14** | 2.30±0.14* |
| Serum iron | μg/dL | C | 103.4±36.5 | 105.9±36.9 | 105.2±40.0 | 108.0±38.7 | 106.1±40.5 |
| | | T | 108.1±37.4 | 117.8±38.0 | 111.3±41.9 | 113.5±34.3 | 118.7±41.6 |

Data are expressed as the means±SD.
C, Control group ($n$=69); T, Test group ($n$=69).
* $p<0.05$, ** $p<0.01$, vs. 0 wk (by Dunnett's test).
# $p<0.05$, vs. Control group (by F/$t$-test).

*Physiological and clinical examination items.* Some significant changes were occasionally detected over time compared to baseline in some parameters from physiological examination, blood tests, and blood biochemical analysis. The mean values of each parameter are shown in Tables 4 and 5.

In the urinalysis, both groups exhibited significantly lower values in specific gravity compared to baseline, and a significant decline was observed in the number of subjects who showed (+/−) reaction for the qualitative analysis of proteins in the test group at week 8 compared to baseline. No significant difference was observed in other parameters including pH, urinary ketone bodies, occult blood reaction, or qualitative analysis of urobilinogen, bilirubin, and glucose (data not shown).

*Survey of food logs, exercise logs, daily life journal, and interviews with doctors.* With regard to total energy and carbohydrate intake calculated from the dietary survey, significantly lower values were observed in the test group at the end of the follow-up period compared to baseline and the control group. No significant intra- or intergroup differences were observed in protein and

fat intake, nor was any significant intra- or intergroup differences observed in the number of steps (data not shown).

## DISCUSSION

In the present clinical trial, test subjects ingested three bottles of tea beverage containing 5 g of RMD with meals every day for 12 wk. We assessed the efficacy of the test beverage on VFA and the safety of long-term ingestion. The results showed that the VFA of the test group decreased over time and there was a significant reduction at week 12 of intake in comparison with the baseline. Furthermore, in terms of intergroup comparison, the test tea group exhibited significantly lower values of VFA at week 12 in comparison with the placebo tea group. These findings suggest that a continuous intake of RMD leads to reduced abdominal visceral fat.

It has been reported that the mechanism of action underlying the effect of RMD intake to reduce visceral fat involves inhibiting intrinsic lipogenesis by improving glucose tolerance, and delaying as well as inhibiting the absorption of dietary exogenous fat (*18*). Rapid elevation of postprandial blood glucose levels leads to excessive insulin secretion that promotes lipogenesis, leading to obesity. Since RMD intake attenuates postprandial elevation of glucose and insulin, it is surmised that the continuous function of these effects improves glucose tolerance over time, leading to the inhibition of lipogenesis (*13*, *14*, *19*).

Furthermore, fat-rich meal intake elevates postprandial serum triglyceride levels and excess triglycerides will be stored in adipose tissue. RMD has been shown to attenuate postprandial elevation of triglyceride levels by inhibiting the absorption of fats consumed with a meal, which are rather excreted via feces (*20*–*22*). Thus, continuous inhibition of lipogenesis and delay of dietary fat absorption is believed to lead to visceral fat reduction. Therefore, in the present trial, we examined the effects over the course of 12 wk, of 5 g RMD (as dietary fiber) per serving with each meal. As a single dose this amount of RMD exerts effects to attenuate the elevation of postprandial glucose and triglyceride levels, which serve as the mechanism of action for decreasing visceral fat. As a result, a significant decrease in VFA was observed in the test group. Although previous studies used a higher single dose of 10 g (*13*, *14*), the findings of the present trial suggest that the smaller single dose of 5 g can also be efficacious.

With regard to parameters related to glucose metabolism, the test group exhibited significantly lower fasting blood glucose levels compared to the controls after 8 wk of intake. No significant changes were observed in fasting insulin levels over time, although a decreasing trend ($p=0.08$) was observed in the test group at week 12 of intake. In general, HOMA-IR (=fasting insulin level$\times$ fasting blood glucose level/405) is known as a simple index of insulin resistance and a score of HOMA-IR $\leq$1.6 is considered as normal. At the baseline, HOMA-IR scores of the control and test groups were 1.679$\pm$1.101 and 1.618$\pm$1.110, respectively, whereas the scores were 1.721$\pm$1.549 and 1.429$\pm$0.659, respectively, at the end of 12-wk intervention. Thus, the test group exhibited an improvement in HOMA-IR score, as it was below 1.6. As for 1,5-AG, an index of postprandial hyperglycemia, significant increases were found in both groups over time, however, the increase was significantly higher in the test group compared to that of the controls. Notably, 1,5-AG in the test group returned to the values close to 0 wk at the time of follow-up. These findings suggest that RMD intake suppresses postprandial blood glucose elevation, improving postprandial hyperglycemia. Although increased GA levels were obserbed in both groups, those fluctuation range was small and stayed in the standard range, suggesting that RMD intake had no effect on GA, which reflects the average blood glucose level for approximately 2 wk. The postprandial hyperglycemia was repeatedly corrected owing to the continuous intake of RMD, which is considered to have led to the improvement of insulin resistance, thereby contributing to VFA reduction. Additionally, although temporary significant elevation in lipid-related parameters was occasionally observed in both groups, it was deemed to be transient.

The use of low-carbohydrate food products to limit available carbohydrate consumption has become a hot topic in recent years. The objective of limiting carbohydrate consumption is to avoid a rapid elevation of postprandial blood glucose levels, which is the purpose behind limiting the intake of available carbohydrates that elevate blood glucose levels. Drastic fluctuations in blood glucose levels can damage vascular endothelial cells and increase the risk of arteriosclerosis, cerebral infarction, and myocardial infarction (*23*). Additionally, drastic increase in blood glucose causes excessive secretion of insulin, resulting in obesity owing to insulin's action related to fat storage (*3*, *24*). Carbohydrate restriction reduces available carbohydrate consumption, which makes it difficult to raise postprandial glucose levels (*25*). Consequently, carbohydrate restriction has been shown to be useful in reducing body weight and preventing obesity (*10*). Since RMD inhibits the absorption of sugars ingested together, moderates the postprandial elevation of blood glucose, thereby inhibiting excessive secretion of insulin, it creates the same state of postprandial blood glucose as consuming a meal that limits available carbohydrate. Similar to carbohydrate restriction, it is deemed that RMD is effective in the prevention of chronic disease and obesity.

With regard to SFA, one of secondary outcomes, a temporary decrease was observed in both groups after 8 wk, however the values returned to baseline levels after 12 wk. This was consistent with results reported in a previous study (*13*) in which ingestion of RMD for 12 wk did not lead to SFA reduction. Visceral fat is metabolically more active than subcutaneous fat. It actively undergoes lipolysis and lipogenesis with the changes being largely affected due to acquired factors such as nutrient intake (diet) and exercise. In contrast, subcutaneous fat plays a role in storing energy and is a tissue

that is difficult to reduce, which may explain the lack of significant decrease observed in the present 12-wk clinical trial. Therefore, the decrease in SFA observed in both groups after 8 wk was deemed to constitute a temporary effect that resulted from the intervention. It has been established that people with visceral fat obesity are more likely to develop complications, as opposed to individuals with subcutaneous obesity who experience few complications (*26*). This suggests that the visceral fat reduction achieved in the present clinical trial may be useful in reducing disease risks along with maintaining and improving overall health.

To confirm the RMD-related determinants of visceral fat-reduction, a stratified analysis according to gender or BMI was performed. Consequently, in the stratified analysis by sex, the effect was more significant in males, while no difference was observed in females. This is probably due to the fact that men have more visceral fat than women. Furthermore, for the stratified analysis based on BMI, there was a significant difference due to the intake of RMD, particularly for subjects whose BMI is 25 and above, but not for subjects whose BMI is below 25. These results suggest that the effect of RMD may be more pronounced in men who tend to accumulate more visceral fat and/or in individuals with a higher BMI. Moreover, the correlation between the VFA value at 0 wk and the change of VFA at 12 wk was evaluated. Interestingly, while no correlation was detected for the control group (correlation coefficient $-0.21$), a tendency of correlation in the test group (correlation coefficient $-0.44$) was confirmed, demonstrating that VFA decreased more significantly in subjects with higher VFA. Our observation is consistent with the previous studies that reported the effect of RMD is more pronounced in subjects with higher VFA. It is considered to be one of unique characteristics of RMD effect to reduce visceral fat. Further research will be needed to investigate the efficacy in women or people with BMI below 25, who showed no difference by the stratified analysis, with sufficient sample size and it is considered to be the future study.

No side effects or serious adverse events were observed consequent to the intake of the study beverages used in this clinical trial. Although adverse events such as catching a cold were occasionally observed, the doctors in charge of the trial determined that there was no causal relationship with the study beverages ingested in this trial. Furthermore, although significant fluctuations in comparison with the baseline were observed in several blood and urine parameters over time, including indicators of lipid metabolism and liver function, the changes were within the standard ranges, and none were clinically problematic. Some studies have been reported in which 10 g or 9 g of RMD were administered, i.e. larger dosages than the present study, three times daily for 12 wk and observed no clinical findings related to the safety parameters (*13*, *14*). Thus, no issues with the safety of long-term RMD intake were revealed.

Based on the results and findings of the present study, it was confirmed that a continuous intake of 5 g of RMD (as dietary fiber) by healthy adults is efficacious in reducing abdominal visceral fat. Therefore, RMD was deemed to be beneficial for individuals with obesity, and is expected to contribute to maintaining and improving overall health. Nevertheless, the duration of RMD intake in the present study was limited to 3 mo; thus, it would be desirable to investigate further effects with a longer duration of intake in the future.

## CONCLUSION

In the present clinical trial, participants in the test group consumed bottled tea beverages, each containing 5 g of RMD, with meals three times daily for 12 wk. The effect of the intervention on abdominal VFA and its safety were evaluated. The result of 12-wk intervention showed a significant reduction in VFA compared to baseline in the test group. Furthermore, a significantly lower VFA was exhibited in the test group compared to the control group, suggesting the reducing function on VFA owing to continuous intake of RMD. Moreover, no serious adverse events were observed stemming from long-term intake of the RMD beverage, nor were any adverse clinical findings noted. Thus, no safety issues were identified.

*Authorship*

Research conception and design: SN, TS, YK, and MK; experiments and statistical analysis of the data: YH, ST, and IF; writing of the manuscript: YK, SK, and MK. All authors read and approved the final manuscript.

*Disclosure of state of COI*

This clinical trial was conducted by Matsutani Chemical Industry Co., Ltd. and Coca-Cola (Japan) Co., Ltd. by entrusting the trial to New Drug Research Center Inc., a third-party organization and conducted at New Drug Research Center Inc. and Fukuhara Clinic.

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