ORIGINAL

Effect of Continuous Intake of Onion Powder on Oxidative Stress Biomarkers and Skeletal Muscle Maintenance in Elderly Bedridden Individuals : A Pilot Study

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Abstract : The number of bedridden elderly is substantially increasing in our aging society. Bedridden patients experience muscle atrophy due to prolonged inactivity. We are concerned about whether the antioxidative flavonoid quercetin can prevent disuse muscle atrophy in elderly people considering that oxidative stress plays a role in this condition. This study explored the links between quercetin intake, oxidative stress, and muscle preservation in bedridden individuals. Onion was selected and a dose of 5 g of onion powder, which contains 99.7 mg of quercetin aglycone equivalent, was given to patients who were bedridden for 30 days. Plasma quercetin concentration was significantly increased in the onion powder group, with regular intake of quercetin meals maintaining high plasma levels (n=9). Higher plasma quercetin levels were linked to lower plasma oxidized low-density lipoprotein (ox-LDL) and urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) content. No correlation was identified in the indexes of muscle maintenance (volume of the quadriceps femoris muscle) and the minimum necessary activities of daily living (ADL). In conclusion, our small-scale pilot study involving bedridden individuals did not demonstrate a positive effect of continuous quercetin intake on the prevention of muscle atrophy. However, efficient dietary quercetin consumption can mitigate the elevation of *in vivo* oxidative stress. J. Med. Invest. 72 : 324-329, August, 2025

Keywords **:** *disuse muscle atrophy, bedridden patient, quercetin, onion, oxidative stress*

INTRODUCTION

An aging society has witnessed a rising number of bedridden elderly due to age-related diseases, such as osteoporosis, osteoarthritis, and cerebrovascular disease (1). Disuse muscle atrophy occurs in bedridden individuals because of prolonged periods of minimal physical activity (2). Muscle weakness along with muscle atrophy appears to reduce individuals' ability to perform the minimum necessary activities of daily living (ADL). Currently, early rehabilitation training is the sole therapy to prevent and slow disuse muscle atrophy. No medicines or dietary supplements have been proven effective for this purpose. Disuse muscle atrophy occurs because of an imbalance between protein synthesis and degradation in skeletal muscle cells (3). Excessive production of reactive oxygen species (ROS) due to mitochondrial dysfunction and oxidative stress likely enhances protein degradation in disuse muscle atrophy (4, 5). Plant polyphenols might help bedridden people maintain ADL by preventing oxidative stress-induced muscle atrophy because of their antioxidant properties (6, 7). Research using rodent models has indicated that plant polyphenol consumption can prevent muscle atrophy (8, 9).

Quercetin (3,3',4',5,7-pentahydroxyflavone) is a potent antioxidant found in onion, lettuce, and various vegetables (10). We previously demonstrated that the dietary intake of quercetin prevented disuse muscle atrophy in a mouse denervation model by targeting mitochondrial ROS (11). The current study aimed to assess the effectiveness of quercetin-containing foods in preventing muscle atrophy in bedridden individuals. Onion peel and bulb powder, rich in quercetin, were given meals for 30 days to nine bedridden hospital patients. This pilot study aimed to examine the relationship between quercetin intake, oxidative stress biomarkers, and skeletal muscle maintenance. The results of this study will provide valuable data for a large-scale study on the effectiveness of quercetin-rich foods in preventing muscle atrophy due to disuse.

MATERIALS AND METHODS

Study subjects

Thirteen volunteers, including nine men aged 51 to 83 years and four women aged 54 to 86 years, were hospitalized at the Inatsugi Orthopedic Hospital in Aizumi-Cho, Tokushima, a private hospital affiliated with Tokushima University Hospital. According to the ECOG performance status (12), the patients were rated with a PS of 2 or 3, indicating that they spent

Abbreviations :
ADL : the minimum necessary activities of daily living, BMI : body mass index, BUN : blood urea nitrogen, MRI : magnetic resonance imaging, 8-OHdG : 8-hydroxy-2'-deoxyguanosine, LDL-C : low-density lipoprotein cholesterol , HDL-C : high-density lipoprotein cholesterol, 3-MeHis : 3-methylhistidine, Ox-LDL : oxidative LDL

Received for publication April 21, 2025 ; accepted May 13, 2025.

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approximately half of the day in bed or in a wheelchair. None of the participants in this study had kidney, nerve, or muscle disease or were undergoing diabetes treatment with corticosteroids. They did not have onion allergies or regularly used plant-extracted supplements.

Test meal

The whole onion, including the peel and bulb, was washed with fresh tap water and heated at 115°C for 2 hours. The mixture was ground using a mixer, and the onion paste was centrifuged to obtain the supernatant. The supernatant was filtered using diatomaceous earth, followed by freeze-drying, grinding, and powdering. The powder contains 19.94 mg/g of quercetin aglycone equivalent, 0.85 g/g carbohydrates, 0.09 g/g proteins, and 0.001 g/g lipids. Placebo powder was prepared by adjusting the basic nutrient content with gluten, glucose, sucrose, fructose, and dietary fiber. Commercial onion flavor and caramel pigments were used to replicate onion color and taste. These two powder preparations were kindly gifted by House Foods group, Inc. (Tokyo, Japan).

Meal intervention examination

The patients' nutritional intake was determined based on the hospital meal menu. The participants were randomly assigned to receive onion powder (n = 9) or placebo powder (n = 4). Basic characteristics of the assigned participants were listed in Table 1. The test meal (5 g including 99.7 mg quercetin aglycone equivalent) was mixed into a standard hospital lunch provided by registered dietitians for 30 days. Neither the subjects nor the researchers knew who took onion powder until the intervention ended. The doctors and nurses at the Inatsugi Orthopedic Hospital monitored the participants' health during the experiment. Participants underwent blood tests, urinalysis, magnetic resonance imaging (MRI), and Functional Independence Measure (FIM) assessments before and after the meal intervention study, as described below.

Ethics

This study was approved by the Ethics Committee of the University Hospital of Tokushima Clinical Trial Center for Developmental Therapeutics (approval number : 1270) and was conducted in accordance with the Declaration of Helsinki. This study was registered at the University Hospital Medical Information Network-Clinical Trial Registry (UMIN-CTR) on April 3, 2016 (registration number : UMIN000006087). We explained the study's purpose and risks to all participants and obtained their informed consent.

Total quercetin concentration in blood plasma

The concentrations of quercetin in blood plasma were determined by HPLC analysis with electrochemical detection after deconjugation treatment to measure the total content of quercetin, which included its conjugated metabolites. After a 12-hour fast, blood was collected from the patient immediately before breakfast. The plasma samples were then prepared via centrifugation and stored in a freezer at -80°C until they were needed for analysis. Deconjugation treatment and HPLC analysis were performed as previously described (13).

Blood and urine analyses

Blood was collected from the subject after a 12-hour fast, one day before and after the study, and plasma samples were immediately prepared using the centrifugation method. The 24-hour urine samples of participants were collected twice before and after the trial, and the volume was measured. Oxidative low-density lipoprotein (Ox-LDL) in plasma and urinary 3-methylhistidine (3-MeHis) were measured using the ELISA method and HPLC method, respectively. The studies were conducted at SRL Inc. (Tokyo, Japan). Urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) was determined using antibody methods (Healthcare Systems (Aichi, Japan)). Blood glutamic oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), blood urea nitrogen (BUN), and creatinine levels were measured at the Inatsugi Orthopedic Hospital. The measurement of plasma total TG, total cholesterol, LDL cholesterol (LDL-C), and high-density proprotein cholesterol (HDL-C) was outsourced to Skylight Biotech Inc. (Akita, Japan).

Measurement of muscle maintenance-related indexes

MRI analysis was performed to calculate the volume of the quadriceps femoris muscle in both the right and left legs using an MRI apparatus (EXCELART Vantage 1.5T, Toshiba Medical Corp., Tokyo, Japan) equipped with the Inatsugi Orthopedic Hospital (14). We captured muscle images and measured muscle volumes following the methodology outlined by Hashimoto *et al*. (15). We selected 25 images to quantify the cross-sectional areas of the quadriceps. The area was measured using ImageJ software (National Institute of Health, Bethesda, MD). The data are presented as the total muscle cross-sectional area for both legs. FIM is an assessment scale for ADL. The measurement according to guideline (16) was evaluated at the Inatsugi Orthopedic Hospital.

Statistical analysis

Statistical analyses were performed using PASW statistics 18.0 (SPSS Inc., Chicago, IL). The paired t-test was used to

Table 1. Basic characteristics of the participants

Variable	Onion powder group	Placebo group	p-value
n	9	4	-
Age (years)	72 ± 4	64 ± 5	0.283
Sex	6 male, 3 female	3 male, 1 female	-
Height (cm)	159 ± 3	161 ± 3	0.773
Weight (kg)	55.9 ± 3.1	61.5 ± 3.0	0.304
BMI (kg/m^2)	22.0 ± 0.8	23.8 ± 0.3	0.203

Data are represented as means ± SEM or numbers.
Statistical analysis between onion powder group and placebo group was calculated by unpaired t-test.
BMI ; Body mass index

assess significant differences (p value <0.05) before and after the trials. The Pearson correlation coefficient was used to analyze the relationship between the increase in plasma quercetin concentration and various biochemical or physiological parameters following the trial (p-value < 0.05).

RESULTS

Changes in plasma quercetin concentrations in the placebo and onion powder groups

We measured plasma quercetin levels in the placebo and onion powder groups before and after the trial (Fig.1). In the onion powder group, the plasma concentration of total quercetin significantly increased after 30 days of onion powder consumption (11.0 ± 3.4 nM vs. 32.6 ± 7.5 nM ; p = 0.046). There were no significant differences in the placebo group before and after the trial. Therefore, we focused on changes in blood and urinary biomarkers and muscle maintenance-related indexes in onion powder supplementation.

Changes in urinary and blood biomarkers in onion powder group

Table 2 presents the results, indicating that urinary and blood biomarkers remained consistent after the intervention. No biochemical changes were detected in the blood and urine following sustained onion powder consumption.

Changes in muscle maintenance-related indexes after onion powder supplementation

Table 3 presents the muscle volumes measured by MRI along with the FIM scores for the onion powder group before and after the trial. No significant change in muscle volumes was observed, but ADL assessed by the FIM score improved after the trial (p = 0.010).

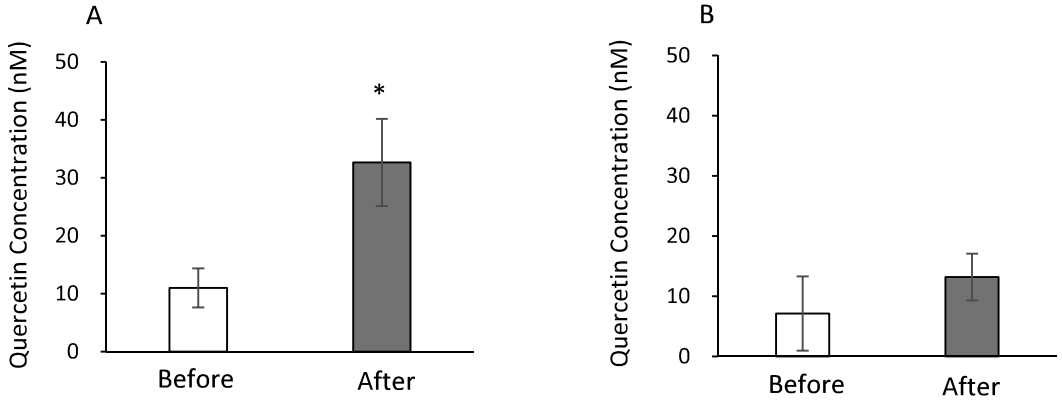

Fig. 1. Variations in basal quercetin concentration in the plasma of the onion powder group (A) and the placebo group (B). White bar : before the trial, black bar : after the trial. Each plasma sample was collected a day before analysis after a 12-hour fast. Quercetin and its metabolites were measured after deconjugation treatment.
Values are means ± SE. * Indicated significant difference vs before meal intervention examination (p < 0.05).

Table 2. Variations in urinary and blood biomarkers in onion powder group

	Before trial	After trial	p-value
Urinary 3-MeHis (umol/g Cre)	189.1 ± 15.4	193.5 ± 16.8	0.883
8-OHdG (ng/mg Cre)	6.6 ± 1.8	10.6 ± 1.7	0.054
Plasma ox-LDL (U/L)	114.6 ± 14.0	125.1 ± 11.7	0.132
GOT (IU/L)	22.6 ± 1.7	24.0 ± 3.2	0.698
GPT (IU/L)	21.7 ± 3.0	19.4 ± 2.4	0.505
BUN (mg/dl)	11.5 ± 0.7	12.6 ± 0.9	0.347
Creatinine (mg/dl)	0.7 ± 0.0	0.7 ± 0.0	0.681
Triglyceride total (mg/dl)	95.9 ± 9.9	96.1 ± 9.2	0.971
cholesterol total (mg/dl)	155.5 ± 6.8	168.9 ± 9.9	0.055
LDL-C (mg/dl)	75.5 ± 5.2	85.0 ± 7.5	0.092
HDL-C (mg/dl)	44.2 ± 2.4	44.8 ± 3.1	0.724

Values are expressed as means ± SEM.
Statistical analysis between before and after trial was calculated by Paired t-test.

Correlation between plasma quercetin concentration, oxidative stress biomarkers, and muscle maintenance-related indexes in the onion powder group

We examined the correlation between plasma quercetin concentration and oxidative stress biomarkers by measuring the change in total quercetin concentration in the plasma of the onion powder group before and after the intervention. Plasma ox-LDL and urinary 8-OHdG were selected as the oxidative stress biomarkers. The values were plotted against the changes in quercetin concentration observed in individuals from the onion powder group (Fig. 2A and B). Increased plasma quercetin concentration showed a negative correlation with plasma ox-LDL content ($r = -0.749$; $p = 0.020$) and a weak negative correlation with urinary 8-OHdG content ($r = -0.326$; $p = 0.392$). The relationship between the increase in plasma quercetin concentration and muscle maintenance-related indexes is shown in Fig. 2C and D. No correlation was found between muscle volume measured by MRI (correlation coefficient 0.173 ; $p = 0.655$) nor ADL calculated by FIM (correlation coefficient 0.169 ; $p = 0.663$).

Table 3. Variations in muscle volume and ADL in onion powder group

	Before trial	After trial	p-value
Muscle volume By MRI	16.6 ± 1.6	16.7 ± 1.7	0.603
ADL by FIM score	96.6 ± 6.6	106.7 ± 6.7	0.010*

Values are expressed as means ± SEM.
Statistical analysis between before and after trial was calculated by Paired t-test.
*Significantly different ($p<0.05$).

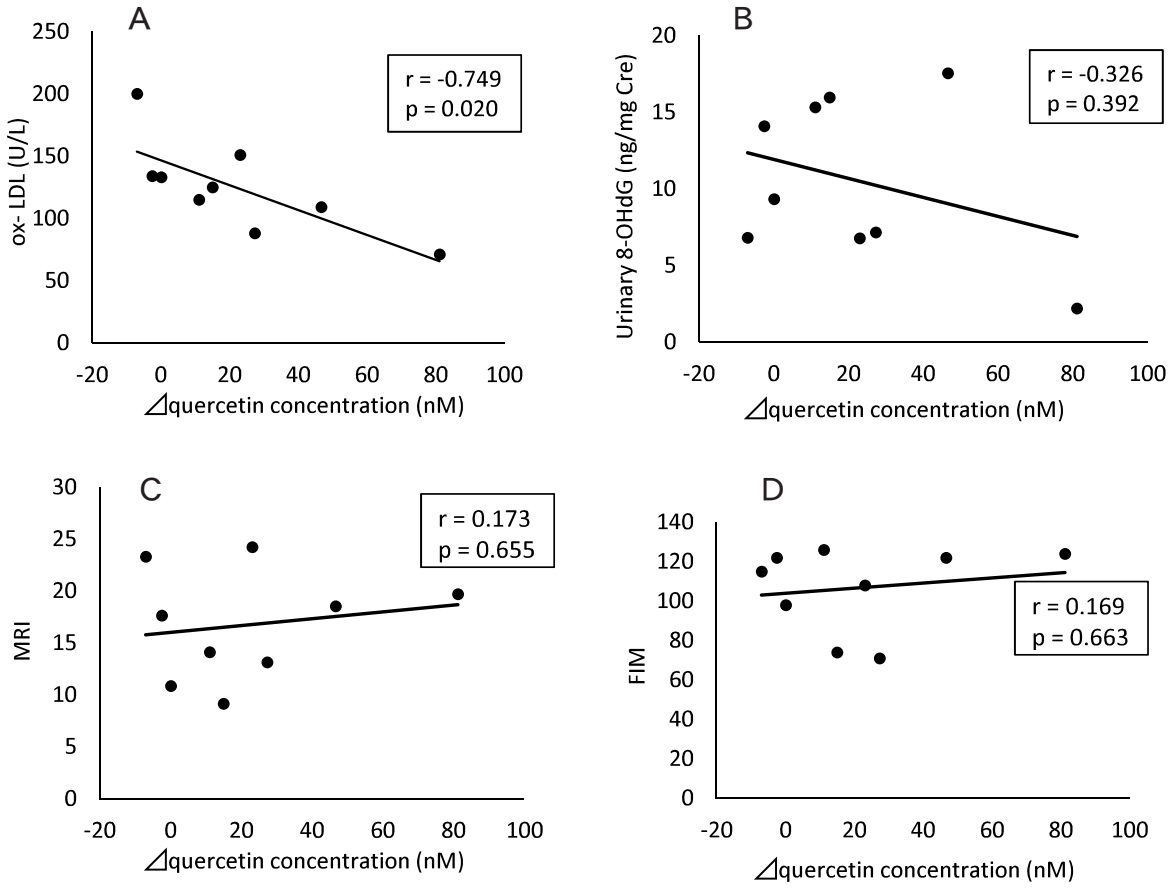

Fig. 2. 2 Relationship between the increase of plasma quercetin concentration and plasma Ox-LDL content (A), urinary 8-OHdG content (B), muscle volume (C), and FIM score (D) after the trial in onion powder group.
r : Peason's correlation coefficient, p : p-value.

DISCUSSION

A 2013 Japanese dietary survey found that the average quercetin intake was 16.2 mg/day, ranging from 0.5 mg to 56.8 mg/day (17). Onions contributed 22 % of total quercetin intake in summer and 65 % in winter. The total quercetin content of 99.7 mg/day, derived from the serving of onion powder in our study, is nearly twice as high as the highest quercetin intake reported in dietary surveys. Studies have indicated that the daily consumption of onions containing either 114 mg or 89.7 mg of quercetin aglycone equivalent is safe for healthy individuals (18, 19). Thus, the quercetin level in our study was within the safe limits for dietary intake. Quercetin in onion powder consists of aglycone from the peel and glucoside derivatives from the bulb (13). Although they are partly absorbed from the small intestines, most of them are transferred into the large intestine where they are subject to de-glycosylation or decomposition by intestinal microbiota, resulting in excretion in the feces (20). During the catabolic process, it is proposed that a portion of quercetin aglycone and its decomposition products are absorbed into the body through the large intestine (10). Quercetin predominantly exists in human plasma in its glucuronide or sulfate conjugated form (20). We therefore measured the total concentration of quercetin in the plasma following deconjugation treatment. *O*-Methylation of aromatic ring hydroxy groups occurs in quercetin metabolism after consuming onion powder (13). *O*-Methylated quercetin (rhamnetin, isorhamnetin and tamarixetin) was not detected in the patients' plasma, possibly due to levels being below the detection limit. Hollman *et al*. (21) noted that plasma quercetin levels increased temporarily to approximately micromolar concentrations within 1–2 hours following the consumption of fried onions containing 64 mg of quercetin aglycone equivalent. They also concluded that quercetin from onion is absorbed and eliminated slowly throughout the day. Our study found that continuous consumption of quercetin meals for 30 days significantly increased basal plasma quercetin levels by delaying its elimination from plasma. It is obvious that consuming quercetin-rich foods regularly maintains plasma quercetin levels high.

Several intervention studies have recently reported that long-term consumption of quercetin-rich onion may protect elderly people from age-related cognitive decline (22), improve motivated behavior in patients with cognitive dysfunction (23), and reduce visceral fat area in subjects with lower HDL-cholesterol levels in their plasma (24). Long-term consumption of quercetin-rich onions improved tear function via the lacrimal gland in healthy volunteers (25). Nevertheless, our intervention study is the first human trial to evaluate the impact of onion powder consumption on disuse muscle atrophy. Quercetin, an onion ingredient, has been shown to prevent muscle atrophy in tail-suspension model mice through intravenous injection (26) and denervated model mice through dietary intake (11). In these animal studies, antioxidant activity was implied as a mechanism for preventing muscle atrophy. Our intervention study found no changes in urinary and blood biomarkers, including the protein catabolism index, 3-MeHis (Table 2). Bioavailability of dietary polyphenols like quercetin varies individually based on gut microbiota, genetics, age, sex, ethnicity, BMI, health status, and physical activity (27). We investigated the relationship between individual biomarkers after the trial and their change in plasma quercetin concentration. The results showed that two oxidative stress biomarkers, plasma ox-LDL and urinary 8-OHdG, were correlated with the increase in plasma quercetin concentration (Fig. 2). This suggests that efficient intake of dietary quercetin may suppress the enhancement of *in vivo* oxidative stress. However, the increase in basal quercetin concentration was not correlated with muscle volume, as measured by MRI, nor with ADL, as indicated by FIM. Quercetin from onion powder appears to have a minimal effect on preventing muscle atrophy in bedridden individuals. Improvements in ADL after the trial (Table 3) may result from factors other than onion powder intake. Our intervention trial period was limited to 30 days. A longer trial period may be necessary to evaluate the preventive effects of onion intake on disuse muscle atrophy. Enhancing the bioavailability of quercetin through various formulations and food matrices should be considered to obtain valid information in short-term intervention trials (28). The other point to note is the influence of combination meals during the trial, as the components of combination meals affect the intestinal absorption (29) or metabolism of dietary quercetin (30).

A limitation of our study is the restricted number of participants, especially within the placebo group. Additional subjects are needed for reliable results. This study did not measure the muscle strength of the subjects, although it is a relevant index to estimate the degree of muscle atrophy.

In conclusion, our small-scale pilot study involving bedridden individuals did not provide evidence of the positive effect of continuous quercetin intake on the prevention of muscle atrophy. This intervention suggests that consuming onion powder increases the basal plasma concentration of quercetin, which is efficiently absorbed by the body and correlates with reduced oxidative stress. We hope this pilot study provides useful information for a future large-scale intervention study of quercetin-rich foods for the prevention of muscle atrophy.

CONFLICT OF INTERESTS-DISCLOSURE

None

ACKNOWLEDGEMENT

We thank all subjects who participated in this study for their time and exceptional dedication. Furthermore, we thank all staff at the Inatsugi Orthopedic Hospital for their help with patient recruitment. We thank C. Sato, and A. Akaishi from the Clinical Trial Center at Tokushima University Hospital supporting this study. We also thank House Foods Group Inc. for providing onion powder and placebo powder.

GRANTS

This study was supported by a grant, "Promotion of Basic Research Activities for Innovative Biosciences", from Bio-oriented Technology Research Advancement Institution, Japan (to J.T.).

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