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The effects of exercise and milk-fat globule membrane (MFGM) on walking parameters in community-dwelling elderly Japanese women with declines in walking ability: A randomized placebo controlled trial☆

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ABSTRACT

Objective: To investigate the effects of exercise and milk fat globule membrane (MFGM) supplementation on walking ability and walking parameters in community-dwelling elderly Japanese women with declined walking ability.

Methods: A randomized placebo controlled trial was performed on 126 elderly community-dwelling women over 79 years old. Participants were randomly assigned to one of four three-month interventions: exercise and MFGM (Ex + MFGM), exercise and placebo (Ex + P), MFGM, and placebo interventions. The exercise intervention group performed one-hour progressive exercise classes twice a week. The MFGM supplementation included ingesting 1 g of MFGM per day. Medical history, physical function measurements included grip strength, knee extension strength, walking speed, as well as walking parameters, and blood components were analyzed.

Results: Significant group × time interactions were observed in usual walking speed, stride, and foot progression angle between the groups. Walking speed improved in both exercise groups ($P < 0.001$). Similarly, stride significantly increased in the exercise groups compared to the MFGM and placebo groups ($P < 0.001$). Foot progression angle decreased in the exercise groups ($P = 0.023$) but not in MFGM or placebo groups. Participants with decreased or unchanged walking speed had significantly lower knee extension strength at baseline ($P = 0.016$), and a higher prevalence of knee OA ($P = 0.033$, $P = 0.010$, respectively).

Conclusion: The exercise interventions alone or combined with nutrition were effective in improving walking speed as well as other walking parameters. Improvement in stride and foot progression angle may have contributed to the increase in walking speed. However, augmented effects of MFGM with exercise could not be confirmed.

1. Introduction

The ability to live independently in old age with a high quality of life not only requires prevention of diseases, but also the maintenance of activities of daily living (ADL). Physical function, and walking ability in particular is important for a long health life expectancy among the elderly. Previous studies have reported that walking speed is a good predictor for the maintenance of instrumental ADL (Suzuki et al., 2003), as well as a predictor of the risk of adverse outcomes (Abellan van Kan et al., 2009), onset of functional dependence (Shinkai et al., 2000), long dependence periods (Woo, Ho, & Yu, 1999), and mortality (Blain et al., 2010).

Previous studies have shown that exercise interventions have positive effects in improving walking speed as well as walking parameters (Buchner et al., 1996; Hausdorff et al., 2001). Based on a recent review, the reduction in walking speed with age may be a compensatory strategy to improve stability, avoid falls, or reduce the energetic cost of mobility by taking shorter steps, increasing step width, and prolonging

☆ Clinical Trial Registration: The Japan Medical Association Clinical Trial Registry (JMACCT) JMA-IIA00167.

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double support time (Aboutorabi, Arazpour, Bahramizadeh, Hutchins, & Fadayevatan, 2016; Kim et al., 2013). The loss of muscle quality and power with aging may underlie the impairments in control and balance in walking that may lead to falls and adverse outcomes (Martinikorena et al., 2016). Therefore, development of interventions to counteract the loss of muscle strength and mass is of vital importance for the improvement or maintenance of walking ability.

The role of nutrition on muscle mass and strength improvement has been widely researched. Several studies have reported beneficial effects of milk ingestion in muscle protein synthesis after exercise in adults (Elliot, Cree, Sanford, Wolfe, & Tipton, 2006; Josse, Tang, Tarnopolsky, & Phillips, 2010; Wilkinson et al., 2007). However, the benefits of milk on muscle strength and mass in older is poorly understood. Recently, publications have suggested that milk-fat globule membrane (MFGM), a complex structure made from protein and lipid components of milk, may be a potentially valuable ingredient for developing food products (El-Loly, 2011). While one mice study reported that MFGM in combination with exercise was effective in suppressing age-associated muscle mass and strength deterioration in mice, our study conducted on frail elderly human women did not show any additive effects of MFGM with exercise. Over the 7 month follow-up period, the exercise and MFGM combination group significantly reversed “slow walking speed status” among frail elderly women, more than exercise alone (Kim et al., 2015). However, the literature on MFGM is still in its preliminary stages, and the results are inconsistent.

The purpose of this study was to investigate the efficacy of exercise and MFGM supplementation both in combination and alone, on walking parameters in community-dwelling older Japanese women with declines in walking ability.

2. Materials and methods

2.1. Participants

The participants of this study were selected from two separate cohorts: the 2002 and 2008 cohorts. Community-dwelling elderly women over 70 years of age in 2002 and over 75 years of age in 2008 were invited by letter to participate in a comprehensive geriatric health survey was sent to residents of the Itabashi ward in Tokyo, Japan. A total of 1016 people participated in the geriatric health survey in 2002 and 1289 different people participated in 2008. In a follow-up survey in 2012, 475 people from 2002 (10-year follow-up) and 575 people from 2008 (4-year follow-up) were surveyed. Among them, 152 people from the 2002 cohort, and 169 people from the 2008 cohort, a total of 321 had walking ability declines (Fig. 1).

Participants who were operationally defined as having walking ability declines were included in the intervention. Those who had one of the three following characteristics were operationally defined with walking ability declines: slow walking speed (< 1.0 m/s), step width greater than 10.0 cm, and/or stride length < 100.0 cm. Exclusion criteria included people with severely impaired mobility (were unable to attend the intervention classes), missing baseline data, and with unstable cardiac conditions such as ventricular dysrhythmias, pulmonary edema, or other conditions. Medical history and chronic conditions were assessed via face-to-face interviews with a nurse, where chronic conditions; age of diagnosis, diagnostic medical institution, treatment status (currently in treatment, in maintenance, healed, ceased or terminated treatment), were thoroughly analyzed in detail. This information was used in the selection/exclusion of participants. Based on the inclusion and exclusion criteria, 321 (30.6%) were defined as having walking ability declines, and a letter detailing the objectives, methods, and use of personal data in the study were mailed to each potential participant. A total of 126 (39.3%) agreed to participate in the study and were randomized, while 195 people declined participation or were excluded.

2.2. Randomization

Randomization was performed after the baseline assessment, and any variable that identified personal information was not included in the randomization process. Computer-generated random numbers were assigned to 126 participants, who were then sorted and equally divided into four groups. The groups were randomly assigned to one of the four interventions: exercise and MFGM supplementation (Ex + MFGM; $n = 31$), exercise + placebo (Ex + P; $n = 32$), MFGM supplementation ($n = 32$), or placebo ($n = 31$) groups (Fig. 1). All participants agreed to the group allocations. There was no attempt to equalize the size of the groups based on their characteristics or to recruit subjects with specific characteristics. All co-investigators were blind to the randomization procedure and group allocations, and data collection was conducted by separate physical therapy staff members who were also blind to the allocation of treatments.

Data based on interviews, body composition, and physical function were collected at baseline (28–29 August, 2013) and after the 3-month intervention (27–28 November, 2013).

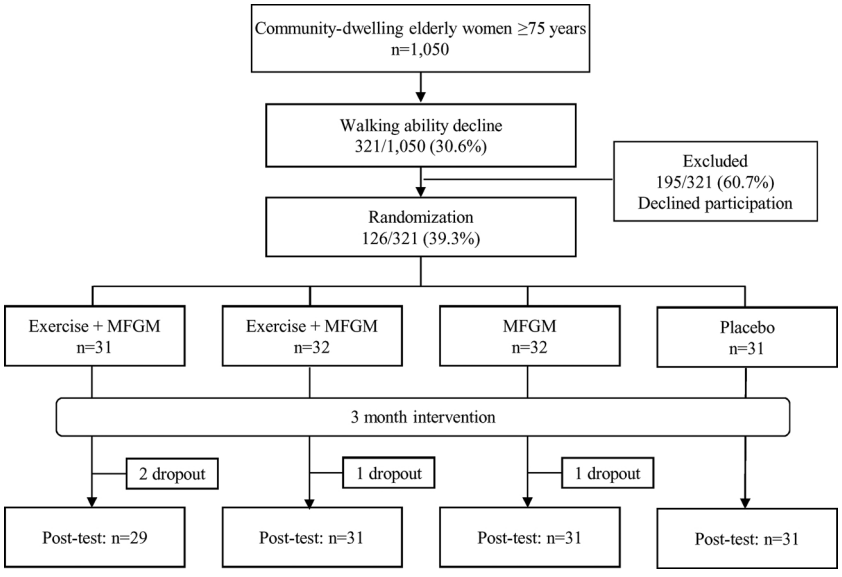

Fig. 1. Flow chart of participant recruitment during the randomized controlled trial of exercise and/or nutrition supplementation.

2.3. Outcome variables

2.3.1. Interview survey

Each participant was interviewed face-to-face to assess the individual's history of chronic illness, medications, falls and fractures, fear of falling, self-rated health, hospitalization, knee pain, back pain, Tokyo Metropolitan Institute of Gerontology (TMIG) Index, ADL, urinary incontinence, frequency of going out, exercise habits and other lifestyle behaviors.

2.3.2. Anthropological and body composition assessments

Height was carefully measured, using a digital stadiometer. Measurements of height and weight were used to calculate BMI (kg/m^2). Muscle mass, bone mineral density, and body fat mass were determined using dual-energy X-ray absorptiometry (DXA; Hologic QDR 4500A, USA)

2.3.3. Physical function assessment

Grip strength was assessed using a handheld Smedley-type dynamometer in the dominant hand. Isometric knee extension strength was measured twice using a handheld dynamometer (μTasMF-01, ANIMA, Japan), with the participants seated, knees at a 90 degree angle. The device sensor was placed against the anterior side of the ankle in the dominant leg (or the leg with no pain), and the participant was asked to extend the knee as hard as possible. The higher of two scores were recorded and used for analysis. In participants with knee pain in both legs, measurements were taken on the leg with less pain. Participants were asked not to push too hard as to aggravate their pain, and only push as long as they do not feel any discomfort.

2.3.4. Walking ability and parameter assessments

Usual walking speed across 5 m was measured as the participants walked on a flat 11 m path with markers at the 3 m and 8 m points. Participants were asked to walk normally, at their usual speed. A stop watch was used to measure the time taken to walk between the markers, and the faster of two trials was recorded.

A stop watch was also used to measure timed up & go (TUG) from the moment the participant stood up from the chair, walked around a cone placed 3 m away, and returned to starting position (seated on the chair), and the faster of two trials was recorded. Assistive walking devices were only used upon the participant's request, or if the investigators observed any risk of falling.

Walking parameters were assessed using a 2.4 m sensor gait analyzer (Sheet Type Gait Analyzer Walk Way MW-1000, Anima, Tokyo, Japan). Stride, cadence, step length, step width, and foot progression angles were measured. Participants began walking 1.5 m from the beginning of the walk way, up to 1.5 m beyond the end of the walk way. The faster of two trials was used in analysis. While both legs were measured for stride, step length, step width, and foot progression angle, the left was used for the purposes of this study.

2.3.5. Hematological analysis

Non-fasting blood samples were collected at baseline and post-intervention. Analyses were performed centrally in one laboratory (Special Reference Laboratories, Tokyo, Japan). Total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, albumin, and creatinine were assessed.

2.4. Intervention

The participants of this study included those not only with walking ability declines, but also lower back pain, knee pain, fall history, and urinary incontinence; therefore retaining the risk of adverse events during the intervention such as falls or worsening knee or back pain. In order to prevent such adverse events, the instructor was a physical trainer specialized in training the elderly, and two or more able-bodied supporters were standing by during the exercise sessions. The adjoining hospital was also notified in advance in case of adverse event occurrence, and the exercise sessions, and assessments were performed in close proximity to the emergency room.

2.4.1. Exercise

The participants in the exercise group were provided with a physical comprehensive training program of moderate intensity with an emphasis on balance and gait training. Each exercise class was 60 min, held at the TMIG twice per week for 3-months. The exercise session included a 5 min warm-up, 20 min of strengthening exercises, 30 min of balance and gait training, followed by a five minute cool-down. The strengthening exercises aimed to improve walking ability were performed in a progressive sequence from the seated to standing positions, and progressive resistance was applied through the use of the Thera-bands, and increasing repetition of each time of exercise.

Balance and gait training: Exercises included standing on one leg and multidirectional weight shifts. Participants were instructed on and practiced proper gait mechanics that focused on the maintenance of stability during walking, and increasing stride length, toe elevation of the forward limb, heel elevation of the rear limb, frequency of stepping, and arm swinging.

Chair exercise: Repetitions of toe raises, heel raises, knee lifts, knee extensions and others, were performed while seated on a chair. To increase difficulty and resistance, participants then performed; hip flexions, lateral leg raises, and repetitions of other exercises while standing upright behind the chair and holding the back of the chair for stability.

Exercises using a resistance band (Thera-Band): Resistance bands were used to further strengthen the upper and lower body. Lower body exercises consisted of leg extensions, hip flexions, and more. Upper body exercises included double-arm pull downs, bicep curls, and others.

2.4.2. MFGM supplementation

The MFGM group was provided with supplements in pill form, every 2 weeks. MFGM was purchased from Megmilk Snow Brand Co., Ltd. (Sapporo, Japan). The composition of the MFGM was 21.5% protein, 44.0% fat, 26.5% carbohydrate, 6.4% ash, and 1.6% moisture. Each pill contained 167 mg of MFGM, and six pills (total 1 g MFGM) were ingested in the mornings, prior to activity. The pills were yogurt-flavored so the participants chewed or swallowed the pill according to their preference. Participants kept a daily diary provided by the research team to recording supplement intake, such as whether or not they took the full amount of the supplement (if not, how much), and the time of day. These diary sheets were collected every two weeks to monitor compliance.

2.4.3. Placebo

The placebo group followed the same protocol as the MFGM supplementation group; however, the contents of the pill differed. The placebo included whole milk powder instead of MFGM, and the placebo consisted of pills of similar shape, taste, and texture of the MFGM pills. Whole milk powder was purchased from Meiji Milk Products Co. Ltd (Tokyo, Japan). The composition of the milk powder was 26.3% protein, 25.2% fat, 39.5% carbohydrate, 5.7% ash, and 3.3% moisture.

The study protocol was approved by the Clinical Research Ethics Committee of the TMIG. The intervention procedures were fully explained to all participants and written informed consents were obtained. The study was registered at The Japan Medical Association Clinical Trial Registry (JMACCT) JMA-IIA00167.

2.5. Data analysis

Sample size calculations using G-Power, *F*-Test, analysis of variance (ANOVA): Fixed effects, special, main effects and interactions. Setting the power at 0.80, alpha value of 0.05, effect size of 0.4, and number of groups at 4, the total sample size required was estimated to be 111

subjects. With a potential attrition rate of 12%, 126 subjects were recruited.

Differences in baseline measures between the groups was assessed using a one-way ANOVA for continuous variables, and chi-square tests were performed on categorical variables. The generalized estimating equation was used to compare the effects between the groups after the three month intervention. Percent changes in walking parameter variables were calculated using the formula: % change = ((post intervention value-baseline value)/baseline value × 100), and one-way ANOVA was performed to determine significant differences in percent changes within or between the groups from baseline to post-intervention, with values expressed as differences with 95% confidence intervals. The Scheffe post hoc method was used for significant values.

In order to compare baseline values between participants in the exercise groups (Ex + MFGM and Ex + P) with improved and decreased or unchanged walking speed, those with zero or negative values (post value – baseline value), were grouped as decreased or unchanged walking speed, and those with positive values were grouped as increasing walking speed. Student's *t*-tests were used to compare the groups for continuous variables and chi-square test for categorical variables.

All analyses were performed using SPSS software, Windows version 20.0 (SPSS, Inc., Tokyo, Japan).

3. Results

There were no significant differences in any of the interview, physical function, body composition, walking ability and parameters, or blood components between any of the groups at baseline, except for albumin levels (Table 1).

Four participants were unable to complete the study after randomization due to wrist fracture ($n = 1$), spouse care ($n = 1$), surgery ($n = 1$) and death ($n = 1$). No dropouts were due to adverse effects of the interventions.

Table 2 shows the comparison of physical function, body composition, walking parameters, and hematological factors between the groups after the three month intervention. The results show no significant differences in blood pressure, heart rate, TUG, muscle mass, or hematological factors between the groups. However, an increasing trend in knee extension strength was observed in both exercise groups, and leg muscle mass in the Ex + P group. Walking ability and parameter results showed that there were significant differences in usual walking speed ($P < 0.001$), stride ($P < 0.001$) and foot progression angle ($P = 0.010$) between the groups.

Usual walking speed increased by 19.6% in the Ex + MFGM group, 18.6% in the Ex + P, 2.5% in the MFGM, and 3.8% in the placebo group ($P < 0.001$, Table 3). The improvements in walking speed observed in both exercise groups were significantly greater than the MFGM and placebo groups. Further, stride increased in the Ex + MFGM group by 6.8%, 6.1% in the Ex + P, 0.8% in the MFGM group, and declined by 2.3% in the placebo group, where the change in the Ex + P group was significantly greater than both the MFGM and placebo groups, and the Ex + P group was greater than the placebo group ($P < 0.001$). Percent changes in step width were minimal for both exercise groups (−0.4% and 0.4% in the Ex + MFGM and Ex + P groups, respectively), although increases were seen in the MFGM (7.2%) and P groups (4.9%). Similarly, foot progression angle decreased in both exercise groups (−3.6% and −5.8% in the Ex + MFGM and Ex + P groups, respectively), while increases were observed in the MFGM (5.1%) and placebo (8.1%) groups ($P = 0.023$). Step length significantly increased in the Ex + MFGM and Ex + P groups (6.2% and 6.5%, respectively), whereas minimal changes were detected in the MFGM and *P* groups ($P < 0.001$, Table 3).

4. Discussion

The results of this study showed that exercise interventions, both with MFGM and without MFGM were beneficial in improving walking speed and stride length, while also reducing foot progression angle, signifying more stable walking patterns in community-dwelling Japanese elderly women with walking ability declines.

The analyses revealed no additive effects of MFGM with exercise. However, walking speed and stride increased in the Ex + MFGM group by 19.6% (95%CI = 10.3–28.9) and 6.8% (95%CI = 3.2–10.4),

Table 1
Baseline comparison of selected variables.

Variables	Ex + MFGM ($n = 31$)			Ex + Placebo ($n = 32$)			MFGM ($n = 32$)			Placebo ($n = 31$)			ANOVA	
													F value*	*P* value
Age (years)	82.8	±	2.8	83.1	±	3.3	82.9	±	2.9	83.8	±	3.3	0.591	*0.622*
Height (cm)	145.4	±	5.4	144.6	±	5.8	146.8	±	5.7	145.4	±	5.2	0.954	*0.417*
Weight (kg)	49.8	±	7.4	52.4	±	10.5	48.4	±	9.5	51.2	±	8.1	1.204	*0.311*
Arm muscle mass (kg)	3.7	±	0.5	3.5	±	0.5	3.4	±	0.5	3.5	±	0.5	2.295	*0.081*
Leg muscle mass (kg)	10.6	±	1.3	10.1	±	1.3	10.3	±	1.5	10.6	±	1.3	0.943	*0.422*
Appendicular muscle mass (kg)	14.3	±	1.7	13.5	±	1.7	13.8	±	1.9	14.1	±	1.7	1.209	*0.309*
Timed up & go (s)	10.7	±	3.6	11.6	±	5.2	10.9	±	2.4	11.4	±	3.3	0.401	*0.753*
Grip strength (kg)	19.4	±	3.4	19.8	±	4.5	18.9	±	3.7	18.4	±	4.6	0.978	*0.567*
Knee extension strength (N)	157.1	±	47.6	166.6	±	64.3	161.4	±	39.7	160.4	±	50.4	0.186	*0.906*
Usual walking speed (m/s)	0.9	±	0.2	0.9	±	0.3	1.0	±	0.2	0.9	±	0.2	0.601	*0.616*
Stride (cm)	93.0	±	15.7	90.3	±	15.4	98.6	±	12.8	94.2	±	15.0	1.783	*0.154*
Foot progression angle (deg)	12.0	±	3.9	14.4	±	6.4	11.6	±	4.3	13.6	±	5.7	2.112	*0.102*
Cadence (steps/min)	127.2	±	15.1	120.6	±	16.1	125.8	±	12.7	122.9	±	12.1	1.37	*0.255*
Step length (cm)	46.8	±	7.8	45.1	±	7.5	49.5	±	6.3	47.1	±	8.1	1.911	*0.131*
Step width (cm)	8.8	±	2.2	10.3	±	3.8	8.7	±	3.1	9.9	±	3.4	1.927	*0.129*
Creatinine (mg/dL)	0.9	±	0.4	0.8	±	0.2	0.9	±	0.3	0.8	±	0.3	0.570	*0.636*
Total cholesterol (mg/dL)	204.3	±	28.3	214.0	±	28.2	211.7	±	41.3	212.3	±	29.9	0.547	*0.651*
HDL cholesterol (mg/dL)	66.7	±	19.3	64.0	±	12.5	64.9	±	18.5	65.7	±	13.4	0.163	*0.921*
Albumin (g/dL)	4.1	±	0.3	4.3	±	0.2	4.1	±	0.2	4.2	±	0.2	3.056	*0.031*
Lower back pain (%, yes)	61.3			65.6			56.2			54.8			0.959	*0.811*
Knee pain (%, yes)	61.3			37.5			46.9			45.2			3.719	*0.293*
Falls (%, yes)	29.0			21.9			25.0			25.8			0.431	*0.934*
Urinary incontinence (%, yes)	51.6			56.2			43.8			58.1			1.557	*0.669*
Regular exercise habit (%, yes)	25.8			29.0			31.2			29.0			0.231	*0.972*

Note: Ex = exercise, MFGM = milk fat globule membrane, ANOVA = analysis of variance.
* One-way analysis of variance for continuous variables and chi-square test for categorical variables.

Table 2
Comparison of functional fitness, muscle mass, walking parameters and blood component variables between groups after 3-month interventions.

Variables*	Group†	Baseline			After 3-month intervention			ANOVA (G × T)‡ (*P*-value)
Arm muscle mass (kg)	Ex + MFGM	3.7	±	0.5	3.5	±	0.5	*F = 1.313*
	Ex + Placebo	3.4	±	0.5	3.5	±	0.5	*0.274*
	MFGM	3.5	±	0.5	3.3	±	0.5	
	Placebo	3.6	±	0.5	3.6	±	0.5	
Leg muscle mass (kg)	Ex + MFGM	10.6	±	1.4	10.3	±	1.4	*F = 2.669*
	Ex + Placebo	10.0	±	1.4	10.5	±	1.6	*0.051*
	MFGM	10.4	±	1.6	9.8	±	1.3	
	Placebo	10.6	±	1.3	10.8	±	1.4	
Skeletal muscle mass (kg)	Ex + MFGM	14.3	±	1.8	13.8	±	1.8	*F = 2.365*
	Ex + Placebo	13.5	±	1.8	14.0	±	2.1	*0.075*
	MFGM	13.8	±	2.0	13.1	±	1.7	
	Placebo	14.2	±	1.7	14.4	±	1.8	
Timed up & go (sec)	Ex + MFGM	8.57	±	2.23	8.47	±	2.15	*F = 1.009*
	Ex + Placebo	9.15	±	2.90	8.60	±	2.11	*0.392*
	MFGM	9.43	±	2.38	9.62	±	2.77	
	Placebo	9.68	±	2.91	9.74	±	2.42	
Knee extension strength (N)	Ex + MFGM	161.5	±	49.3	171.0	±	62.8	*F = 2.620*
	Ex + Placebo	170.5	±	66.1	188.1	±	65.4	*(0.054)*
	MFGM	161.8	±	42.3	162.0	±	44.5	
	Placebo	163.8	±	52.6	187.2	±	62.4	
Grip strength (kg)	Ex + MFGM	19.2	±	3.6	18.9	±	4.5	*F = 0.161*
	Ex + Placebo	19.6	±	4.6	19.7	±	4.4	*0.922*
	MFGM	18.4	±	3.5	18.4	±	3.9	
	Placebo	18.6	±	4.5	18.6	±	4.7	
Usual walking speed (m/s)	Ex + MFGM	0.97	±	0.20	1.14	±	0.23	*F = 7.211*
	Ex + Placebo	0.94	±	0.26	1.09	±	0.28	*< 0.001*
	MFGM	0.99	±	0.22	1.02	±	0.24	
	Placebo	0.92	±	0.20	0.94	±	0.19	
Stride (cm)	Ex + MFGM	93.9	±	15.9	100.0	±	16.6	*F = 8.915*
	Ex + Placebo	90.3	±	16.0	95.9	±	19.1	*< 0.001*
	MFGM	98.4	±	13.2	99.2	±	14.6	
	Placebo	94.3	±	15.3	92.2	±	16.6	
Cadence (step/min)	Ex + MFGM	128.5	±	14.9	129.0	±	10.8	*F = 2.068*
	Ex + Placebo	120.3	±	16.7	125.4	±	15.2	*0.108*
	MFGM	126.1	±	12.8	128.1	±	14.5	
	Placebo	122.6	±	12.2	123.8	±	9.9	
Step width (cm)	Ex + MFGM	8.9	±	2.2	8.9	±	2.6	*F = 1.174*
	Ex + Placebo	10.4	±	4.0	10.2	±	3.6	*0.323*
	MFGM	8.9	±	3.2	9.4	±	3.3	
	Placebo	10.0	±	3.4	10.3	±	3.5	
Foot progression angle (deg)	Ex + MFGM	11.2	±	3.7	10.6	±	4.1	*F = 3.967*
	Ex + Placebo	13.8	±	6.5	12.9	±	6.4	*0.010*
	MFGM	10.5	±	4.4	11.2	±	5.2	
	Placebo	12.6	±	5.8	13.1	±	5.8	
Creatinine (mg/dl)	Ex + MFGM	0.92	±	0.44	0.84	±	0.46	*F = 0.551*
	Ex + Placebo	0.80	±	0.21	0.80	±	0.30	*0.648*
	MFGM	0.84	±	0.29	0.78	±	0.27	
	Placebo	0.82	±	0.35	0.76	±	0.26	
Total cholesterol (mg/dL)	Ex + MFGM	204.4	±	29.6	201.9	±	29.1	*F = 1.409*
	Ex + Placebo	213.7	±	29.2	204.5	±	29.2	*0.244*
	MFGM	211.6	±	42.1	214.6	±	31.6	
	Placebo	212.3	±	30.4	200.1	±	33.1	
Albumin (g/dL)	Ex + MFGM	4.14	±	0.26	4.18	±	0.24	*F = 0.898*
	Ex + Placebo	4.29	±	0.19	4.26	±	0.22	*0.444*
	MFGM	4.16	±	0.22	4.21	±	0.17	
	Placebo	4.20	±	0.19	4.20	±	0.22	

* Data are presented as mean and standard deviation.
† Ex = exercise group; MFGM = milk fat globule membrane.
‡ ANOVA = analysis of variance, G = group, T = time.

respectively; and in the Ex + P group by 18.6% (95%CI = 10.8–26.4) and 6.1% (95%CI = 2.8–9.4), respectively. One previous mice study reported that MFGM in congruence with exercise may promote neuromuscular development and neuromuscular junction formation to improve muscle function deficits in mice (Haramizu et al., 2014). Further, Soga et al. found that the consumption of 1 g of MFGM together with moderate intensity exercise can improve strength through increased motor unit activity and recruitment in healthy middle-aged Japanese men (Soga, Ota, & Shimotoyodome, 2015). Ex + MFGM was effective in improving walking speed and parameters such as stride, foot progression angle, and step length; however, the Ex + P group was also as effective as Ex + MFGM and no additive benefits were observed. A recent systematic review reported that nutritional supplementation, specifically protein supplementation, does not augment the effects of resistance exercise in elderly people (Thomas, Quinn, Saunders, & Greig, 2016). The results of the current study corroborate the results of the review as MFGM also did not augment the results of moderate intensity exercise training in elderly women with walking ability declines.

Ferrandez et al., in the earlier years of walking parameter research in the elderly, found that slowing due to age was exclusively from decreased stride (Ferrandez, Pailhous, & Durup, 1990). Among community-dwelling elderly women with walking ability declines in the

Table 3
Baseline to post-intervention percent change comparison of selected walking parameter variables between groups.

Variables	Ex + MFGM			Ex + Placebo			MFGM			Placebo			*P*-value*	Post hoc analysis†
	Mean	±	SE	Mean	±	SE	Mean	±	SE	Mean	±	SE		($P < 0.05$)
Usual walking speed	19.6	±	4.5	18.6	±	3.9	2.5	±	3.0	3.8	±	2.8	< 0.001	Ex + MFGM, Ex + P > MFGM, P
(95% CI for mean)	(10.3 to 28.9)			(10.8 to 26.4)			(−3.6 to 8.6)			(−2.0 to 9.7)				
Stride	6.8	±	1.8	6.1	±	1.6	0.8	±	1.3	−2.3	±	1.3	< 0.001	Ex + MFGM > MFGM, P; Ex + P > P
(95% CI for mean)	(3.2 to 10.4)			(2.8 to 9.4)			(−1.8 to 3.4)			(−5.0 to 0.40)				
Step width	−0.4	±	3.4	0.4	±	3.7	7.2	±	4.1	4.9	±	3.3	0.393	
(95% CI for mean)	(−7.4 to 6.6)			(−7.2 to 8.0)			(−1.1 to 15.6)			(−1.7 to 11.6)				Ex + P > P
Foot progression angle	−3.6	±	3.4	−5.8	±	3.5	5.1	±	4.1	8.1	±	3.6	0.023	
(95% CI for mean)	(−10.5 to 3.3)			(−13.0 to 1.5)			(−3.2 to 13.5)			(0.61 to 15.5)				
Step length	6.2	±	1.8	6.5	±	1.7	0.2	±	1.3	−1.3	±	1.4	< 0.001	Ex + MFGM > P; Ex + P > MFGM, P
(95% CI for mean)	(2.4 to 9.9)			(3.0 to 10.1)			(−2.5 to 2.9)			(−4.1 to 1.5)				
Timed up & go	0.7	±	3.7	−3.8	±	2.0	2.7	±	3.0	3.1	±	3.5	0.371	
(95% CI for mean)	(−6.9 to 8.4)			(−8.0 to 0.3)			(−3.4 to 8.8)			(−4.1 to 10.2)				
Step count	69.3	±	17.4	88.9	±	26.1	45.4	±	11.7	27.4	±	9.5	0.075	
(95% CI for mean)	(33.5 to 105.2)			(35.3 to 142.6)			(21.4 to 69.3)			(7.8 to 47.1)				

Notes: Data are presented as mean and standard error, with 95% confidence intervals.
CI = confidence interval, Ex = exercise, MFGM = milk fat globule membrane, P = placebo, SE = standard error.
* One-way analysis of variance.
† A post hoc analysis was performed using the Scheffe method.

current study, stride significantly increased in the Ex + MFGM and Ex + P groups ($P < 0.001$), while foot progression angle significantly decreased in both exercise groups ($P = 0.010$). Although investigation into the mechanism of slow walking speed was beyond the scope of our study, the results suggest that with the beneficial effects of exercise, decreased foot progression angle may allow for greater stride length and in turn, faster walking speed.

Although walking speed significantly increased in both exercise groups (Ex + MFGM and Ex + P; $n = 63$), there were 17 elderly women did not show improvements in walking speed (Table 4). *T*-test comparisons showed that those who did not improve had significantly weaker knee extension strength at baseline ($P = 0.016$). Another factor that has a restrictive impact on the intervention results is knee OA. As seen in Table 4, 64.7% of people with a history knee OA, and 60.0% of those undergoing knee OA treatment had unchanging or decreased walking speeds ($P = 0.033$ and 0.010, respectively). Within the exercise groups, there were several participants who showed no improvements or even decreases in walking speed after the three month intervention. Those with decreased or unchanged walking speed had significantly lower knee extension strength at baseline, and a greater likelihood of having knee OA or receiving treatment for OA. One previous study reported that differences in gait parameters between knee OA and healthy subjects appear to be a result of freely chosen walking speed than disease progression (Zeni & Higginson, 2009). Greater quadriceps strength may be protective of cartilage loss, and those with greater quadriceps strength had less pain as well as better physical

Table 4
Baseline comparison between participants with improved walking speed and participants with decreased or unchanged walking speed after Ex + MFGM or Ex + P interventions.

Variables*	Decreased/unchanged WS ($n = 17$)			Improved WS ($n = 46$)			*P*-value†
Age (years)	83.6	±	3.1	84.3	±	3.1	*0.464*
Stride (cm)	58.0	±	13.3	92.9	±	16.2	*0.263*
Foot progression angle (deg)	12.7	±	5.5	13.5	±	5.4	*0.763*
Step length (cm)	44.6	±	6.9	46.4	±	7.9	*0.387*
Step width (cm)	9.6	±	3.4	9.6	±	3.2	*0.988*
Walking speed (m/s)	0.95	±	0.3	0.93	±	0.2	*0.788*
Knee extension strength (N)	139.8	±	33.8	170.0	±	61.1	*0.016*
Grip strength (kg)	20.3	±	3.7	19.4	±	4.1	*0.420*
Timed up & go (s)	9.4	±	3.9	9.4	±	3.5	*0.962*
Creatinine (mg/dl)	0.9	±	0.5	0.8	±	0.3	*0.330*
Total cholesterol (mg/dL)	212.4	±	31.3	208.1	±	27.6	*0.600*
HDL cholesterol (mg/dL)	64.7	±	12.5	65.5	±	17.4	*0.864*
Albumin (g/dL)	4.1	±	0.2	4.2	±	0.3	*0.106*
Back pain (%, yes)	64.7			63.0			*0.903*
Knee pain (%, yes)	64.7			43.5			*0.135*
Hypertension (%, yes)	64.7			69.6			*0.713*
Hyperlipidemia (%, yes)	17.6			30.4			*0.310*
Heart disease (%, yes)	29.4			32.6			*0.809*
Diabetes (%, yes)	5.9			8.7			*0.714*
COPD (%, yes)	5.9			0.0			*0.097*
Osteoporosis (%, yes)	47.1			47.8			*0.957*
Hip OA (%, yes)	23.5			6.5			*0.057*
Knee OA (%, yes)	64.7			34.8			*0.033*
Knee OA treatment (%, yes)	60.0			23.1			*0.010*

* Data are presented as mean and standard deviation for continuous variables, and percentages for categorical variables. COPD = chronic obstructive pulmonary disorder, OA = osteoarthritis, WS = walking speed.
† Student's *t*-test for continuous variables and chi-square test for categorical variables.

function (Amin et al., 2009). Further, the literature shows that quadriceps strengthening exercise can reduce pain and disability in people with knee OA (Roddy, Zhang, & Doherty, 2005). While the specific biomechanical changes in walking due to exercise are uncertain (Beijersbergen, Granacher, Vandervoort, DeVita, & Hortobagyi, 2013), previous studies have shown that changes in knee extensor strength is correlated with changes in stride length (Persch, Ugrinowitsch, Pereira, & Rodacki, 2009). Elderly people with poor balance and knee extension strength has been shown to be five times more likely to develop severe walking disability than their stronger counterparts (Rantanen et al., 2001). The results of the current study showed increasing trends for knee extension strength and leg muscle mass in both Ex + MFGM and Ex + P groups. Perhaps different forms of exercise training focusing on quadriceps strengthening may be necessary for older women with very low knee extension strength or knee OA in order to improve function, stability, and walking ability. Furthermore, since improvement in walking ability among knee OA participants is limited with exercise and/or nutrition, further study with the cooperation of an orthopedic specialist is warranted.

There are several limitations in this study. First, there may be potential placebo effects and bias as the MFGM supplementation could be blinded, but the exercise intervention could not. Second this study focused solely on elderly women, and the results of this study cannot be generalized to the population as a whole. Third, though the participants were instructed on the provided MFGM or placebo intake, they were asked to continue their regular dietary habits throughout the course of the study. Therefore, it was not possible to analyze how, and to what extent the participants dietary habits may have acted as confounding variables to the results. Further, the investigators were unable to control or collect full comprehensive daily dietary and nutritional intake information of each participant. Fourth, out of 321 people with walking ability declines, 126 (39.3%) were included in this study, and 195 (60.7%) declined or were excluded. The results should be carefully interpreted as they were based on the smaller percentage of included participants (39.3%), and the sample in this study may not have been representative of the general population with walking ability declines. Further research may be necessary to investigate the effects of a similar intervention on non-participants (those excluded or decline to participate).

5. Conclusion

In conclusion, while significant additive effects of the MFGM with exercise could not be confirmed, exercise and MFMG were beneficial in improving walking speed, and other walking parameters such as stride, foot progression angle, and step length. Further, those with unchanged or reduced walking speed had significantly lower knee extension strength as well as a greater likelihood of knee OA, and thus further research is needed on different exercise training for those with weak lower extremities and knee OA among community-dwelling elderly women.

Conflicts of interest

There are no conflicts of interest to declare. While Kao Corporation provided the MFGM supplementation, they played no role in the design, data collection, analysis, interpretation, or preparation of the manuscript.

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References

Abellan van Kan, G., Rolland, Y., Andrieu, S., Bauer, J., Beauchet, O., Bonnefoy, M., et al. (2009). Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. *Journal of Nutrition Health and Aging, 13*(10), 881–889.

Aboutorabi, A., Arazpour, M., Bahramizadeh, M., Hutchins, S. W., & Fadayevatan, R. (2016). The effect of aging on gait parameters in able-bodied older subjects: A literature review. *Aging Clinical and Experimental Research, 28*(3), 393–405. https://doi.org/10.1007/s40520-015-0420-6.

Amin, S., Baker, K., Niu, J., Clancy, M., Goggins, J., Guermazi, A., et al. (2009). Quadriceps strength and the risk of cartilage loss and symptom progression in knee osteoarthritis. *Arthritis and Rheumatism, 60*(1), 189–198. https://doi.org/10.1002/art.24182.

Beijersbergen, C. M., Granacher, U., Vandervoort, A. A., DeVita, P., & Hortobagyi, T. (2013). The biomechanical mechanism of how strength and power training improves walking speed in old adults remains unknown. *Ageing Research Reviews, 12*(2), 618–627. https://doi.org/10.1016/j.arr.2013.03.001.

Blain, H., Carriere, I., Sourial, N., Berard, C., Favier, F., Colvez, A., et al. (2010). Balance and walking speed predict subsequent 8-year mortality independently of current and intermediate events in well-functioning women aged 75 years and older. *Journal of Nutrition Health and Aging, 14*(7), 595–600.

Buchner, D. M., Cress, M. E., Esselman, P. C., Margherita, A. J., de Lateur, B. J., Campbell, A. J., et al. (1996). Factors associated with changes in gait speed in older adults. *Journals of Gerontology Series A, Biological Sciences and Medical Sciences, 51*(6), M297–M302.

Elliot, T. A., Cree, M. G., Sanford, A. P., Wolfe, R. R., & Tipton, K. D. (2006). Milk ingestion stimulates net muscle protein synthesis following resistance exercise. *Medicine and Science in Sports and Exercise, 38*(4), 667–674. https://doi.org/10.1249/01.mss.0000210190.64458.2500005768-200604000-00009 [pii].

El-Loly, M. M. (2011). Composition properties and nutritional aspects of milk fat globule membrane – A review. *Polish Journal of Food and Nutrition Sciences, 61*, 7–32.

Ferrandez, A. M., Pailhous, J., & Durup, M. (1990). Slowness in elderly gait. *Experimental Aging Research, 16*(1–2), 79–89. https://doi.org/10.1080/07340669008251531.

Haramizu, S., Mori, T., Yano, M., Ota, N., Hashizume, K., Otsuka, A., et al. (2014). Habitual exercise plus dietary supplementation with milk fat globule membrane improves muscle function deficits via neuromuscular development in senescence-accelerated mice. *SpringerPlus, 3*, 339. https://doi.org/10.1186/2193-1801-3-339.

Hausdorff, J. M., Nelson, M. E., Kaliton, D., Layne, J. E., Bernstein, M. J., Nuernberger, A., et al. (2001). Etiology and modification of gait instability in older adults: A randomized controlled trial of exercise. *Journal of Applied Physiology, 90*(6), 2117–2129.

Josse, A. R., Tang, J. E., Tarnopolsky, M. A., & Phillips, S. M. (2010). Body composition and strength changes in women with milk and resistance exercise. *Medicine and Science in Sports and Exercise, 42*(6), 1122–1130. https://doi.org/10.1249/MSS.0b013e3181c854f6.

Kim, H., Suzuki, T., Yoshida, H., Shimada, H., Yamashiro, Y., Sudo, M., et al. (2013). Are gait parameters related to knee pain, urinary incontinence and a history of falls in community-dwelling elderly women? *Nihon Ronen Igakkai Zasshi, 50*(4), 528–535.

Kim, H., Suzuki, T., Kim, M., Kojima, N., Ota, N., Shimotoyodome, A., et al. (2015). Effects of exercise and milk fat globule membrane (MFGM) supplementation on body composition, physical function, and hematological parameters in community-dwelling frail Japanese women: A randomized double blind, placebo-controlled, follow-up trial. *PLOS ONE, 10*(2), e0116256. https://doi.org/10.1371/journal.pone.0116256.

Martinikorena, I., Martinez-Ramirez, A., Gomez, M., Lecumberri, P., Casas-Herrero, A., Cadore, E. L., et al. (2016). Gait variability related to muscle quality and muscle power output in frail nonagenarian older adults. *Journal of the American Medical Directors Association, 17*(2), 162–167. https://doi.org/10.1016/j.jamda.2015.09.015.

Persch, L. N., Ugrinowitsch, C., Pereira, G., & Rodacki, A. L. (2009). Strength training improves fall-related gait kinematics in the elderly: A randomized controlled trial. *Clinical Biomechanics, 24*(10), 819–825. https://doi.org/10.1016/j.clinbiomech.2009.07.012.

Rantanen, T., Guralnik, J. M., Ferrucci, L., Penninx, B. W., Leveille, S., Sipila, S., et al. (2001). Coimpairments as predictors of severe walking disability in older women. *Journal of the American Geriatrics Society, 49*(1), 21–27.

Roddy, E., Zhang, W., & Doherty, M. (2005). Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. *Annals of the Rheumatic Diseases, 64*(4), 544–548. https://doi.org/10.1136/ard.2004.028746.

Shinkai, S., Watanabe, S., Kumagai, S., Fujiwara, Y., Amano, H., Yoshida, H., et al. (2000). Walking speed as a good predictor for the onset of functional dependence in a Japanese rural community population. *Age and Ageing, 29*(5), 441–446.

Soga, S., Ota, N., & Shimotoyodome, A. (2015). Dietary milk fat globule membrane supplementation combined with regular exercise improves skeletal muscle strength in healthy adults: A randomized double-blind, placebo-controlled, crossover trial. *Nutrition Journal, 14*, 85. https://doi.org/10.1186/s12937-015-0073-5.

Suzuki, T., Yoshida, H., Kim, H., Yukawa, H., Sugiura, M., Furuna, T., et al. (2003). Walking speed as a good predictor for maintenance of I-ADL among the rural community elderly in Japan: A 5-year follow-up study from TMIG-LISA. *Geriatrics and Gerontology International, 3*, S6–S14.

Thomas, D. K., Quinn, M. A., Saunders, D. H., & Greig, C. A. (2016). Protein supplementation does not significantly augment the effects of resistance exercise training in older adults: A systematic review. *Journal of the American Medical Directors Association, 17*(10), https://doi.org/10.1016/j.jamda.2016.07.002 959e1–9.

Wilkinson, S. B., Tarnopolsky, M. A., Macdonald, M. J., Macdonald, J. R., Armstrong, D., & Phillips, S. M. (2007). Consumption of fluid skim milk promotes greater muscle protein accretion after resistance exercise than does consumption of an isonitrogenous and isoenergetic soy-protein beverage. *American Journal of Clinical Nutrition, 85*(4), 1031–1040. https://doi.org/10.1093/ajcn/85.4.1031 [pii].

Woo, J., Ho, S. C., & Yu, A. L. (1999). Walking speed and stride length predicts 36 months dependency, mortality, and institutionalization in Chinese aged 70 and older. *Journal of the American Geriatrics Society, 47*(10), 1257–1260.

Zeni, J. A., Jr., & Higginson, J. S. (2009). Differences in gait parameters between healthy subjects and persons with moderate and severe knee osteoarthritis: A result of altered walking speed? *Clinical Biomechanics, 24*(4), 372–378. https://doi.org/10.1016/j.clinbiomech.2009.02.001.