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The combined effect of leucine-enriched essential amino acid supplements and locomotion training on physical functions and quality of life in hemodialysis patients

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Abstract

Background Locomotive syndrome (LS) is a condition of reduced mobility (locomotive organ impairment) that is associated with reduced quality of life (QOL) in patients undergoing hemodialysis (HD), and effective interventions for patients with LS undergoing HD are unclear. We conducted a clinical trial to assess the effects of exercise and oral nutritional supplementation (ONS) on QOL in this cohort.

Methods This study was an open-label, randomized controlled trial. The participants were patients with LS undergoing HD. The intervention period was 3 months. The primary outcome was a change in the physical component summary (PCS) of QOL, and the secondary outcomes were changes in other QOL scores, physical function, body composition, and nutritional status assessed by using the geriatric nutritional risk index. Participants were divided into the locomotion training (LT) and LT + ONS groups. Both groups were instructed on LT that comprised one-leg standing and squats to be carried out four or more times per week. The ONS consisted of 3 g leucin-rich essential amino acids and 800 IU vitamin D per pack, and the participants in the LT + ONS group received one pack of the supplement per day.

Results In total, 40 individuals undergoing HD were included in the study; 3 patients in the LT + ONS group were excluded from the analysis because of hospitalization and incomplete assessment. The median age was 73 years (interquartile range: 62–80 years), 23 participants were men (62%), and the duration of dialysis treatment was 6 years (interquartile range: 3–16 years). The change in PCS of the LT + ONS group did not differ from that in the LT group [LT + ONS: −1.6 (−5.3, 6.8) versus LT: −0.1 (−5.3, 6.2), $p = 0.94$]. In contrast, the LT + ONS group showed maintenance in mental health (MH) and improvement of the two-step value.

Conclusions The LT + ONS group did not show an effect on PCS in QOL compared with only LT in patients with LS undergoing HD. However, maintenance of MH and improvement of two-step value were confirmed in the LT + ONS group. Future research is need to confirm whether leucine-rich essential amino acids and vitamin D help mental health and physical function in patients with LS undergoing HD with larger sample sizes and long-term interventions.

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Keywords Locomotive syndrome, Locomotion training, Oral nutritional supplementation, Hemodialysis, Quality of life, Intervention

Background

Quality of life (QOL) is impaired with the progression of chronic kidney disease (CKD) and is associated with increased mortality [1–3]. In patients undergoing hemodialysis (HD), impaired physical function is a major factor that adversely affects QOL [4, 5]. Exercise is an effective intervention for improving QOL [6, 7]; however, patients undergoing HD face numerous barriers to engaging in exercise, such as fatigue, comorbid health conditions, frequent HD treatments, fear of falling, pain, and other obstacles [8, 9]. Nutritional management is critical to achieve better clinical outcomes for patients undergoing HD. Several reports have suggested that oral nutritional supplementation (ONS) effectively improves QOL [10, 11]. Therefore, physicians should consider exercise programs and nutritional management to enhance the QOL of patients on HD with physical dysfunction.

The Japanese Orthopedic Association (JOA) proposed the concept of locomotive syndrome (LS), a condition of reduced mobility owing to the impairment of locomotive organs, including muscles, nerves, bones, and joints [12, 13]. Severe LS is a sensitive indicator of future disability, fragility fractures, the need for long-term care, anemia, poor sleep quality, social frailty, and mortality [14–20]. Kidney disease is a well-known risk factor for LS [21]. Previously, we reported a high prevalence of LS among patients on HD, and its severity was associated with poor QOL [22].

The JOA recommends two locomotion training (LT) exercises for patients with LS: squatting and one-leg standing [13]. LT improves muscle mass, physical function, and QOL in older adults with LS [23–25]. Oral leucine and vitamin D intake were shown to improve muscle strength and physical function in non-dialysis patients [26]. In addition, intake of low-dose leucine-rich essential amino acids stimulates muscle anabolism equivalently to bolus whey protein in old women [27]. However, there are no existing reports on the efficacy of a combination of LT and ONS, including vitamin D and leucine-rich essential amino acids, for patients with LS undergoing HD.

In this open-label, randomized controlled trial, we aimed to assess the effect of LT and ONS on QOL compared with LT alone in patients with LS undergoing HD.

Methods

Study design and participants

This study was an open-label, randomized controlled trial. The participants were randomly divided into two groups: the LT and LT + ONS groups who were instructed to engage in LT, while ONS was administered to the LT + ONS group only. The intervention period was 3 months. The primary outcome was a change in the physical component summary (PCS) of QOL assessed at baseline and 3 months later. Changes in other QOL scores, physical function, body composition, and nutritional status were considered secondary outcomes. The study protocol was in accordance with the Helsinki Declaration of 1975, as revised in 2013. The study protocol was approved by the Shinkohkai Murakamikinen Hospital Ethics Committee (ethics approval number: 1701; 2 August 2017) and registered at the University Hospital Medical Information Network Center (UMIN 000032457). The criteria for enrollment in this study were as follows: outpatients of two HD centers, dialysis vintage > 1 year, and having LS [LS was defined as any one of the following conditions: inability to stand up with one leg from a 40 cm high seat, length of two steps (cm)/height (cm) was < 1.3, a Geriatric Locomotive Function Scale-25 (GLFS-25) score of ≥ 7] [28]. All participants provided written informed consent before enrollment in the study.

Locomotion training (LT)

Members of each group were instructed to perform one-leg standing and squats four times or more per week (K.K.). One-leg standing was conducted, alternating between each leg, for 1 min three times a day. If the participants experienced instability while performing one-leg standing, they were permitted to use a chair, table, or wall for support to prevent falls. The participants completed five sets of squats three times daily. If the squats were challenging for some participants, they were given the option of standing up from a chair. We instructed the participants to practice LT according to their variation of lifestyle. The participants recorded their practice on a log sheet and one of the authors verified their performance.

Oral nutritional supplementation (ONS)

We selected Amino-yell® Jelly type (Ajinomoto CO., Inc., Tokyo, Japan) as ONS, and we provided the ONS to the participants. The ONS is composed of 30 kcal energy, 9.7 g carbohydrates, 3 g essential amino acids (including 1.2 g leucine, 0.3 g isoleucine, 0.3 g valine, and 1.2 g other amino acids), 800 IU vitamin D, 0.2 mg vitamin B1, 0.2 mg vitamin B6, and 0.4 mg vitamin B12 per 100 g per pack. We informed participants that the supplement contained good nutrition for muscles. The participants consumed one pack of the supplements once daily, and we recommended ONS intake after locomotion training to the participants. The participants recorded their intake on a log sheet and one of the authors verified the information.

QOL assessment

We used the SF-36 v2®, the Japanese version of the short-form questionnaire, to assess the QOL of the participants. K.K. and Y.K. were responsible for evaluating eight subscale scores [physical functioning (PF), role physical (RP), bodily pain (BP), social functioning (SF), general health perceptions (GH), vitality (VT), role emotional (RE), and mental health (MH)] as well as three component scores [physical component summary (PCS), mental component summary (MCS), and role-social component summary (RCS)] by using a software package (iHope International Inc., Kyoto, Japan).

Physical assessment

We assessed physical function with the Locomo-test, which consists of three tests [29].

Stand-up test: the participants stood up from a 40 cm high seat using one leg (right or left).

Two-step test: first, the participants stood behind the starting line with their toes aligned. They were then instructed to take two steps, that were as large as possible, and align both feet. We measured the length of the two steps from the starting line to the tips of the toes. The score was calculated using the following formula: length of two steps (cm)/height (cm).

GLFS-25: the GLFS-25 is a self-reported comprehensive survey with 25 questions that refer to daily life experiences in the preceding month. The scale consists of four dimensions (pain, activities of daily living, social functions, and mental health status). The 25 questions were graded using a 5-point scale from no impairment (0 points) to severe impairment (4 points), and all the points were added to produce a total score (ranging from 0 to 100).

Anthropometric measurements and body composition assessment

Body weight, body mass index (BMI), extracellular water/total body water (ECW/TBW) ratio, skeletal muscle index (SMI), and body fat were measured after each HD session. Body composition was assessed using a bioelectrical impedance analyzer (InBody S10; Biospace, Seoul, Korea). SMI was calculated as appendicular skeletal muscle mass (kg) divided by height squared (m^2).

Biochemical measurements

Non-fasting blood samples were collected before the HD sessions at the beginning of the week. Serum albumin, C-reactive protein, blood urea nitrogen, serum creatinine, calcium, phosphorus, and hemoglobin levels were analyzed. In cases of hypoalbuminemia (< 4.0 g/dL), the calcium level was corrected using the following formula:

corrected calcium concentration = measured calcium concentration (mg/dL) + [4 − serum albumin (g/dL)].

Nutritional screening

The geriatric nutritional risk index (GNRI) was used for nutritional screening. The GNRI was calculated from the serum albumin and body weight using the following equation: GNRI = [14.89 × albumin (g/dL)] + [41.7 × body weight after hemodialysis (kg)/ideal body weight (kg)]. If the patient's body weight exceeded their ideal body weight, body weight was set to 1 [30].

Statistical analysis

The sample size for this trial was calculated by using PS software (version 3.1.2; Vanderbilt University, TN, USA). We estimated the result with a 5 ± 5 difference of change value in PCS between the LT and LT + ONS groups, $\alpha = 0.05$, power = 80%, and using an unpaired t-test that indicated a requirement of 34 participants in our clinical trial. Considering an estimated 20% attrition rate, the total number of participants required to be registered in the study was set at 40 individuals.

Continuous variables were summarized as medians and interquartile ranges (IQR), while categorical variables were expressed as numbers and percentages. The Mann–Whitney *U* and chi-square tests were used to analyze the differences between the LT and LT + ONS groups at baseline. We analyzed the differences in parameter changes after the intervention using the Wilcoxon signed-rank test, Mann–Whitney *U* test, chi-square test, and McNemar's test. The estimated effect size was assessed by Hodges–Lehmann estimators as the efficacy of LT + ONS compared with LT. Levels of $p < 0.05$ and

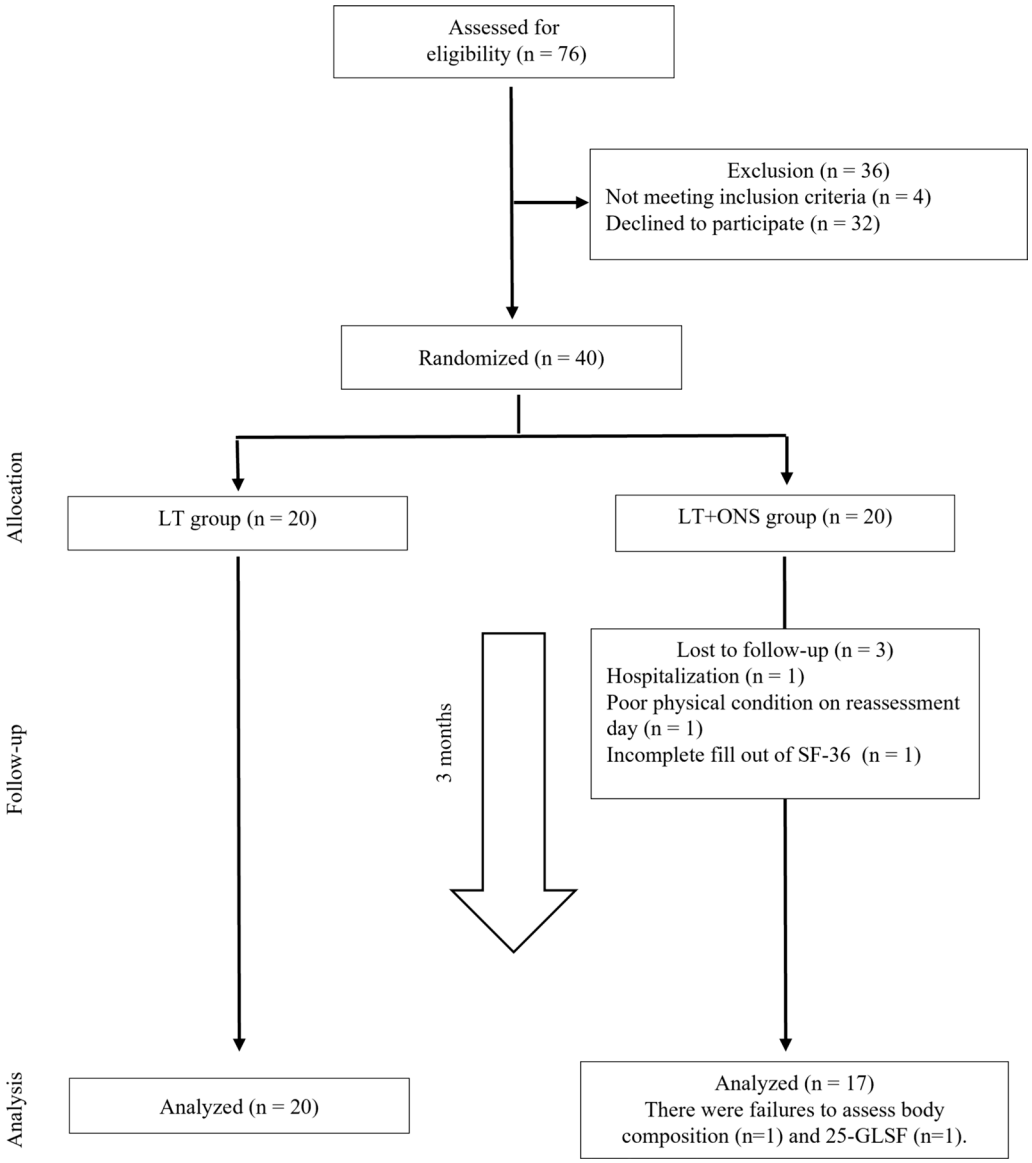

Fig. 1 The CONSORT diagram. GLSF-25, the 25-question geriatric locomotive function scale; LT, locomotive training; ONS, oral nutritional supplementation; SF-36, short form-36

95% confidence interval (CI) were considered statistically significant. All statistical analyses were performed using the SPSS version 26 for Windows software package (IBM Corp. Armonk, New York, USA).

Results

Among the 76 patients undergoing HD, we excluded 5 participants who did not meet the criteria for LS, and 31 participants refused to participate, leaving us with 40 participants enrolled in the study (Fig. 1). The participants were then randomly allocated to either the LT or LT + ONS groups. Three participants in the LT + ONS group were subsequently excluded from the study for the following reasons: one was hospitalized, another did not have data for physical function on the day of reassessment, and the third participant had an incomplete SF-36 fill-out. Despite the inability to assess body composition for one participant and the lack of GLSF-25 data for another, we still included these subjects in the analysis. Finally, we analyzed data from the LT ($n = 20$) and LT + ONS ($n = 17$) groups (Fig. 1).

Compliance rates for one-leg standing and squats in the LT group were 70% and 60%, respectively. In the LT + ONS group, compliance rates for these exercises

were 71% and 71%, respectively. Additionally, two participants in the LT + ONS group reported taking ONS less than once a day.

Characteristics of subjects

The demographic, QOL, and physical function data of the 37 participants included in the study are presented in Table 1. The median age was 73 years (IQR 62–80 years) and 62% of the patients were males. The median dialysis vintage was 6 years (IQR 3–16 years), and in 46% of cases, the primary cause of end-stage kidney disease was diabetes mellitus. The median PCS score was 38.7 (IQR 20.2–43.1). The results of the Locomo test were as follows: the success rate for the stand-up test was 11%, and the median value of the two-step test was 1.0 cm/cm (IQR 0.8–1.2 cm/cm). The median GLSF-25 score was 13 (IQR 6–29).

The background factors between the LT and LT + ONS groups did not show significant differences, except for dialysis vintage [LT group: 5 (IQR 1–10) years, LT + ONS group: 11 (IQR 6–21) years; $p = 0.02$].

Changes in QOL with LT or LT + ONS

Table 2 presents the changes in the QOL scores before and after the intervention. No significant difference in the PCS change was found between LT only and LT + ONS groups (estimated effect size $d = 0.2$, calculated 95% CI −5.3 to 5.9, $p = 0.94$). However, the LT + ONS group showed a significant effect in the MH category compared with the LT group (estimated effect size $d = 5.4$, estimated 95% CI 0.0–13.4, $p = 0.04$). When comparing the pre- and post-intervention QOL domains, there were no differences in any of them between the two groups (Additional Table 1).

Table 3 shows changes in physical function, body composition, and nutritional status. There were no significant differences in these parameters between the LT + ONS and LT groups. The results in each group are presented in Additional Table 2. In the LT + ONS group, the two-step value [pre-intervention (pre), 0.9 (IQR 0.8–1.1) cm/cm; post-intervention (post), 1.1 (IQR 0.8–1.2) cm/cm, $p < 0.01$] improved after the intervention. In the LT group, the SMI showed a significant decline [pre, 6.1 (IQR 5.2–7.5) kg/m^2; post, 6.1 (IQR 5.2–7.1) kg/m^2; $p < 0.04$], and body fat showed a significant difference [pre, 29.4 (21.5–37.7) %; post, 32.3 (24.0–39.8) %, $p < 0.01$] (Additional Table 2).

Additional analysis was conducted for participants with good adherence to the study protocol. As a result, a significant effect of the LT + ONS group on VT of SF-36 was found. Furthermore, we found significant declines in MH and MCS, significant improvement in two-step value, and significant rise in body fat in the LT group. On the other hand, GH and two-step value significantly increased in the LT + ONS group (Additional Tables 3, 4, 5, 6, and 7).

Discussion

In this study, we assessed the effect of LT and ONS on changes in QOL compared with LT without ONS in patients with LS undergoing HD in an open-label, randomized control trial. Our results show that ONS including vitamin D and leucine-rich essential amino acids added to LT did not improve QOL, physical function, and nutritional parameters compared with LT alone. However, maintenance of MH and improvement of two-step value were confirmed in the LT + ONS group.

Our previous report showed a higher prevalence of LS in patients with HD [22], compared with community-dwelling elderly people [31]. LS severity was associated with poor QOL, including PCS, MCS, PF, and RE components in patients with HD [22]. Therefore, we hypothesized that a dual intervention targeting physical function and nutritional supplementation may improve the QOL of patients with HD and LS.

In this study, LT + ONS did not change the PCS of QOL, whereas the two-step test value did show improvement in patients with LS undergoing HD. A previous study showed that chair stand-up exercises improved the physical function and PCS of QOL in patients on maintenance HD [32]. Furthermore, interventions with ONS and exercise were more effective than exercise alone in improving QOL in patients with HD [33, 34]. This study showed an apparent effect of the LT plus ONS intervention on performance in the two-step test (but not on PCS of QOL) in patients with LS undergoing HD. LT may not be sufficient intensity to improve the physical function of patients with LS undergoing HD. In addition, LT intervention for 3 months may be too short to find the effect. Indeed, Aoki et al. [24] have reported that daily practice of LT for 11 months increases PCS of SF-8. Another possibility is that pain or fatigue owing to exercise may negatively affect QOL [35, 36]. Long-term exposure to LT and ONS may be more successful in showing an effect on QOL after improved physical function in patients with HD and LS. On the other hand, the data in Additional Table 7 suggest a potential improvement in two-step value owing to LT in participants with good adherence, albeit with a small effect. A previous study for the general population demonstrated a clear improvement in the two-step value after 24 weeks of LT [23]. Thus, it is possible that long-term LT intervention could lead to enhanced physical function in patients with LS undergoing HD.

Table 1 Demographic data of participants

	Total ($n=37$)	LT group ($n=20$)	LT + ONS group ($n=17$)	*p* Value
Male (%)	62	55	71	0.33
Age (years)	73 (62, 80)	70 (61, 77)	77 (60, 80)	0.56
BMI (kg/m^2)	20.3 (19.0, 24.3)	20.5 (19.5, 25.9)	19.5 (18.2, 20.8)	0.06
Dialysis vintage (years)	6 (3, 16)	5 (1, 10)	11 (6, 21)	**0.02**
Primary cause of ESKD (%)				0.26
Diabetes mellitus	46	40	53	
Chronic glomerulonephritis	35	35	35	
Renal sclerosis	11	5	6	
Others	8	20	0	
Past history (%)				
Cardiovascular disease		5	6	0.97
Cerebrovascular disease	11	10	12	
QOL				
PF	32.6 (18.1, 48.8)	36.2 (19.9, 49.7)	32.6 (16.3, 47.0)	0.62
RP	42.4 (29.1, 52.4)	42.4 (29.1, 51.6)	42.4 (30.8, 55.7)	0.89
BP	49.2 (35.4, 54.6)	49.2 (35.4, 54.6)	44.3 (35.6, 54.6)	0.58
GH	37.8 (32.5, 45.5)	37.0 (30.5, 42.7)	41.5 (33.8, 48.2)	0.23
VT	46.6 (40.2, 53.0)	46.6 (41.0, 55.5)	46.6 (40.2, 53.0)	0.62
SF	50.6 (37.7, 57.0)	53.8 (44.1, 57.0)	50.6 (37.7, 57.0)	0.71
RE	47.7 (31.1, 56.1)	49.8 (34.2, 56.1)	43.6 (29.0, 56.1)	0.68
MH	49.1 (39.8, 57.2)	54.5 (39.1, 61.3)	46.5 (41.1, 51.8)	0.22
PCS	38.7 (20.2, 43.1)	39.2 (21.1, 42.6)	38.5 (19.9, 44.2)	0.85
MCS	51.6 (45.4, 55.8)	51.1 (42.3, 57.2)	51.6 (46.9, 55.7)	1.00
RCS	51.9 (38.3, 60.1)	56.3 (40.7, 60.1)	44.9 (37.2, 60.2)	0.54
Success of stand-up test (%)	11	15	6	0.61
Two-step value (cm/cm)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	0.9 (0.7, 1.2)	0.28
25-GLSF (score)	13 (6, 29)	14 (7, 31)	11 (6, 23)	0.48
ECW/TBW	0.397 (0.388, 0.402)	0.395 (0.386, 0.400)	0.399 (0.391, 0.402)	0.34
SMI (kg/m^2)	6.1 (5.3, 6.8)	6.1 (5.2, 7.5)	6.1 (5.4, 6.6)	0.79
Body fat (%)	24.9 (21.2, 35.9)	29.4 (21.5, 37.7)	23.8 (18.5, 30.1)	0.15
GNRI	92.0 (86.1, 94,3)	92.7 (86.2, 95.1)	90.8 (85.7, 94.9)	0.52
Body mass index (kg/m^2)	20.3 (19.0, 24.3)	20.5 (19.5, 25.9)	19.5 (18.2, 20.8)	0.06
Dry weight (kg)	54.4 (47.1, 59.8)	54.5 (48.8, 62.5)	51.8 (45.1, 58.2)	0.28
Serum albumin (g/dL)	3.5 (3.3, 3.9)	3.5 (3.3, 3.8)	3.6 (3.3, 3.9)	0.71
C-reactive protein (mg/dL)	0.07 (0.03, 0.22)	0.07 (0.03, 0.38)	0.07 (0.02, 0.20)	0.64
Blood urea nitrogen (mg/dL)	62.0 (50.1, 66.6)	57.5 (42.8, 64.1)	63.0 (54.3, 72.5)	0.056
Serum creatinine (mg/dL)	10.59 (8.62, 11.85)	10.64 (8.24, 11.64)	10.21 (9.27, 12.11)	0.48
Hemoglobin (g/dL)	10.9 (10.4, 11.2)	10.8 (10.2, 11.5)	10.9 (10.5, 11.2)	0.89
Serum potassium (mEq/L)	4.9 (4.5, 5.5)	5.0 (4.5, 5.6)	4.9 (4.6, 5.4)	0.71
Corrected calcium (mg/dL)	9.1 (8.7, 9.5)	9.0 (8.5, 9.4)	9.3 (9.0, 9.8)	0.09
Ignore phosphorus (mg/dL)	5.2 (4.7, 6.3)	5.3 (4.7, 6.2)	5.0 (4.1, 6.4)	0.52

BMI, body mass index; BP, bodily pain; ESKD, end stage kidney disease; GH, general health; GLSF, geriatric locomotive function scale; GNRI, geriatric nutritional risk index; LT, locomotion training; MCS, mental component summary; MH, mental health; ONS, oral nutritional supplementation; PCS, physical component summary; PF, physical function; QOL, quality of life, RCS, role-social component summary; RE, role emotional; RP, role physical; SF, social functioning; SMI, skeletal muscle index; VT, vitality

Date presented as median (interquartile ranges) or %

Bold value is $p<0.05$

ECW/TBW, SMI, body fat, and 25-GLSF in LT + ONS group are $n=16$

Table 2 Change of QOL scores in the LT group and LT + ONS group

	LT group ($n=20$) Median (IQR)	LT + ONS group ($n=17$) Median (IQR)	Effect size *d* Estimated value [95% CI]	*p* Value
PF	0.0 (0.0, 2.7)	0.0 (−9.0, 10.8)	0.0 [−7.2, 7.2]	0.78
RP	0.0 (−3.4, 3.4)	0.0 (−6.6, 5.0)	−3.3 [−6.6, 6.6]	0.50
BP	0.0 (−8.2, 3.6)	0.0 (−7.2, 8.7)	4.5 [−0.5, 9.8]	0.19
GH	0.0 (−3.5, 2.7)	2.7 (−1.8, 5.9)	2.6 [−2.6, 6.4]	0.27
VT	0.0 (−6.4, 3.2)	3.2 (−1.6, 6.5)	3.2 [0.0, 9.6]	0.13
SF	0.0 (−6.4, 0.0)	0.0 (0.0, 6.4)	6.4 [0.0, 6.5]	0.13
RE	0.0 (−4.2, 3.2)	0.0 (−2.1, 2.1)	0.0 [−4.2, 4.2]	0.87
MH	−2.6 (−12.7, 2,7)	2.7 (−1.4, 6.8)	5.4 [0.0, 13.4]	**0.04**
PCS	−0.1 (−5.3, 6,2)	−1.6 (−5.3, 6.8)	0.2 [−5.3, 5.9]	0.94
MCS	−2.4 (−9.5, 3.7)	1.6 (−2.7, 9.7)	5.7 [−1.0, 11.8]	0.10
RCS	−0.6 (−4.9, 2.2)	2.0 (−9.4, 5.1)	0.3 [−8.9, 6.2]	1.00

BP, bodily pain; CI, confidence interval; GH, general health; IQR, Interquartile range; LT, locomotion training; MCS, mental component summary; MH, mental health; ONS, oral nutritional supplementation; PCS, physical component summary; PF, physical function; QOL, quality of life, RCS, role-social component summary; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality

Bold value is $p < 0.05$

Table 3 Physical function, body composition, and nutritional status changed in the LT group and LT + ONS group

	LT group ($n=20$) Median value (IQR)	LT + ONS group ($n=17$) Median value (IQR)	Effect size *d* Estimated value [95% CI]	*p* Value
Success of stand-up test (%)				
Maintenance of success	15	6	–	0.54
Success after intervention	5	12		
Maintenance of failure	80	82		
2-step value (cm/cm)	0.1 (−0.1, 0.2)	0.1 (0.0, 0.2)	0.1 [−0.1, 0.1]	0.27
25-GLSF (score)	−1 (−5, 2)	−1 (−4, 3)	1 [−2, 5]	0.62
ECW/TBW	0.003 (−0.002, 0.006)	0.000 (−0.003, 0.004)	−0.002 [−0.006, 0.002]	0.31
SMI (kg/m^2)	−0.2 (−0.3, 0.1)	−0.1 (−0.3, 0.1)	0.1 [−0.1, 0.2]	0.54
Body fat (%)	1.8 (0.2, 3.3)	0.8 (−1.4, 2.8)	−1.0 [−2.8, 0.6]	0.21
GNRI	0.2 (−2.2, 2.6)	1.0 (−2.1, 3.1)	0.5 [−1.4, 3.0]	0.56
BMI (kg/m^2)	0.1 (−0.1, 0.2)	0.0 (−0.3, 0.4)	0.0 [−0.2, 0.3]	0.78
Dry weight (kg)	0.2 (−0.2, 0.5)	0.0 (−0.8, 1.0)	0.0 [−0.6, 0.7]	0.99
Serum albumin (g/dL)	0.0 (−0.1, 0.2)	0.1 (−0.1, 0.2)	0.1 [−0.1, 0.2]	0.37
C-reactive protein (mg/dL)	0.00 (−0.04, 0.04)	0.00 (−0.15, 0.01)	0.00 [−0.10, 0.03]	0.81
Blood urea nitrogen (mg/dL)	3.5 (−4.9, 12.7)	−2.6 (−9.4, 16.0)	−1.2 [−9.4, 11.0]	0.89
Serum creatinine (mg/dL)	−0.04 (−0.42, 0.49)	−0.19 (−0.72, 0.03)	0.29 [−0.72, 0.19]	0.27
Hemoglobin (g/dL)	−0.6 (−1.6, 0.6)	−0.2 (−0.6, 0.7)	0.4 [−0.3, 1.3]	0.21
Serum Potassium (mEq/L)	0.2 (−0.3, 0.4)	0.2 (−0.1, 0.4)	0.1 [−0.3, 0.5]	0.64
Corrected calcium (mg/dL)	0.1 (−0.4, 0.3)	0.0 (−0.3, 0.3)	0.0 [−0.4, 0.3]	0.85
Ignore phosphorus (mg/dL)	−0.3 (−1.0, 0.5)	0.3 (−1.3, 1.7)	0.1 [−0.3 1.4]	0.66

BMI, body mass index; CI, confidence interval; GLSF, geriatric locomotive function scale; GNRI, geriatric nutritional risk index; IQR, Interquartile range; LT, locomo training; ONS, oral nutritional supplementation; SMI, skeletal muscle index;

ECW/TBW, SMI, body fat, and 25-GLSF in the LT + ONS group are $n=16$

MH of QOL improved after the LS + ONS intervention (Table 2). This suggests that participants in the LT + ONS group felt psychological sufficiency owing to LT + ONS. A previous clinical study has shown that cognitive function and the quality of social interaction are associated with physical functions assessed using a six-minute walking test in patients undergoing HD [37]. Previous reports have suggested that vitamin D supplementation

improves depression in nonCKD adults [38, 39]. An animal study has shown that depression-like behavior is attenuated by exercise and leucine intake [40]. A cross-sectional study showed that leucine intake was inversely related to depression and anxiety in adults in general [41]. Therefore, our results suggest that supplementation with vitamin D and leucine improves MH in patients with LS undergoing HD.

Meta-analysis showed that combined vitamin D and leucine intake were improvement in physical function [26]. However, several reports used for meta-analysis were reinforcement of not only vitamin D and leucine intake but also protein intake. Possibly, we should consider reinforcement of protein intake added to vitamin D and leucine for improvement of the physical component in QOL. On the other hand, maintenance of MH in the LT + ONS group is possibly due to the placebo effect by the feeling of satisfaction with ONS intake.

Our study had several limitations. Although the intervention of LT and ONS was recorded in writing, it was performed in an unsupervised situation. Nutritional intake was not evaluated during the study. Serum leucine and serum 25 (OH) vitamin D were not measured in this study. A bias cannot be ruled out in the LS + ONS group, who believed in the benefits of the nutritional supplements. This was a short-term study with a small sample size. Further research is needed to confirm the validity of our results with long-term observations and larger sample sizes. Despite these limitations, this is the first randomized controlled trial to demonstrate an intervention of physical training and nutrition in patients with LS undergoing HD.

Conclusions

We demonstrated that the LT + ONS intervention did not show an effect on the PCS of QOL compared with LT alone in patients with LS undergoing HD. However, maintenance of MH and improvement of two-step value were confirmed in the LT + ONS group. Future research is need to confirm whether leucine-rich essential amino acids and vitamin D help mental health and physical function in patients with LS undergoing HD using larger sample sizes and long-term interventions.

Abbreviations

BMI	Body mass index
BP	Bodily pain
CI	Confidence interval
ECW	Extracellular water
GH	General health perceptions
GLFS	Geriatric locomotive function scale
HD	Hemodialysis
IQR	Interquartile range
LS	Locomotive syndrome
LT	Locomotion training
MCS	Mental component summary
MH	Mental health
MNA-SF	Mini nutritional assessment-short form
ONS	Oral dietary supplementation
PCS	Physical component summary
QOL	Quality of life
PF	Physical functioning
RCS	Role-social component summary
RE	Role emotional
RP	Role physical
SF	Social functioning
SMI	Skeletal muscle index
TBW	Total body water
VT	Vitality

Supplementary Information

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Additional file 1.

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Author contributions

Conception, study design, interpretation, measurement, and analysis of the data were performed by K.K., Y.K., and S.Y.; the manuscript was drafted by K.K., S.Y., and I.N.; approval of the final version was performed by K.K., Y.K., S.Y., and I.N.

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Availability of date and materials

The datasets used and analyzed during the present study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the institutional review board at Shinkohkai Murakami-Kinen Hospital (approval number: 1701).

Consent for publication

Not applicable.

Competing interests

They authors declare that they have no competing interests.

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