International Journal of Chronic Obstructive Pulmonary Disease Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Effects of Ninjin'yoeito on Patients with Chronic Obstructive Pulmonary Disease and Comorbid Frailty and Sarcopenia: A Preliminary Open-Label Randomized Controlled Trial

Hiroyuki Ohbayashi, Mitsue Ariga, Kunihiro Ohta, Sahori Kudo, Osamu Furuta, Akinori Yamamoto

Medical Corporation, Syureikai, Tohno Chuo Clinic, Mizunami City, Gifu, Japan

Correspondence: Hiroyuki Ohbayashi, Medical Corporation, Syureikai, Tohno Chuo Clinic, 1-14-1, Matsugase Cho, Mizunami City, Gifu, 509-6134, Japan, Tel +81-572-67-1118, Fax +81-572-67-2277, Email ohbayasi@nn.iij4u.or.jp; aims_reserve@yahoo.co.jp

Purpose: To present the preliminarily findings regarding the effects of a herbal medicine, Ninjin'yoeito, on comorbid frailty and sarcopenia in patients with chronic obstructive pulmonary disease (COPD).

Patients and Methods: Patients with COPD (GOLD II or higher) and fatigue were randomly assigned to Group A (n = 28; no medication for 12 weeks, followed by 12-week administration) or B (n= 25; 24-week continuous administration). Visual analog scale (VAS) symptoms of fatigue, the COPD assessment test (CAT), and the modified Medical Research Council (mMRC) Dyspnea Scale were examined. Physical indices such asknee extension leg strength and walking speed, skeletal muscle mass index (SMI), and respiratory function test were also measured.

Results: VAS fatigue scales in Group B significantly improved after 4, 8, and 12 weeks compared to those in Group A (each $p<0.001$, respectively). Right and left knee extension leg strength in Group B significantly improved after 12 weeks compared to that in Group A ($p=0.042$ and $p=0.037$, respectively). The 1-s walking speed for continued to increase significantly over 24 weeks in Group B ($p=0.016$, $p<0.001$, $p<0.001$, $p=0.004$, $p<0.001$, and $p<0.001$ after 4, 8, 12, 16, 20, and 24 weeks, respectively); it also significantly increased after the administration of Ninjin'yoeito in Group A. In Group B, the SMI significantly increased at 12 weeks in patients with sarcopenia ($p=0.025$). The CAT scores in Group B significantly improved after 12 weeks compared to those in Group A ($p=0.006$). The mMRC scores in Group B also significantly improved after 8 and 12 weeks compared to those in Group A ($p=0.045$ and $p<0.001$, respectively). The changes in %FEV1.0 in Group B were significantly improved at 12 and 24 weeks ($p=0.039$ and $p=0.036$, respectively).

Conclusion: Overall, Ninjin'yoeito significantly improved patients' quality of life, physical activity, muscle mass, and possibly lung function, suggesting that Ninjin'yoeito may improve frailty and sarcopenia in patients with COPD.

Keywords: clinical study, frailty, Ninjin'yoeito, sarcopenia, therapeutic effect

Introduction

Chronic obstructive pulmonary disease (COPD) is currently defined as a common preventable disease that is characterized by chronic airway inflammation and progressive airflow limitations. COPD is also characterized by various comorbidities that significantly affect patients' quality of life (QOL), exacerbation frequency, and mortality.[1] Among the COPD comorbidities, frailty and sarcopenia should be acknowledged as important conditions.[2,3] Frailty and sarcopenia are geriatric syndromes characterized by multisystem decline, and are closely related to and reflected by markers of skeletal muscle dysfunction. They are emerging as important comorbid syndromes in COPD, and are strongly associated with an increased risks of incident disability, hospitalization, and mortality.[4] Sarcopenia, characterized by the loss of skeletal muscle mass and strength, is a common systemic consequence of COPD. Skeletal muscle dysfunction is a well-recognized manifestation of COPD that demonstrates common changes in limb muscle dysfunction — including quadriceps weakness,[5] atrophy, and muscle fiber

Received: 26 October 2023
Accepted: 19 April 2024
Published: 7 May 2024

phenotype shift,[6] — each of which is an independent prognostic factor for pulmonary function decline.[7] Despite their importance, frailty and sarcopenia tend to be overlooked in primary care clinical settings.

Progressive resistance training (PRT) is the best-studied form of exercise to increase muscle strength and improve function; it is considered the primary intervention for counteracting sarcopenia-induced changes.[8] However, the debate about the optimal volume of PRT according to the degree of aging is ongoing. PRT is usually performed at least 2–3 times a week for 8–12 weeks, but community dwelling elderly may lack access to and motivation for embarking on a strenuous exercise training program. Additionally, PRT requires trained therapists and special equipment which are not routinely available to everyone. Pulmonary rehabilitation improves outcomes in patients with both frailty and sarcopenia;[9] however, effective methods other than pulmonary rehabilitation and nutritional management have not yet been established, making it more difficult to approach patients' treatment in primary care clinical settings.

COPD is a common disease in primary care; nevertheless, there are not always enough staff, particularly general practitioners, and facilities to provide and/or continue rehabilitation and nutrition guidance for these patients. Furthermore, a recent study raised the question of whether respiratory rehabilitation should be continued even after a therapeutic effect has been achieved. Patients with COPD have a higher potential to benefit from pulmonary rehabilitation, but also a higher risk of steeper decline after treatment.[10] The mean 6-minute walking distance (6MWD) and peak oxygen uptake ($V'O2_{peak}$), both exercise training-mediated predictors of change, increased in patients with and without frailty during pulmonary rehabilitation, and declined after its completion. Conversely, the COPD assessment test (CAT) score showed an initial improvement that was followed by a steep decline during training, and a mild decliner after training. This decline in the CAT score, coupled with the limited persistent therapeutic effect of pulmonary rehabilitation, is a serious problem in the treatment of COPD. Additionally, decreasing or loss of appetite significantly worsens patients' general health condition and QOL in various diseases - such as COPD, cancer, and depression - and promotes the progression of frailty and sarcopenia. Decreased appetite may occur upstream of frailty and sarcopenia, which becomes a heavy burden in the treatment of diseases such as COPD. Nutritional supplementation promotes significant improvements in respiratory muscle strength and QOL in malnourished patients with COPD.[11] However, continuous nutritional support is often difficult due to staff and facility limitations, particularly in primary care clinical settings. Appetite stimulants, including steroids, progesterone-based agents such as megestrol acetate (MPA) and cannabinoids, are the oldest and best-studied drugs for sarcopenia and cachexia,[12] and hence maybe medications that clinicians are required to use with sufficient knowledge. However, long-time routine use of these agents may not be best in primary care clinical settings. Hence there remains a continued need for alternative treatment methods to solve the growing problem of frailty and sarcopenia.

Ren-shen-yang-rong-tang (Japanese name: Ninjin'yoeito) is a traditional Chinese herbal medicine composed of 12 crude ingredients: peony root, *Japanese angelica acutiloba, Citrus unshiu* peel, *Astragalus* root, *cinnamon* bark, *ginseng, Atractylodes rhizome, Glycyrrhiza, Rehmannia* root, *Schisandra* fruit, *Poria sclerotium, and Polygala* root. Ninjin'yoeito is used to treat fatigue in patients with anorexia nervosa and autistic spectrum disorders in Japan.[13] A Phase I/II open-label study showed that administering Ninjin'yoeito twice daily for six weeks significantly decreased fatigue severity in cancer survivors without anemia.[14] A recent clinical examination in Japan also reported that Ninjin'yoeito improved the QOL of patients receiving outpatient chemotherapy for non-small cell lung cancer.[15] Little is known about the underlying mechanisms of action of these herbal medicines; however, an in vitro study showed that Ninjin'yoeito influences neuropeptide Y (NPY)- and/or ghrelin-responsive neurons in the hypothalamic arcuate nucleus (ARC), which is considered a feeding center.[16] NPY and ghrelin are the most potent central and peripheral inducers of appetite, respectively. Ninjin'yoeito directly targets both ghrelin-responsive and unresponsive NPY neurons in the arcuate nucleus, and was found to preserve food intake and body weight in cisplatin-treated anorectic mice. These results suggest that signaling from Ninjin'yoeito through the ghrelin-responsive and ghrelin-unresponsive NPY pathways may provide a strong mechanistic basis for the treatment of fatigue and anorectic conditions associated with COPD, cancer, depression, frailty, sarcopenia, and aging. Owing to its efficacy, Ninjin'yoeito is frequently used in elderly patients in Japan.

A recent in vivo study by Miyamoto et al[17] suggested the use of Ninjin'yoeito for the treatment of sarcopenia. Unlike age-related sarcopenia, sarcopenia associated with COPD is considered secondary sarcopenia, and involves changes in the structure and function of skeletal muscle fibers that differ from those observed with aging. In patients with COPD, abnormal mitochondrial function often shifts the distribution of muscle fiber types from type I to type II.[18,19] These

changes can be partially explained by the decreased expression of peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), which is involved in the regulation of muscular mitochondrial biogenesis.[20] Ninjin'yoeito was observed to ameliorate skeletal muscle complications in a COPD mouse model by upregulating PGC-1α expression.[17] suggesting the possibility of improving secondary sarcopenia in COPD. These results prompted us to investigate the effects of Ninjin'yoeito in patients with COPD, frailty, and sarcopenia. The purpose of this study was to determine whether Ninjin'yoeito improves fatigue, depression, decrease in appetite, skeletal muscle complications, and decreased in pulmonary functions, which represent comprehensive complications experienced by most patients with COPD.

Materials and Methods

Study Subjects

The study included outpatients with COPD; patients who met the inclusion criteria and did not meet the exclusion criteria were sequentially enrolled after written informed consent was obtained. The planned number of entries was 60, and the entry period was from 26, January 2022, to March 31, 2023. The inclusion criteria were as follows: (1) patients with COPD who were visited our institution and had Global (GOLD) stage II or higher, (2) patients who continued standard therapy for at least 4 weeks after providing consent, (3) patients with stable respiratory symptoms, (4) patients with fatigue, (5) patients who provided written consent to participate in this study, and (6) patients aged more than or equal to 20 years. The exclusion criteria were as followings: (1) a diagnosis of respiratory diseases other than COPD, such as asthma (excluding ACO); (2) having newly started pulmonary rehabilitation within 3 months prior to the start of this study (excluding physical therapy); (3) having newly started pulmonary rehabilitation since the start of this study (excluding physical therapy); (4) having changed the content and frequency of pulmonary rehabilitation during the study; (5) suffering from acute exacerbations and acute illness within 4 weeks prior to the start of this study; (6) any pronounced musculoskeletal, central nervous system, or neuromuscular disease that affects walking ability; (7) significant neuromuscular disorders due to central nervous system diseases, such as cerebral infarction; (8) taking Kampo medicine within 4 weeks prior to the start of this study to avoid influences from other herbal crude ingredients; (9) having received treatment for malignant tumors within 5 years prior to the start of this study, or currently undergoing treatment; (10) serious complications (liver disease, kidney disease, heart disease, blood disease, etc.); (11) having experienced drug allergies caused by herbal medicines; (12) dementia; (13) poor drug adherence; (14) pregnant and lactating women, and patients undergoing fertility treatment; and (15) being judged as inadequate for study inclusion by the medical attendant during examination.

This study strictly adhered to the ethical principles detailed in the Declaration of Helsinki (revised in 2013) and the Ethical Guidelines for Human Life Science and Medical Research Guidance (established on April 16, 2021), and was approved by the Ethical Review Committee (Review Board of Human Rights and Ethics for Clinical Studies (HURECS), full accreditation from AAHRPP on January, 11 2022, approval number: jRCTs031210583). The registration data were managed using a subject identification code in accordance with the Personal Information Protection Law. The participants were fully debriefed on the content of the research trial and a written consent was provided out of their free will.

Study Protocol

This study was an open-label, non-placebo, randomized controlled trial (Figure 1). After obtaining informed consent at Visit 0, patients were randomly assigned to one of two groups (30 subjects per each group) at Visit 1, according to two allocation factors: COPD GOLD stages and the presence of sarcopenia. The study duration was 24 weeks after randomization. In Group A, Ninjin'yoeito was not administered in the first 12 weeks and was administered daily during the last 12 weeks. In Group B, Ninjin'yoeito was administered daily throughout the 24-week study period. The black circles in Figure 1 indicate that the corresponding evaluation items (shown in the section Evaluation Items) were implemented for each visit.

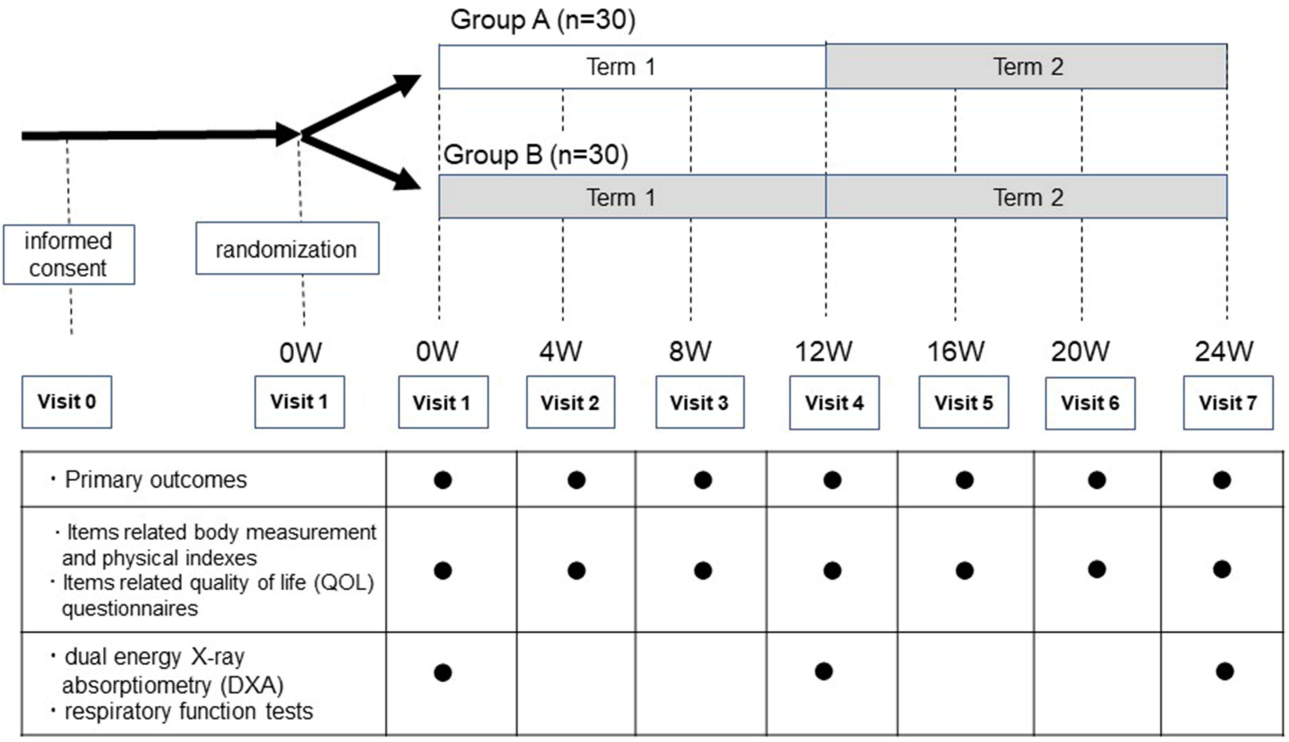

Figure 1 Study protocol. Group A: In Term1 (12 weeks), the study drug is not administered, and in Term2 (12 weeks) the study drug is administered. Group B: The study drug is administered during both Term 1 (12 weeks) and Term 2 (12 weeks). Each gray zone shows the duration of administration with the study drug.

Dosage and Method of Study Drug Administration

Ninjin'yoeito extract fine granules (KB-108; Kracie Pharmaceutical Ltd., Tokyo, Japan) were orally administered either before or between meals twice a day for a daily dosage of 7.5 g. Each 3.75 g was packaged in aluminum in the form of a stick, and one packet was orally ingested per dose. To determine medication adherence, patients were asked to bring all remaining Ninjin'yoeito packages at every visit, which were used to calculate the medication continuation rate.

Evaluation Items

As shown in Figure 1, the participants completed all evaluation items related to body measurements, physical indices, and QOL— including the primary outcomes— at each 4-week interval visit (Visits 0–7). Dual-energy X-ray absorptiometry (DXA) and respiratory function tests were performed at Visits 0, 4, and 7 for both groups. The primary outcomes were symptoms of fatigue (VAS), knee extension leg strength, and walking speed. The secondary outcomes were items related to body measurements and physical indices including leg circumference, femoral circumference, 6MWD, grip strength, finger pinch strength, and body mass index (BMI). The items related to QOL were symptoms of apathy (VAS), the Hospital Anxiety and Depression Scale (HADS),[21,22] the Simplified Nutritional Appetite Questionnaire (SNAQ),[23] the CAT, and the modified Medical Research Council (mMRC) Dyspnea Scale. Copyright permission was obtained for each questionnaire before its use, along with permission to reuse the questionnaire when necessary. The laboratory tests were based on DXA to determine the skeletal muscle mass index (SMI), and respiratory function tests. To avoid the influences of short acting beta 2 agonist on cardiovascular and physical muscles, respiratory function indexes including the FEV1/FVC ratio were tested under the condition of no pre-treatment with a bronchodilator. Adverse effects that occurred during or after the trial were confirmed in individual patients at each visit.

Statistical Analysis

The levels of statistical significance level were set at 5%. Inter-group comparisons of the items related to body measurements, physical indices, and pulmonary function tests for 12 weeks were analyzed as parametric data using an

unpaired *t*-test, while items related to the QOL questionnaires and SMI were analyzed as nonparametric data using the Wilcoxon rank-sum test. Within-group timecourse comparisons of the items related to body measurements, physical indices, and pulmonary function tests were analyzed as parametric data using a paired *t*-test. Within-group timecourse comparisons of the items related to the QOL questionnaires and SMI were analyzed as nonparametric data using the Wilcoxon signed-rank test. Pearson's correlation coefficient was used to analyze the correlations between items (change from week 0 to 24). Statistical analyses were performed by the statistical manager and outsourced to the Statistical Analysis Department of the IROM Group (CRO, Tokyo, Japan, https://www.iromgroup.co.jp, accessed on May 18, 2023). JMP®-Windows version 14.1.0 (SAS Institute Inc., Cary, NC, USA) was used.

Results

In total, the 58 participants provided consent among the 60 participants enrolled in the study; 53 patients completed the study (Group A, n =28; Group B, n =25) (Table 1). The reasons for the discontinuation among the five cases were as follows: three patients wished to discontinue the study for personal reasons, one patient had poor adherence, and one patient stopped attending without contacting the medical institution. There were no adverse effects leading to withdrawal from the trial. In the final statistical analysis, the SMI values obtained based on DXA were used to divide each group into two subgroups: a non-sarcopenia group with an SMI value of ≥7.0, and a sarcopenia group with an SMI value <7.0. The diagnostic criteria for sarcopenia were used for Asian subjects.[24]

Table 1 Comparisons of Patient Characteristics Between Both Group a and B

		Group A	Group B	p value
Numbers of patients	N	28	25	–
Mean Age (yrs) all male	Mean	75.4	76.3	p1=0.693
	SD	8.4	7.0	
COPD stages				
GOLD stage 2	N	17	14	p2=0.769
GOLD stage 3	N	8	8	
GOLD stage 4	N	3	3	
Body Mass Index (kg/㎡)	Mean	22.2	22.7	p1=0.546
	SD	3.5	3.5	
Knee extension leg strength Right (kgf)	Mean	32.4	31.3	p1=0.741
	SD	11.5	11.6	
Knee extension leg strength Left (kgf)	Mean	30.5	29.6	p1=0.740
	SD	10.0	10.5	
Lower leg circumference Right (cm)	Mean	32.6	32.7	p1=0.874
	SD	3.8	3.0	
Lower leg circumference Left (cm)	Mean	32.9	33.0	p1=0.870
	SD	3.7	3.3	
Femoral circumference Right (cm)	Mean	41.6	42.2	p1=0.701
	SD	5.9	4.3	

(*Continued*)

Table 1 (Continued).

		Group A	Group B	p value
Femoral circumference Left (cm)	Mean	41.6	41.9	p1=0.859
	SD	5.5	4.4	
Grip strength Right (kg)	Mean	32.1	33.4	p1=0.593
	SD	8.5	9.0	
Grip strength Left (kg)	Mean	29.4	31.7	p1=0.361
	SD	9.4	9.0	
Finger pinch force Right (kgf)	Mean	8.4	8.9	p1=0.406
	SD	2.1	2.3	
Finger pinch force Left (kgf)	Mean	7.9	7.8	p1=0.815
	SD	2.1	2.5	
Walking speed (m/s)	Mean	0.9	1.1	p1=0.151
	SD	0.3	0.3	
6MWD (m)	Mean	334.3	368.6	p1=0.288
	SD	116.2	116.8	
SMI (kg/㎡)	Mean	6.0	6.2	p1=0.510
	SD	1.1	1.1	
Lean body mass (kg/㎡)	Mean	15.3	15.7	p1=0.566
	SD	2.2	2.2	
Bone mineral density (g/c㎡)	Mean	1.05	1.06	p1=0.742
	SD	0.10	0.10	
%VC (%)	Mean	81.8	76.6	p1=0.225
	SD	17.5	12.3	
%FVC (%)	Mean	79.1	74.1	p1=0.287
	SD	17.5	16.0	
FEV1.0% (%)	Mean	57.1	56.0	p1=0.802
	SD	18.1	15.1	
%FEV1.0 (%)	Mean	56.2	53.5	p1=0.600
	SD	17.8	20.1	
CAT (point)	Mean	17.0	16.4	p3=0.810
	SD	7.9	8.8	
mMRC (point)	Mean	1.6	2.0	p3=0.305
	SD	1.1	1.0	

(*Continued*)

Table 1 (Continued).

		Group A	Group B	p value
SNAQ (point)	Mean	14.5	14.3	p3=0.841
	SD	1.7	1.5	
VAS: fatigue scale (mm)	Mean	70.5	75.4	p1=0.143
	SD	10.9	13.1	
VAS: motivation scale (mm)	Mean	65.0	69.6	p1=0.289
	SD	16.8	14.7	
HADS: anxiety scale (point)	Mean	5.4	6.4	p3=0.263
	SD	4.3	4.2	
HADS: depression scale (point)	Mean	7.7	7.0	p3=0.610
	SD	4.1	4.3	

Notes: p1: unpaired *t*-test, p2: χ^2 test, p3: Wilcoxon rank-sum test.
Abbreviations: 6MWD, 6-minute walking distance; SMI, Skeletal muscle mass index; FEV1.0, forced expiratory volume in 1second; VC, Vital Capacity; CAT, COPD Assessment Test; mMRC, Modified Medical Research Council Dyspnea Scale; SNAQ, Simplified Nutritional Appetite Questionnaire; VAS, Visual Analogue Scale; HADS, hospital anxiety and depression scale.

Medication Adherence

The mean dosing rate during the treatment period was 92.1 ± 13.3% at Visits 5–7 in Group A (n=28) and 94.0 ± 6.6% at Visits 1–7 in Group B (n=25). Medication adherence was generally good throughout the trial and did not affect any item of evaluation.

Results of Comparison Between Groups A and B for 12 Weeks

Comparisons of the magnitudes of changes in the primary endpoints are shown in Figure 2. Symptom of fatigues (as measured by the VAS scales) in Group B significantly improved after 4, 8, and 12 weeks compared to that in Group A ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively) (Figure 2A). Walking speed increased in Group B compared to that in Group A, but the increase was not statistically significant (Figure 2B). Right knee extension leg strength in Group B significantly improved after 12 weeks compared to that in Group A ($p = 0.042$) (Figure 2C). Left knee extension leg strength in Group B also significantly improved after 12 weeks compared to that in Group A ($p=0.037$) (Figure 2D).

Figure 3 shows comparisons of QOL questionnaire-related items as secondary endpoints. The CAT scores in Group B significantly improved after 12 weeks after the administration of Ninjin'yoeito compared to those in Group A ($p=0.006$) (Figure 3A). The magnitudes of these changes after 4 and 8 weeks in Group B were clinically significant according to the minimal clinically important difference (MCID) value of 2 points in the CAT.[25] The mMRC scores in Group B also significantly improved after 8 and 12 weeks compared to those in Group A ($p=0.045$ and $p = 0.001$, respectively) (Figure 3B). The magnitudes of these changes in Group B were clinically significant according to the MCID value of −0.5 to −1.0 in the mMRC.[26,27] SNAQ scores significantly improved after 8 and 12 weeks after the administration of Ninjin'yoeito in Group B compared to those in Group A ($p = 0.003$ and $p = 0.004$, respectively) (Figure 3C). HADS anxiety scale scores in Group B significantly improved after 8, and 12 weeks compared to those in Group A ($p = 0.031$ and $p < 0.001$, respectively) (Figure 3D). HADS depression scale scores also significantly improved after 4, 8, and 12 weeks compared to those in Group A ($p = 0.002$, $p = 0.034$ and $p = 0.003$, respectively) (Figure 3E). The magnitude of these changes in Group B were clinically significant according to the MCID value of 1.5 in the HADS.[28]

Comparisons in the magnitudes of changes in other secondary endpoint items are shown in Table 2. Motivation scale scores (VAS scales) in Group B significantly improved after 4, 8, and 12 weeks compared to those in Group A ($p < 0.001$,

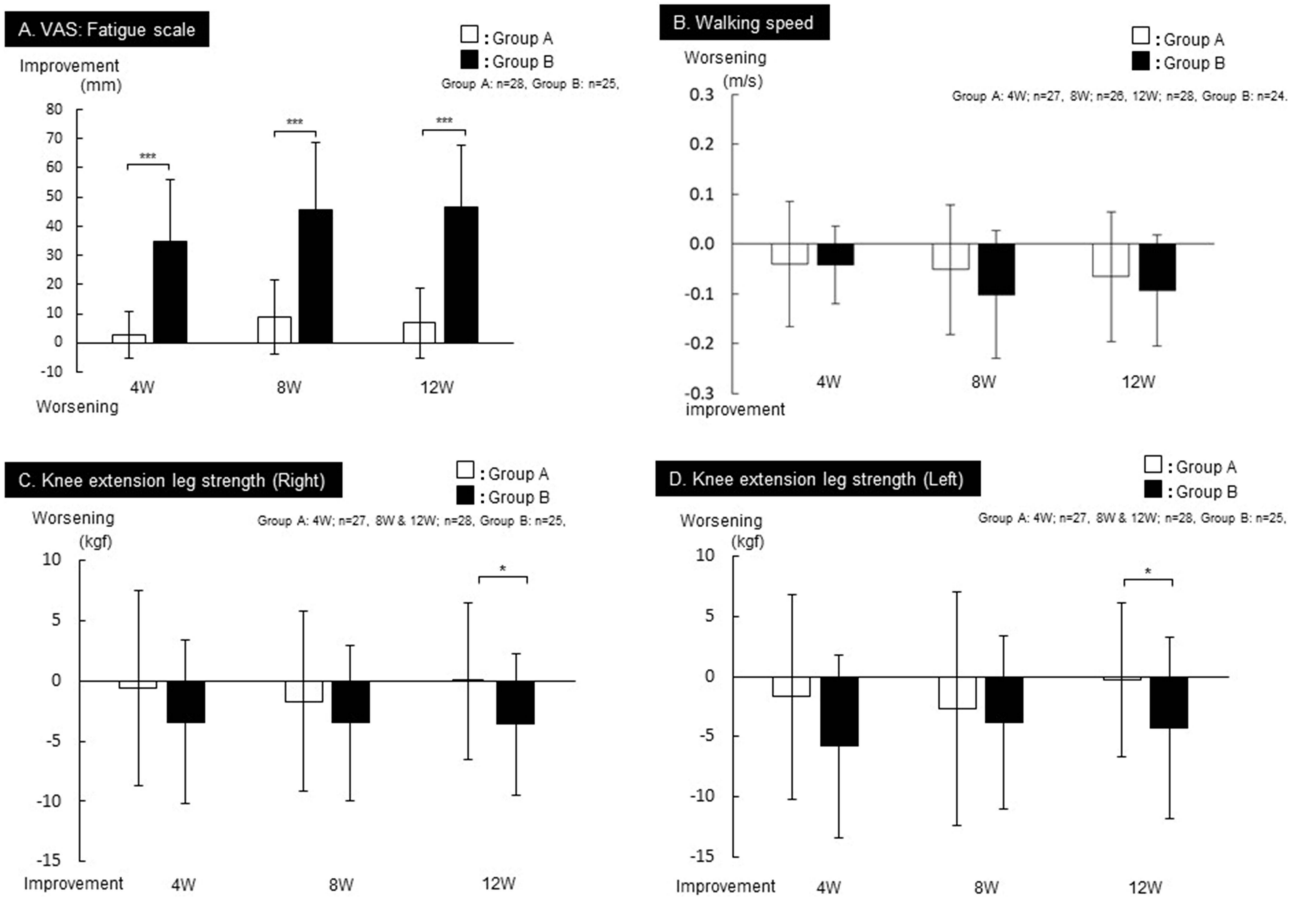

Figure 2 Group comparison of primary endpoints by changes from Visit1 in (**A**) VAS fatigue scale, (**B**) walking speed, (**C**) knee extension leg strength (Right), and (**D**) knee extension leg strength (Left) in Groups A and B. Mean ±SD, Comparison between groups: *p<0.05 and ***p<0.001, unpaired *t*-test.

p <0.001, and p <0.001, respectively). The 6MWD in Group B showed a tendancy to increase after 8 weeks compared to that in Group A (p =0.060). The pulmonary function index %FEV1.0(%) (from 0W to 12W) in Group B was significantly improved compared to that in Group A (p=0.040).

Results of Time-Course Changes for 24 Weeks in Each Groups A and B Results of Items Related to Body Measurements and Physical Indices

The results of the items related to body measurements and physical indices, including the primary outcomes — knee extension leg strength, 6MWD, and 1-s walking speed, are shown in Figure 4. The values for knee extension leg strength significantly increased 4, 8, 12, 16, 20, and 24 weeks after the administration of Ninjin'yoeito (right leg: p=0.018, p=0.013, p=0.006, p=0.006, p=0.007, and p<0.001; left leg: p<0.001, p=0.014, p=0.008, p=0.003, p=0.010, and p<0.001, respectively) in Group B, but not in Group A (Figure 4A). When evaluated within each group according to the presence or absence of sarcopenia, knee extension leg strength (left leg alone) significantly improved after 16 and 20 weeks in the absence of sarcopenia in Group A (p=0.007 and p=0.033, respectively). In Group B, significant improvements were observed in knee extension leg strength after 12, 16, 20, and 24 weeks in the right leg (p=0.046, p=0.034, p=0.036, and p=0.004, respectively) and after 4, 8, 12, 16, 20, and 24 weeks in the left leg (p=0.016, p=0.035, p=0.013, p=0.018, p=0.044, and p=0.008, respectively) in the presence of sarcopenia. In the absence of sarcopenia in Group B, significant improvements were observed in right leg strength after 24 weeks (p=0.040), and in left leg strength after 4 and 24 weeks (p=0.029 and p=0.003, respectively) (Figure 4A).

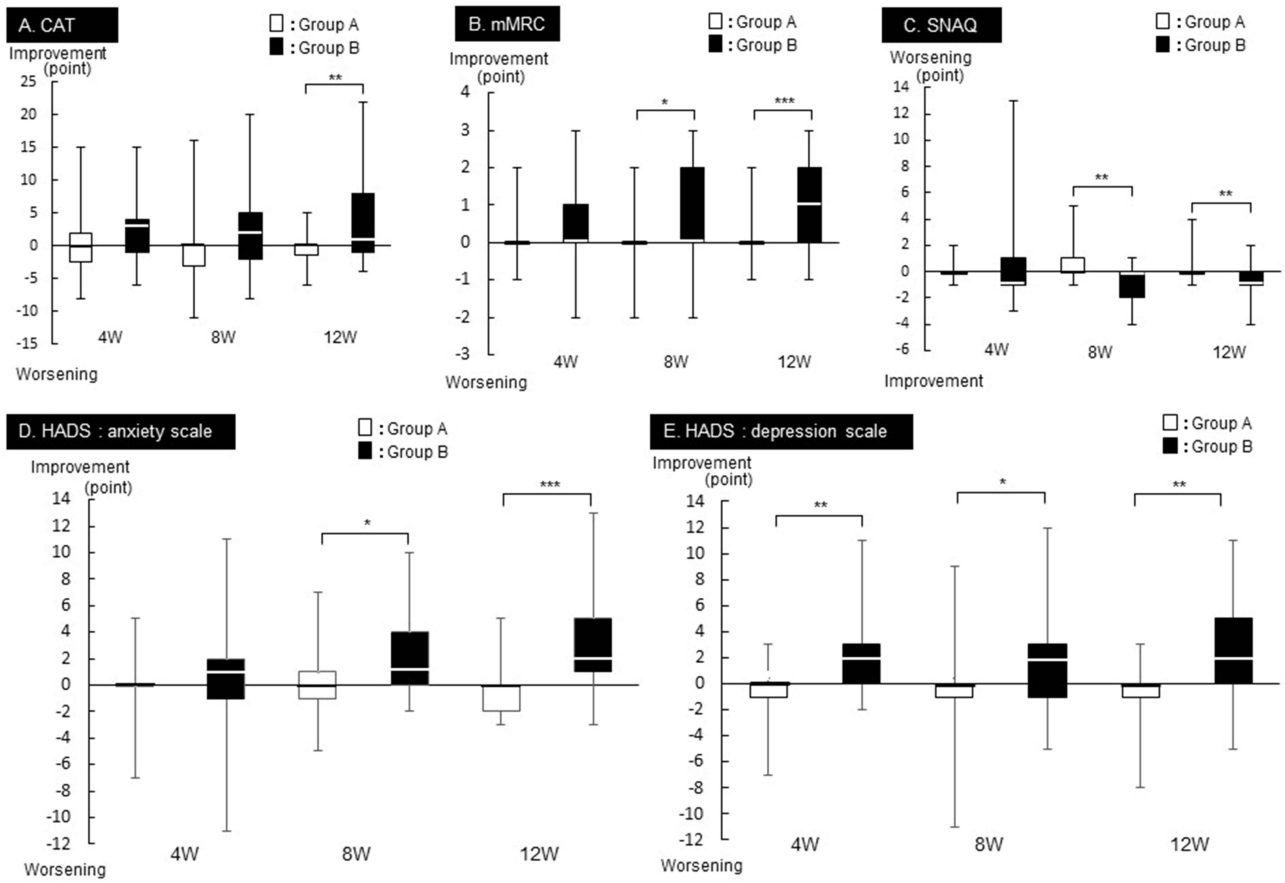

Figure 3 Group comparison by changes from Visit1 in (**A**) CAT, (**B**) mMRC, (**C**) SNAQ, (**D**) HADS anxiety scale, and (**E**) HADS depression scale. All values are expressed as the median. Comparison between groups: *p<0.05, **p<0.01, and ***p<0.001, Wilcoxon signed-rank tests. The numbers of participants who underwent the CAT, mMRC, SNAQ and HADS (anxiety, depression) are all 28 in Group A and 25 in Group B.

The 6MWD values significantly increased 4, 8, 12, 16, 20, and 24 weeks after the administration of Ninjin'yoeito in Group B (p=0.007, p<0.001, p<0.001, p<0.001, p<0.001, and p<0.001, respectively), and 16, 20, and 24 weeks after initiating the study (also after 4, 8, and 12 weeks of Ninjin'yoeito administration) in Group A (p=0.023, p<0.001, and

Table 2 Comparisons of Change in the Other Secondary Endpoints for 12 Weeks Between Group a and B

Secondary Endpoints		Group A			Group B			p-value
		n	Mean	SD	n	Mean	SD	
Body Mass Index (kg/m^2)	4w	26	0.1	0.3	25	0.1	0.3	p=0.732
	8w	28	0.2	0.5	25	0.4	0.4	p=0.225
	12w	28	0.4	0.8	25	0.5	0.6	p=0.835
Lower leg circumference Right (cm)	4w	27	−0.3	1.0	25	0.1	0.9	p=0.244
	8w	28	−0.2	1.3	25	−0.1	0.7	p=0.672
	12w	28	−0.1	1.3	25	−0.2	0.9	p=0.762
Lower leg circumference Left (cm)	4w	27	0.0	0.9	25	0.1	0.7	p=0.669
	8w	28	0.1	0.9	25	0.0	0.5	p=0.493
	12w	28	0.2	1.0	25	0.1	1.0	p=0.888

(*Continued*)

Table 2 (Continued).

Secondary Endpoints		Group A			Group B			p-value
		n	Mean	SD	n	Mean	SD	
Femoral circumference Right (cm)	4w	27	0.0	1.2	25	0.1	1.4	p=0.716
	8w	28	−0.1	1.1	25	0.0	1.0	p=0.669
	12w	28	0.1	1.3	25	−0.2	1.7	p=0.505
Femoral circumference Left (cm)	4w	27	−0.2	1.2	25	−0.1	1.4	p=0.758
	8w	28	0.1	1.0	25	−0.2	1.0	p=0.377
	12w	28	0.0	1.0	25	−0.6	1.4	p=0.081
Grip strength Right (kg)	4w	27	0.1	3.9	25	−1.4	3.7	p=0.165
	8w	28	−0.1	3.5	25	−1.3	4.0	p=0.244
	12w	28	0.0	4.1	25	−0.8	4.2	p=0.505
Grip strength Left (kg)	4w	27	0.9	3.7	25	−0.1	2.9	p=0.325
	8w	28	1.0	3.4	25	−0.7	3.1	p=0.065
	12w	28	1.1	3.5	25	−0.6	3.4	p=0.092
Finger pinch force Right (kgf)	4w	27	−0.1	1.4	25	−0.4	1.4	p=0.427
	8w	28	−0.2	1.4	25	−0.6	1.8	p=0.384
	12w	28	−0.5	2.0	25	−0.7	2.0	p=0.775
Finger pinch force Left (kgf)	4w	27	0.1	1.4	25	−0.4	1.4	p=0.233
	8w	28	−0.5	1.3	25	−1.0	2.0	p=0.313
	12w	28	−0.1	1.9	25	−1.2	1.9	p=0.055
6MWD (m)	4w	27	−11.1	44.5	25	−16.6	27.8	p=0.600
	8w	26	−15.0	46.4	25	−39.5	44.4	p=0.060
	12w	28	−17.0	48.6	25	−38.8	39.1	p=0.080
Lean body mass (kg/m^2)	12w	28	0.4	0.5	25	0.4	0.4	p=0.978
Bone mineral density (g/cm^2)	12w	28	0.0	0.0	25	0.0	0.0	p=0.010
%VC (%)	12w	28	−3.4	11.6	25	−6.7	8.9	p=0.259
%FVC (%)	12w	28	−1.7	5.8	25	−5.2	9.0	p=0.095
FEV1.0% (%)	12w	28	0.8	3.9	25	0.1	3.6	p=0.535
%FEV1.0 (%)	12w	28	0.2	4.2	25	−3.3	7.6	p=0.040
VAS: motivation scale (mm)	4w	28	3.4	9.6	25	30.5	21.0	p<0.001
	8w	28	4.5	19.4	25	41.2	20.3	p<0.001
	12w	28	7.3	13.4	25	37.3	24.0	p<0.001

Note: p: unpaired *t*-test.

Abbreviations: 6MWD, 6 minutes walk distance; SMI, Skeletal muscle mass index; FEV1.0, forced expiratory volume in 1second; VC, Vital Capacity; VAS, Visual Analogue Scale.

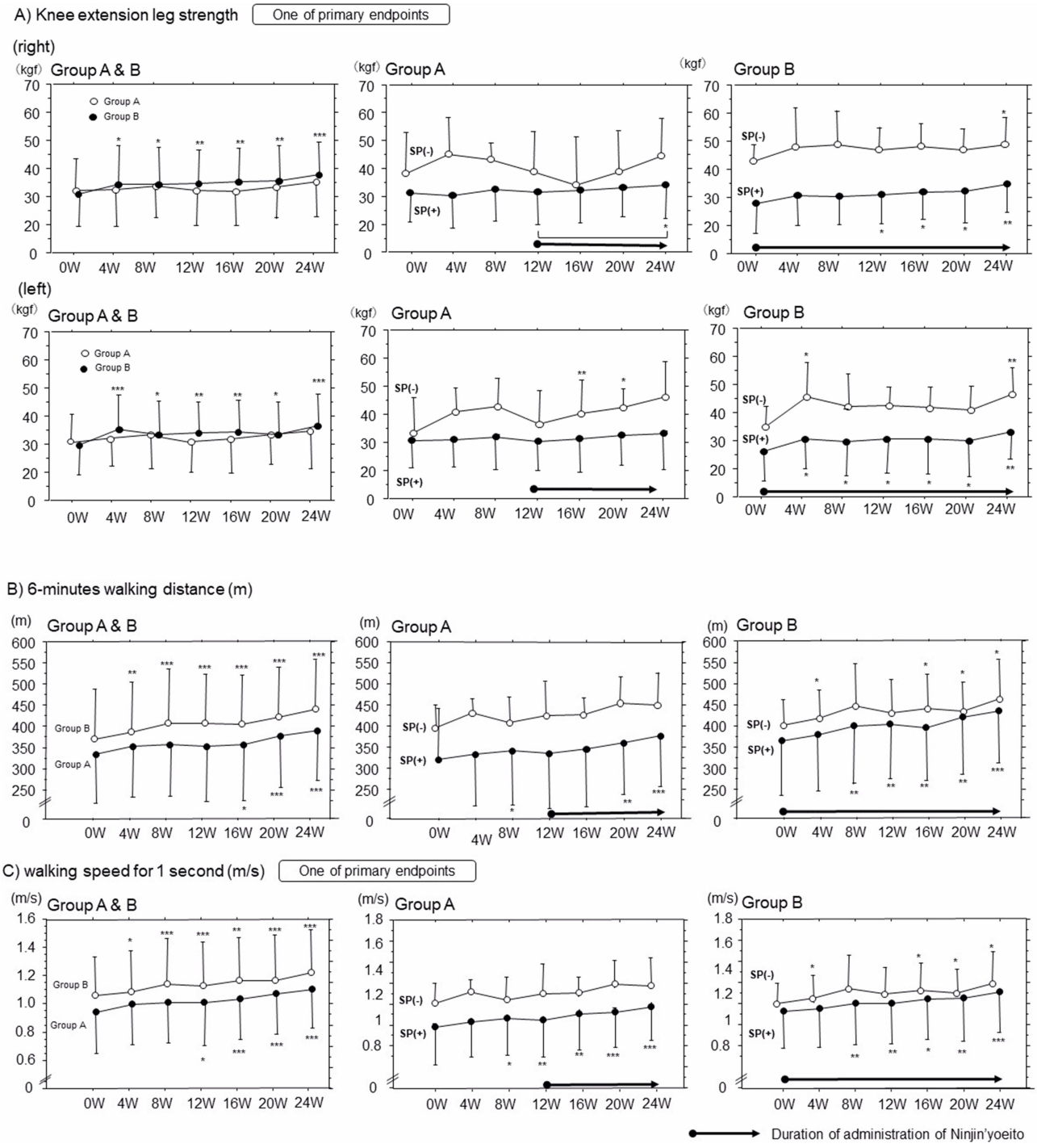

Figure 4 Time-course changes in (**A**) knee extension leg strength (kgf), (**B**) 6-minute walking distance (m) and (**C**) Gait speed for 1 second (m/s) in Groups A and B with or without sarcopenia (SP). Comparison with the values at 0W in each group. * p<0.05, **p<0.01 and ***p<0.001, paired Student's *t*-test.

$p<0.001$, respectively; Figure 4B. In Group A, significant improvements were observed in the sarcopenia group 20 and 24 weeks after initiating the study (8 and 12 weeks after Ninjin'yoeito administration; $p<0.001$ and $p<0.001$, respectively). In Group B, significant improvements were observed after 4, 16, 20, and 24 weeks in patients without sarcopenia ($p=0.033$, $p=0.028$, $p=0.025$, and $p=0.013$, respectively), and after 8, 12, 16, 20, and 24 weeks in the sarcopenia group ($p=0.002$, $p=0.001$, $p=0.001$, $p=0.001$, and $p<0.001$, respectively).

The 1-s walking speed also significantly increased 4 weeks after Ninjin'yoeito administration in Group B (p=0.016, p<0.001, p<0.001, p=0.004, p<0.001 and p<0.001 after 4, 8, 12, 16, 20, and 24 weeks, respectively), but not Group A (p=0.013 after 12 week alone) (Figure 4C). In Group B, significant improvements were observed after 4, 16, 20, and 24 weeks in the absence of sarcopenia (p=0.033, p=0.027, p=0.025, and p=0.011, respectively) and after 8, 12, 16, 20 and 24 weeks in the sarcopenia group (p=0.007, p=0.003, p=0.019, p=0.002, and p<0.001, respectively). Other items related to body measurements and physical indices—such as BMI, body weight, lower leg circumference, femoral circumference, grip strength, and finger pinch strength—are shown in Supplement Table 1. Although BMI was significantly reduced during the study periods in both groups, the magnitudes of reduction in its absolute value were very small. There were no statistically significant changes in the right and left lower leg or femoral circumferences, over time in either group. During the study period, there were also almost no significant changes in right and left grip strengths in either groups, with or without sarcopenia. By contrast, significant increases were observed in the right and left finger pinch strengths, especially during the periods of treatment with Ninjin'yoeito in both groups.

Results of Items Related to QOL Questionnaires

The results of the items related to the QOL questionnaires, including the primary outcomes and symptoms of fatigue (VAS), are shown in Supplement Figure 1A. The fatigue scale scores significantly improved from week 8 in Group A and from week 4 in Group B. In particular, fatigue scale scores in the sarcopenia group significantly and remarkably improved four weeks after the administration of Ninjin'yoeito in both Groups A (p<0.001 at week 16) and B (p<0.001 at week 4). Motivation scale scores significantly improved from week 12 after the entry of the study in Group A, and week 4 in Group B. In particular, the motivation scale scores in the sarcopenia group significantly improved four weeks after the administration of Ninjin'yoeito in both Groups A (p=0.002 at week 16) and B (p<0.001 at week 4). In Group A, the HADS anxiety scale scores did not significantly change throughout the treatment period, while depression scale scores significantly improved four weeks after treatment with Ninjin'yoeito (p=0.032 at week 16; Supplement Figure 1B); particularly, HADS depression scale scores significantly improved 4, 8, and 12 weeks after the administration of Ninjin'yoeito in the sarcopenia group (p=0.026, p=0.028, and p=0.042 at weeks 16, 20, and 24, respectively).

By contrast, the HADS anxiety scale scores in Group B significantly changed 8 weeks after the administration of Ninjin'yoeito; this significant improvement continued throughout the treatment period. The HADS depression scale scores in Group B also significantly improved 4 weeks after the administration of Ninjin'yoeito, and continued to significantly improve during treatment. A significant improvement was also observed in the sarcopenia group. SNAQ scores significantly improved 8 weeks after the administration of Ninjin'yoeito in Group A (the sarcopenia group alone) (p=0.013 and p=0.010 at weeks 20 and 24, respectively, compared with the start of the study at week 16), and 8 weeks after the administration in whole Group B (p=0.006, p=0.007, p=0.005, p=0.019, and p=0.016 at weeks 8, 12, 16, 20, and 24, respectively); this significant improvement was also observed in Group B with sarcopenia (Supplement Figure 1C). In Group A, the CAT scores did not significantly change throughout the treatment period, while in Group B, the CAT scores significantly improved 4, 12, and 20 weeks after the administration of Ninjin'yoeito (p=0.015, p=0.012, and p=0.040, respectively, compared with the start of the study at week 0); this significant improvement was also observed in the sarcopenia group in Group B (Supplement Figure 1D).

The mMRC scores did not significantly change throughout the treatment period in Group A.; in Group B, the scores significantly improved at 8, 12, 16, 20, and 24 weeks after the administration of Ninjin'yoeito (p=0.016, p<0.001, p=0.002, p=0.007, and p=0.004, respectively, compared with the start of the study at week 0); a significant improvement was also observed in the sarcopenia group in Group B (Supplement Figure 1E).

DXA Results

Group comparison of the SMI due to changes from Visit1 between Group A and B were shown to be not statistically significant for 12 and 24 weeks (p =0.830 and p= 0.253 respectively, Wilcoxon rank-sum test). The timecourse changes in the SMI in Groups A and B, both with and without sarcopenia, are shown in Supplement Figure 1F. In Group A, no significant change in SMI was observed during the study period in the group without sarcopenia; in the sarcopenia group,

a significant decrease in the SMI was observed in the first half of the study period without Ninjin'yoeito treatment (p=0.044, Wilcoxon signed-rank test), while a significant increase in the SMI was observed in the second half of the study period with the use of Ninjin'yoeito (p=0.012, Wilcoxon signed-rank test). By contrast, both patients with and without sarcopenia in Group B exhibited a significant increase in the SMI during the first half of the study period, when Ninjin'yoeito was administered (p =0.028 and p= 0.025, respectively, Wilcoxon signed-rank test).

Pulmonary Function Test Results

The timecourse changes in the indices of the pulmonary function tests in Groups A and B, both with or without sarcopenia, are shown in Supplement Figure 1G. The mean value of %FEV1.0 significantly increased from 53.5±20.1% on entry to 56.8±19.5% (p =0.039) at week 12 and 57.9±19.6% (p =0.036) at week 24 in Group B. The mean value of %VC also significantly increased from 76.6±12.3% on entry to 83.3±12.5% (p =0.001, paired student t test) in week 12 and 84.0±13.6% (p =0.001) in Group B. The mean value of %FVC also significantly increased from 74.1±16.0% on entry to 79.3±13.7% (p=0.008) in week 12 and 79.9±16.1% (p =0.019). In particular, when group B was examined in groups with and without sarcopenia, the mean value of %VC significantly increased from 73.6±12.6% on entry to 82.0±13.5% (p =0.004, paired student t test) in week 12 and 82.7±14.5% (p =0.005) in week 24 among patients with sarcopenia in Group B. The mean value of %VC significantly increased from 83.5±7.5% on entry to 87.5±7.6% (p =0.006) in week 12 and 87.7±10.4% (p =0.032) in week 24 among patients without sarcopenia in Group B. The mean value of %FVC also significantly increased from 71.8±16.8% on entry to 78.7±14.8% (p=0.004) in week 12 and 79.0±17.5% (p =0.021) in week 24 among patients with sarcopenia in Group B.

Examination of Correlations Between Items

The results of the examination of correlations between the items are shown in Supplement Table 2. The changes in FEV1.0 and %FEV1.0 value were significantly but weakly correlated with the lower leg circumference (left) values in Group B (Pearson's correlation coefficient: r =0.502, p =0.011 and r =0.427, p =0.033, respectively).

Discussion

This study showed that Ninjin'yoeito significantly improved fatigue, decreased appetite, depression, QOL, physical activity, skeletal muscle dysfunction, and possibly lung function, suggesting that Ninjin'yoeito may play a role as a complementary medicine in patients with COPD and comorbid frailty, and sarcopenia.

When frailty or sarcopenia is comorbid in patients with COPD, the prognosis is generally poor.[2] Physical activity and exercise tolerance are important factors that predict the prognosis of patients with COPD; thus, the importance of physical activity and exercise tolerance have attracted increasing attention.[29] Exercise tolerance is an assessment of how much a patient can move at their best; it can be evaluated using tests such as the 6MWD in clinical practice and is an indicator separate from the activity state of daily life. Although rehabilitation is performed to improve exercise tolerance, it is often difficult to continue rehabilitation in daily clinical settings. However, in patients with COPD, frailty, and sarcopenia, it is more important to determine the amount of movement in patients' daily lives, rather than the maximum amount of exercise possible. Patients with COPD who have a long sedentary time during daily activities have a poor life prognosis.[30] Decreased physical activity occurs earlier than a decline in respiratory function, preceding the onset of breathlessness.[31] Therefore, it is important to prevent and improve the decline in physical activity during COPD treatment.

Various questionnaires were used to evaluate physical activity. In our examination of Ninjin'yoeito, as shown in Supplement Figure 1A–E, a significant improvement was observed in questionnaire scores related to physical activity during the administration period, indicating that Ninjin'yoeito significantly improved physical activity. This result agrees with the report by Hirai et al.[32] Hochuekkito, another Japanese traditional herbal medicine, is also often used to treat chronic diseases in elderly patients complaining of general fatigue and appetite loss. A previous study showed that Hochuekkito improved systemic inflammation and nutritional status and reduced the number of acute exacerbations in elderly patients with COPD[33] Hamada et al showed that mMRC score, VAS scores for dyspnea and fatigue, and CAT scores in patients with COPD significantly improved after 12 weeks of treatment with Hochuekkito, however, the

treatment did not improve the 6MWD and peripheral muscle strength.[34] In contrast, as shown in Figure 4, the administration of Ninjin'yoeito resulted in a significant improvement in the left and right knee extension leg strength, 6MWD, and walking speed for 1 s in both Groups A and B, especially among patients with sarcopenia. Along with the improvement in body measurements and physical indices, which indicate physical performance, the results suggest that exercise tolerance may be improved by the administration of Ninjin'yoeito alone, without additional rehabilitation intervention. Lower limb muscle strength, including knee extension leg strength, is an important indicator and is a prognostic factor for COPD.[35] As mentioned in the introduction, Ninjin'yoeito increases muscle strength by restoring mitochondrial function and avoids a shift in the distribution of muscle fiber types from type I to type II by upregulating PGC-1α expression,[17] thereby improving secondary sarcopenia in patients with COPD. Physical activity and exercise tolerance are closely associated with muscle mass volume. As shown in Supplement Figure 1F, both groups demonstrated a significant increase in the SMI 12 weeks after the administration of Ninjin'yoeito. Nevertheless, as shown in Supplement Table 1, the BMI significantly decreased during the periods of Ninjin'yoeito administration in both groups. This may be due to the effects of weight loss (shown in Supplement Table 1). The reasons for body weight loss, accompanied by increased appetite and physical exertion, are unclear. However, this result also suggested that the administration of Ninjin'yoeito alone may improve sarcopenia without the need for additional therapeutic interventions. Although we found no significant correlation between the SMI and other items (Supplement Table 2), improvements in the patients' mental health and appetite may have contributed to the improvement in the SMI. Additionally, as shown in Supplement Figure 1G, some respiratory functions significantly improved, however, it is not clear why respiratory functions improved. As respiratory muscles are independent of the skeletal muscles, including the lower limbs, patients' mental health and appetite may have contributed to a significant improvement in respiratory functions.

A limitation of this study is that the sample size was small; thus, the significant correlation data could not demonstrate a clear causal relationship. The small sample size may also have affected the result, for example, VAS fatigue improved significantly in Group A after 8 weeks, which is the time when Ninjin'yoeito was not administered (Supplement Figure 1A). In order to assess appetite, it is necessary to assess swallowing and digestive functions. Unfortunately, however, this study was conducted in a clinical setting in primary care, making it difficult to proceed with such investigations.

Additionally, the results were not obtained from a comparative study using placebo.

Conclusion

There are various comorbidities in COPD, among which frailty and sarcopenia are the most important as they seriously affect QOL and increase the risks and frequency of exacerbations, hospitalization, and mortality. Still, few effective supplementary treatments are available for pulmonary rehabilitation and nutrition. Ninjin'yoeito may thus serve as a complementary drug for the treatment of COPD in patients with comorbid frailty and sarcopenia.

Institutional Review Board Statement

This study was conducted in accordance with the ethical principles detailed in the Declaration of Helsinki (revised in 2013) and the "Ethical Guidelines for Human Life Science and Medical Research Guidance (established on 16 April 2021)". This study was approved by the Ethical Review Committee (Review Board of Human Rights and Ethics for Clinical Studies (HURECS, full accreditation from AAHRPP, CRB3200001) and Tokyo Medical and Dental University Certified Clinical Research Review Board (CRB3180020), approval number and date: jRCTs031210583, 11 January 2022). The registration data were managed using a subject identification code in accordance with the Personal Information Protection Law.

Data Sharing Statement

We have provided details in the paper regarding where the data supporting the reported results can be found.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. The participants were fully debriefed on the content of the research trial and a written consent was obtained out of their own free will. Written informed consent was also obtained from the participants to publish this paper.

Acknowledgments

This research was funded by Kracie Pharmaceutical Ltd. (Tokyo, Japan). There are no other matters to be reported regarding the implementation of this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Conceptualization, H.O.; methodology, H.O.; software, H.O. and S.K.; validation, K.O. and A.Y.; formal analysis, H.O. and S.K.; investigation, O.F. and M.A.; resources, S.K., O.F., and M.A.; data curation, K.O., A.Y., and M.A.; writing—original draft preparation, H.O.; writing—review and editing, S.K. and M.A.; visualization, H.O. and S.K.; supervision, O.F. and M.A.; project administration, K.O. and A.Y.; funding acquisition, H.O. and S.K. All authors have read and agreed to the published version of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Smith MC, Wrobel JP. Epidemiology and clinical impact of major comorbidities in patients with COPD. *Int J Chronic Obstr Pulmon Dis*. 2014;9:871–888. doi:10.2147/COPD.S49621
2. Marengoni A, Vetrano DL, Manes-Gravina E, Bernabei R, Onder G, Palmer K; The Relationship Between COPD and frailty. A systematic review and meta-analysis of observational studies. *Chest*. 2018;154(1):21–40. doi:10.1016/j.chest.2018.02.014
3. Benz E, Trajanoska K, Lahousse L, et al. Sarcopenia in COPD: a systematic review and meta-analysis. *Eur Respir Rev*. 2019;28(154):190049. doi:10.1183/16000617.0049-2019
4. Bone AE, Hepgul N, Kon S, Maddocks M. Sarcopenia and frailty in chronic respiratory disease. *Chronic Respir Dis*. 2017;14(1):85–99. doi:10.1177/1479972316679664
5. Seymour JM, Spruit MA, Hopkinson NS, et al. The prevalence of quadriceps weakness in COPD and the relationship with disease severity. *Eur Respir J*. 2010;36(1):81–88. doi:10.1183/09031936.00104909
6. Natanek SA, Gosker HR, Slot IG, et al. Heterogeneity of quadriceps muscle phenotype in chronic obstructive pulmonary disease (COPD); implications for stratified medicine? *Muscle Nerve*. 2013;48(4):488–497. doi:10.1002/mus.23784
7. Swallow EB, Reyes D, Hopkinson NS, et al. Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax*. 2007;62(2):115–120. doi:10.1136/thx.2006.062026
8. Beckwée D, Delaere A, Aelbrecht S, et al. Exercise interventions for the prevention and treatment of sarcopenia. A systematic umbrella review. *J Nutr Health Aging*. 2019;23(6):494–502. doi:10.1007/s12603-019-1196-8
9. Jones SE, Maddocks M, Kon SSC. Sarcopenia in COPD: prevalence, clinical correlates and response to pulmonary rehabilitation. *Thorax*. 2015;70 (3):213–218. doi:10.1136/thoraxjnl-2014-206440
10. Finamore P, Scarlata S, Delussu AS, Traballesi M, Incalzi RA, Laudisio A. Frailty Impact during and after Pulmonary Rehabilitation. *COPD*. 2021;18(5):518–524. doi:10.1080/15412555.2021.1967915
11. Ferreira IM, Brooks D, White J, Goldstein R. Nutritional supplementation for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2012;12:CD000998. doi:10.1002/14651858.CD000998.pub3
12. Ali S, Garcia JM. Sarcopenia, cachexia and aging: diagnosis, mechanisms and therapeutic options - A mini-review. *Gerontology*. 2014;60 (4):294–305. doi:10.1159/000356760
13. Sato S. Apathy and fatigue in autistic spectrum disorder improved by Japanese herbal medicine: TSUMURA Ninjin'yoeito extract. *Psychiatry Clin Neurosci*. 2018;72(7):540. doi:10.1111/pcn.12667
14. Xu Y, Chen Y, Li P, Wang XS. Ren Shen Yangrong Tang for Fatigue in cancer survivors: a Phase I/II Open-Label Study. *J Altern Complement Med*. 2015;21(5):281–287. doi:10.1089/acm.2014.0211
15. Ishiura Y, Shiba Y, Terasaki Y, et al. 非小細胞肺癌外来化学療法患者のQOL に対する人参養栄湯の効果 [Effect of Japanese Traditional Medicine, Ninjin-Youei-To (TJ-108), on the Quality of Life of Patients with Non-Small Cell Lung Cancer Receiving Outpatient Chemotherapy]. *Gan to Kagaku Ryoho*. 2018;45:1071–1074. Japanese.
16. Goswami C, Dezaki K, Wang L, Inui A, Seino Y, Yada T. Ninjin-yoeito activates ghrelin-responsive and unresponsive NPY neurons in the arcuate nucleus and counteracts cisplatin-induced anorexia. *Neuropeptides*. 2019;75:58–64. doi:10.1016/j.npep.2019.03.001

17. Miyamoto A, Asai K, Kadotani H, et al. Ninjin'yoeito ameliorates skeletal muscle complications in COPD model mice by upregulating peroxisome proliferator-activated receptor γ Coactivator-1α expression. *Int J Chronic Obstr Pulm Dis*. 2020;15:3063–3077. doi:10.2147/COPD.S280401
18. Puente-Maestu L, Pérez-Parra J, Godoy R, et al. Abnormal mitochondrial function in locomotor and respiratory muscles of COPD patients. *Eur Respir J*. 2009;33(5):1045–1052. doi:10.1183/09031936.00112408
19. Jobin J, Maltais F, Doyon JF, et al. Chronic obstructive pulmonary disease: capillarity and fiber-type characteristics of skeletal muscle. *J Cardiopulm Rehabil*. 1998;18(6):432–437. doi:10.1097/00008483-199811000-00005
20. Koves TR, Li P, An J, et al. Peroxisome proliferator-activated receptor-gamma co-activator 1alpha-mediated metabolic remodeling of skeletal myocytes mimics exercise training and reverses lipid-induced mitochondrial inefficiency. *J Biol Chem*. 2005;280(39):33588–33598. doi:10.1074/jbc.M507621200
21. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*. 1983;67(6):361–370. doi:10.1111/j.1600-0447.1983.tb09716.x
22. Kitamura T. Hospital Anxiety and Depression Scale (Hads). *Arch Psychiatr Diagn Clin Eval*. 1993;4:371–372. Japanese.
23. Wilson MM, Thomas DR, Rubenstein LZ, et al. Appetite assessment: simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents. *Am J Clin Nutr*. 2005;82(5):1074–1081. doi:10.1093/ajcn/82.5.1074
24. Chen LK, Liu LK, Woo J, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc*. 2014;15(2):95–101. doi:10.1016/j.jamda.2013.11.025
25. Kon SS, Canavan JL, Jones SE, et al. Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. *Lancet Respir Med*. 2014;2(3):195–203. doi:10.1016/S2213-2600(14)70001-3
26. Araújo Oliveira AL, Andrade L, Marques A. Minimal clinically important difference and predictive validity of the mMRC and mBorg in acute exacerbations of COPD. *Eur Respir J*. 2017;50(Suppl 61):PA4705.
27. Cazzola M, Hanania NA, MacNee W, Rüdell K, Hackford C, Tamimi N. A review of the most common patient-reported outcomes in COPD--revisiting current knowledge and estimating future challenges. *Int J Chronic Obstr Pulm Dis*. 2015;10:725–738. doi:10.2147/COPD.S77368
28. Puhan MA, Frey M, Büchi S, Schünemann HJ. The minimal important difference of the Hospital Anxiety and Depression Scale in patients with chronic obstructive pulmonary disease. *Health Qual Life Outcomes*. 2008;6:46. doi:10.1186/1477-7525-6-46
29. Waschki B, Kirsten A, Holz O, et al. Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. *Chest*. 2011;140(2):331–342. doi:10.1378/chest.10-2521
30. Furlanetto KC, Donária L, Schneider LP, et al. Sedentary behavior is an independent predictor of mortality in subjects with COPD. *Respir Care*. 2017;62(5):579–587. doi:10.4187/respcare.05306
31. Gouzi F, Préfaut C, Abdellaoui A, et al. Evidence of an early physical activity reduction in chronic obstructive pulmonary disease patients. *Arch Phys Med Rehabil*. 2011;92(10):1611–1617. e2. doi:10.1016/j.apmr.2011.05.012
32. Hirai K, Homma T, Matsunaga T, et al. Usefulness of Ninjin'yoeito for chronic obstructive pulmonary disease patients with frailty. *J Altern Complement Med*. 2020;26(8):750–757. doi:10.1089/acm.2020.0083
33. Tatsumi K, Shinozuka N, Nakayama K, Sekiya N, Kuriyama T, Fukuchi Y. Hochuekkito improves systemic inflammation and nutritional status in elderly patients with chronic obstructive pulmonary disease. *J Am Geriatr Soc*. 2009;57(1):169–170. doi:10.1111/j.1532-5415.2009.02034.x
34. Hamada H, Sekikawa K, Murakami I, et al. Effects of Hochuekkito combined with pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. *Exp Ther Med*. 2018;16(6):5236–5242. doi:10.3892/etm.2018.6837
35. Swallow EB, Barreiro E, Gosker H, et al.; ENIGMA in COPD project. Quadriceps muscle strength in scoliosis. *Eur Respir J*. 2009;34(6):1429–1435. doi:10.1183/09031936.00074008