



## Phase Angle following Intradialytic Neuromuscular Electrical Stimulation and Oral Protein Supplementation in Patients undergoing Chronic Hemodialysis

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**Background:** Sarcopenia is a prevalent condition in patients undergoing chronic hemodialysis. Therefore, a convenient and reliable method of monitoring muscle health is required. This study identified the utility of the phase angle (PhA) to estimate muscle health, and evaluated its changes following intradialytic neuromuscular electrical stimulation (NMES) and oral nutritional supplement interventions in patients undergoing chronic hemodialysis. **Methods:** This post-hoc analysis was conducted using data obtained from a 12-week multicenter randomized trial that examined the effects of NMES and protein supplementation. The participants were divided into four groups according to intradialytic NMES and protein supplementation. The PhA, muscle mass, muscle strength, and physical performance were measured every 4 weeks. **Results:** Overall, 59 participants completed the study. PhA values were linearly associated with muscle mass and muscle strength. Additionally, high PhA levels indicated fast gait speed and shortened timed up-and-go test (TUG) results. We further evaluated the association between the PhA slope and muscle health-related parameters. In participants with the PhA slope  $<0^\circ$  over 12 weeks, TUG results worsened over time, relative to those with a slope  $\geq 0^\circ$  over 12 weeks, independent of age, sex, diabetes, and body mass index. NMES did not improve the PhA values over time; however, protein supplementation tended to increase the PhA values. **Conclusion:** PhA is a reliable marker for estimating and monitoring muscle health in patients undergoing chronic hemodialysis, and a strong association exists between PhA and TUG results.

**Key Words:** Chronic hemodialysis, Bioelectrical impedance, Phase angle, Sarcopenia, Physical performance

## INTRODUCTION

Muscle mass loss is prevalent in patients with chronic kidney disease (CKD), and its occurrence increases with disease progression.<sup>1,2)</sup> The etiologies of muscle depletion in CKD are multifaceted and involves aging, kidney disease itself, comorbidities, dialysis procedures, and chronic inflammation, which contributes to a negative protein balance by increasing protein degradation and de-

creasing protein synthesis.<sup>3,4)</sup> Muscle mass loss correlates with reduced muscle strength and function, and has been linked to protein-energy wasting, low quality of life, depression, cardiovascular events, and mortality.<sup>5-7)</sup> However, muscle dysfunction in CKD is not only a result of muscle mass loss. Studies have indicated worse muscle function in patients undergoing hemodialysis than in matched healthy individuals with similar muscle mass<sup>8,9)</sup> and an association between muscle function in these patients and mortality,

irrespective of muscle mass.<sup>10)</sup> Consequently, sarcopenia, characterized by concomitant loss of muscle mass and function, has emerged as a critical concern in patients with CKD. However, accurate muscle quantity and quality assessments are limited by practical issues<sup>11)</sup>; thus, efforts to find a simple and reliable indicator of muscle health are fundamental for vulnerable populations.

Bioelectrical impedance analysis (BIA) may be promising because of its popular, rapid, and noninvasive nature.<sup>12)</sup> Among its derivatives, phase angle (PhA) has been shown to indicate nutritional and inflammatory status, and it can predict the prognosis in individuals, including patients with CKD.<sup>13-15)</sup> Additionally, studies have revealed that PhA reflects muscle quantity and quality, and can help identify sarcopenia in patients with CKD.<sup>16-18)</sup> However, most studies have shown a temporal relationship relying on cross-sectional data, with the utility of longitudinal PhA measurements relatively unexplored. PhA evaluation has gained attention as a surrogate for assessing muscle quality<sup>19)</sup>; thus, its utility needs to be verified in a prospective study, and it would be interesting to examine the effect of interventions in assessing serial PhA changes. Despite its clinical relevance, there is a scarcity of studies examining whether therapeutic interventions, such as exercise and nutritional support, influence PhA values.

We previously conducted a multicenter, randomized-controlled study evaluating the efficacy of intradialytic neuromuscular electrical stimulation (NMES) and oral nutritional supplementation in patients with end-stage kidney disease (ESKD) receiving chronic hemodialysis.<sup>20)</sup> In this post-hoc analysis, we investigated the usefulness of PhA in assessing muscle health by examining the relationship between PhA and various parameters reflecting muscle quantity and quality. We also explored longitudinal changes in PhA in response to therapeutic interventions. Eventually, in the present study, we aimed to determine the potential of PhA measurement to serve as an indicator for treating patients with, or at risk of, muscle wasting, muscle dysfunction, and sarcopenia, and to establish its utility as a surrogate endpoint in conducting clinical trials.

## MATERIALS AND METHODS

### Study Design and Participant

This study used data from a 12-week, multicenter, randomized controlled trial that investigated the efficacy of intradialytic NMES and protein supplementation (P) on muscle strength and physical performance in patients with ESKD receiving chronic hemodialysis.<sup>20)</sup> Participants were randomly allocated into four groups—control group, P group, NMES group, and NMES + P group. In this study, we performed block randomization to divide the

groups, using a block size of four, and a stratified randomization schedule was conducted across four institutions.

The following participants were considered eligible: patients with ESKD who have been receiving hemodialysis for 3 months or more; stable patients who did not experience recent acute kidney injury; and patients who were able to comprehend and adhere to the protocol. The exclusion criteria were as follows: uncontrolled hypertension, diabetes, or heart failure; malignancies under treatment; active infection; positive status for human immunodeficiency virus; history of ischemic heart disease, stroke, or deep vein thrombosis within 3 months before enrollment; contraindication to electronic stimulation, including an implantable defibrillator; skin lesions around the electrical stimulation spots; and allergy to protein supplements; inappropriateness for enrollment in this study, as judged by the researcher.

The sample size was estimated to detect intergroup differences in leg muscle strength (LMS) after a 12-week intervention, calculated based on the results of a previous study.<sup>21)</sup> Assuming a two-tailed hypothesis (alpha value of 0.0083 for correction of multiple comparisons; desired power of 80%), 13 participants were required in each group. Consequently, this study recruited at least 72 participants, considering a 25% dropout rate.

### Interventions

NMES and protein supplements were provided according to the study protocol.<sup>20)</sup> NMES was administered three times a week during each dialysis session using a four-channel functional electrical stimulation instrument (FES-1000/5000; Stratec Co. Ltd., Anyang, South Korea). Adhesive electrodes were attached bilaterally to the four areas of the vastus medialis and lateralis. The participants received NMES with maximal tolerated impulse intensity, ranging from 20–94 mA, for 20 minutes during the first week, and for an additional 2 minutes every week thereafter, up to a total of 30 minutes.

Protein supplements (25 g) were provided as a mixture of kidney-specific supplements (Mediwell; Maeil Co. Ltd., Seoul, South Korea) and a protein isolate powder (Nutria-Bridge protein powder; Maeil Co. Ltd.). The participants consumed the supplements at the beginning of every dialysis session in the P group and immediately after the NMES treatment in the NMES + P group.

### Data Collection

Baseline demographic and clinical data were collected. Measurements, including laboratory data, body composition, muscle strength, and physical performance, were performed every 4 weeks.

Body composition was assessed within 30 min of dialysis treat-

ment using a multifrequency BIA device (InBody S10; Biospace Co. Ltd., Seoul, South Korea). Using parameters derived from BIA, muscle mass parameters including skeletal muscle mass (SMM)/height<sup>2</sup> (kg/m<sup>2</sup>), appendicular SMM (ASM)/height<sup>2</sup> (kg/m<sup>2</sup>), and lower extremity SMM (LESM)/height<sup>2</sup> (kg/m<sup>2</sup>) were calculated. The PhA value was estimated based on the following formula using reactance ( $X_c$ ) and resistance (R) obtained at 50 kHz:

$$\text{Phase angle } (^{\circ}) = \arctangent(X_c/R) \times (180^{\circ}/\pi).$$

Muscle strength was assessed based on handgrip strength (HGS) and LMS using digital hand and leg dynamometers, respectively (T.K.K. 5401 and T.K.K. 5710e/5715, respectively; Takei Scientific Instruments Co. Ltd., Niigata, Japan). Standing and sitting HGS on the opposite side of the hemodialysis access and LMS of both knee joint extension muscles were assessed according to the manufacturer's instructions. Three measurements were obtained at 1–2-minute intervals, and the highest results were selected for the analysis.

Physical performance was assessed using the 6-m gait speed test and timed up-and-go (TUG) test. The participants walked through a 10-m walking course comprised of a 6-m measurement course and 2-m acceleration and deceleration zones (dynamic start method), following the examiner's instructions. The time of completion for the 6-m measurement course was recorded. In the TUG test, the participants were seated in a chair, and the time taken to stand up, walk a 3-m course, turn around, walk back, and sit down was recorded. Each test was conducted twice, and the mean value was selected for analysis.

### Statistical Analysis

Continuous variables were expressed as medians (interquartile ranges) and compared using the Mann–Whitney test or Kruskal–Wallis test. Categorical variables were expressed as numbers (percentages) and analyzed using the chi-squared test. The correlation between PhA and variables was evaluated using linear regression analysis. We explored whether the PhA patterns over time reflected the longitudinal changes in muscle mass, strength, and physical performance. Specifically, we hypothesized that individuals with an increasing PhA slope might show improvements in muscle parameters. Participants were then divided into two groups based on the PhA slope calculated using linear regression analysis: those with a PhA slope < 0° and those with a PhA slope ≥ 0° over a 12-week period. Longitudinal changes in muscle health parameters according to PhA slope were evaluated using a linear mixed-effects model. Group differences in the PhA trajectories were compared

using a linear mixed-effects model. The effects of NMES and protein supplementation on the PhA over time were also assessed. The multivariate analysis was adjusted for age, sex, diabetes, and body mass index (BMI); additionally, the model analyzing changes in muscle mass, strength, and function according to a PhA slope was adjusted for age, sex, diabetes, BMI, and intervention group, categorized as control, P, NMES, or NMES + P. All statistical analyses were performed using the SPSS software (version 23.0; IBM Corp., Armonk, NY, USA). Statistical significance was set at a two-sided p-value of < 0.05.

### Ethical Statement

The trial protocol was approved by the Institutional Review Boards of the participating hospitals—National Medical Center (No. M-1911-018-001), Hanyang University Guri Hospital (No. 2020-01-019-002), Seoul National University Hospital (No. J2009-151-1160), and Dongguk University Ilsan Hospital (No. 2019-11-031)—and registered with the Clinical Research Information Service, Korea (KCT0005573). Written informed consent was obtained from all participants.

## RESULTS

### Participant Characteristics

Overall, 59 participants were classified into four groups: 15 (25.4%), 14 (23.7%), 15 (25.4%), and 15 (25.4%) in the control, P, NMES, and NMES + P groups, respectively. The demographic and laboratory data did not significantly differ between the groups (Table 1). However, some differences were observed when comparing muscle mass and function. Baseline PhA values differed among the intervention groups.

### Correlation between the PhA and Other Variables

Linear regression analysis was conducted to identify the relationships between the initial PhA values and baseline muscle mass, strength, and function. The PhA was associated with muscle mass, including SMM/height<sup>2</sup>, ASM/height<sup>2</sup>, and LESM/height<sup>2</sup> in the univariate analyses; however, the correlation with ASM/height<sup>2</sup> and LESM/height<sup>2</sup> disappeared after adjusting for age, sex, diabetes, and BMI (Table 2). The relationship between the PhA and muscle strength and function, including HGS and TUG, persisted in the multivariate analyses (Table 2).

### Trajectory of Muscle Mass and Function according to the PhA Slope

The PhA slope was estimated using the linear regression model with baseline and 4-, 8-, and 12-week measurements. The partici-

**Table 1.** Baseline characteristics of the patients

|                                               | Control group (n = 15) | P group (n = 14)   | NMES group (n = 15) | NMES + P group (n = 15) | p-value |
|-----------------------------------------------|------------------------|--------------------|---------------------|-------------------------|---------|
| Age (y)                                       | 60 (53–74)             | 62 (51–75)         | 61 (58–75)          | 57 (52–63)              | 0.827   |
| Sex, male                                     | 11 (73.3)              | 12 (85.7)          | 13 (86.7)           | 12 (80.0)               | 0.775   |
| Diabetes                                      | 9 (60.0)               | 9 (64.3)           | 8 (53.3)            | 10 (66.7)               | 0.887   |
| Hemodialysis duration (mo)                    | 41 (18–78)             | 35 (19–56)         | 34 (17–48)          | 11 (4–56)               | 0.492   |
| Blood pressure (mmHg)                         |                        |                    |                     |                         |         |
| Systolic                                      | 145 (139–158)          | 152 (123–162)      | 148 (125–160)       | 160 (131–168)           | 0.884   |
| Diastolic                                     | 80 (73–94)             | 80 (67–85)         | 78 (66–85)          | 83 (66–87)              | 0.703   |
| Dry weight (kg)                               | 63.8 (50.5–69.0)       | 56.1 (50.5–65.0)   | 62.4 (56.0–77.3)    | 63.5 (58.7–71.0)        | 0.465   |
| Kt/V                                          | 1.5 (1.4–1.7)          | 1.5 (1.4–1.6)      | 1.4 (1.3–1.6)       | 1.4 (1.3–1.5)           | 0.413   |
| nPCR                                          | 0.9 (0.8–1.1)          | 1.0 (0.9–1.1)      | 0.9 (0.8–1.3)       | 0.9 (0.8–1.0)           | 0.697   |
| Laboratory value                              |                        |                    |                     |                         |         |
| Hemoglobin (g/dL)                             | 10.4 (9.8–10.7)        | 10.2 (9.8–10.9)    | 10.6 (9.7–11.1)     | 10.1 (9.9–10.6)         | 0.892   |
| Albumin (g/dL)                                | 4.0 (3.7–4.2)          | 3.9 (3.6–4.3)      | 4.0 (3.7–4.2)       | 4.0 (3.9–4.4)           | 0.830   |
| Total cholesterol (mg/dL)                     | 109 (96–138)           | 117 (111–144)      | 116 (100–150)       | 129 (93–146)            | 0.539   |
| Calcium (mg/dL)                               | 8.6 (8.2–8.9)          | 8.7 (8.2–9.2)      | 8.8 (8.0–9.1)       | 8.8 (8.2–9.2)           | 0.575   |
| Phosphorus (mg/dL)                            | 4.8 (3.8–5.9)          | 3.6 (3.3–5.3)      | 4.2 (3.8–5.4)       | 4.8 (3.7–5.8)           | 0.250   |
| Urea nitrogen (mg/dL)                         | 56 (43–78)             | 61 (48–71)         | 59 (50–70)          | 58 (52–68)              | 0.981   |
| Creatinine (mg/dL)                            | 9.5 (7.3–9.8)          | 10.4 (9.0–11.3)    | 9.4 (8.7–11.8)      | 10.4 (8.7–12.0)         | 0.355   |
| Total carbon dioxide (mmol/L)                 | 23.0 (21.0–23.0)       | 22.0 (19.8–23.3)   | 22.0 (20.5–23.0)    | 23.0 (20.0–23.0)        | 0.886   |
| Intact parathyroid hormone (ng/dL)            | 209.6 (120.5–286.0)    | 185.3 (60.7–315.4) | 105.0 (94.1–168.5)  | 225.9 (133.4–262.7)     | 0.257   |
| High-sensitivity CRP (mg/dL)                  | 0.1 (0.0–0.5)          | 0.1 (0.0–0.2)      | 0.1 (0.1–0.2)       | 0.0 (0.0–0.1)           | 0.598   |
| Hemoglobin A1c (%)                            | 6.0 (5.3–7.3)          | 6.2 (5.3–7.6)      | 5.3 (4.8–6.3)       | 6.3 (5.2–6.8)           | 0.239   |
| Body composition                              |                        |                    |                     |                         |         |
| BMI (kg/m <sup>2</sup> )                      | 22.9 (19.7–24.5)       | 21.2 (19.2–23.3)   | 22.0 (20.3–27.4)    | 21.9 (20.4–24.9)        | 0.500   |
| SMM/height <sup>2</sup> (kg/m <sup>2</sup> )  | 9.0 (8.3–9.8)          | 8.5 (7.7–9.7)      | 10.0 (8.8–10.6)     | 9.3 (8.7–10.4)          | 0.077   |
| ASM/height <sup>2</sup> (kg/m <sup>2</sup> )  | 6.9 (6.0–7.7)          | 6.2 (5.9–7.3)      | 7.3 (6.6–8.3)       | 7.3 (6.7–8.0)           | 0.085   |
| LESM/height <sup>2</sup> (kg/m <sup>2</sup> ) | 4.9 (4.5–5.6)          | 4.5 (4.4–5.5)      | 5.2 (4.8–6.0)       | 5.5 (5.1–5.8)           | 0.151   |
| PhA (°)                                       | 4.9 (4.1–5.2)          | 4.5 (3.8–5.3)      | 5.4 (5.0–6.0)       | 4.7 (4.3–5.8)           | 0.032   |
| Muscle function                               |                        |                    |                     |                         |         |
| HGS (kg)                                      | 21.3 (15.8–31.3)       | 22.4 (17.9–28.0)   | 30.4 (21.5–35.4)    | 27.4 (20.7–30.7)        | 0.191   |
| LMS (kg)                                      | 24.1 (20.8–43.0)       | 28.0 (17.8–33.4)   | 37.0 (24.3–42.0)    | 31.1 (28.0–39.9)        | 0.240   |
| Gait speed (m/s)                              | 1.2 (0.9–1.6)          | 1.2 (0.8–1.4)      | 1.2 (0.9–1.3)       | 1.3 (1.0–1.4)           | 0.893   |
| TUG (s)                                       | 7.0 (5.6–9.9)          | 9.4 (7.4–11.2)     | 7.3 (6.4–9.6)       | 7.3 (6.2–8.6)           | 0.196   |

Values are presented as median (interquartile range) or number (%).

P, protein supplementation; NMES, neuromuscular electrical stimulation; NMES + P, neuromuscular electrical stimulation combined with protein supplementation; Kt/V, rate of urea removal (K) times treatment duration (t) divided by the urea distribution volume (V); nPCR, normalized protein catabolic rate; CRP, C-reactive protein; BMI, body mass index; SMM, skeletal muscle mass; ASM, appendicular skeletal muscle mass; LESM, lower extremity skeletal muscle mass; PhA, phase angle; HGS, handgrip strength; LMS, leg muscle strength; TUG, timed up-and-go test.

pants were then divided into two groups: 23 (39.0%) with PhA slope  $< 0^\circ$  over 12 weeks and 36 (61.0%) with PhA slope  $\geq 0^\circ$  over 12 weeks (Fig. 1A). The prevalence of intervention groups did not differ between the different PhA slope groups ( $p = 0.523$ ). The trajectories of SMM/height<sup>2</sup>, ASM/height<sup>2</sup>, LESM/height<sup>2</sup>, HGS, LMS, and gait speed did not differ between groups ( $p = 0.246$ , 0.298, 0.448, 0.227, 0.978, and 0.372, respectively). However, the TUG results of patients with a PhA slope  $< 0^\circ$  over 12 weeks deteriorated during the study period compared with those of the pa-

tients with a PhA slope  $\geq 0^\circ$ , even after adjustment for age, sex, diabetes, BMI, and intervention group ( $p = 0.012$ ) (Fig. 1B).

### Impact of NMES and Protein Supplementation on the Muscle Parameters and PhA

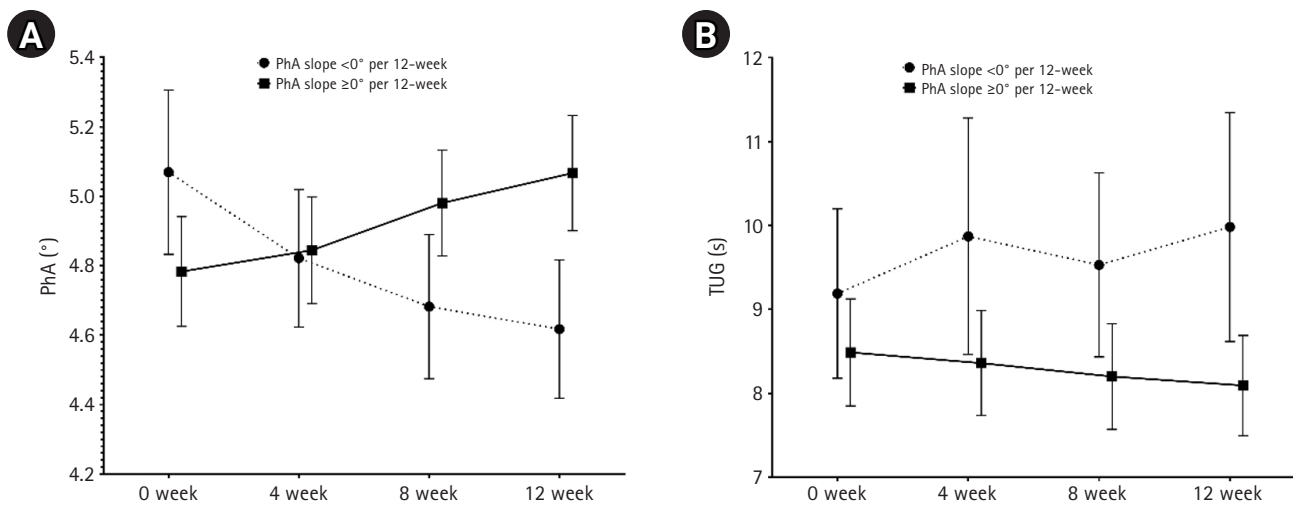
Between the baseline and 12-week measurements, some parameters of muscle mass and gait speed showed differences. However, the effects of NMES and protein supplementation were not remarkable (Table 3). In contrast, gait speed improved in the NMES

**Table 2.** Relationship between the PhA and muscle mass, strength, and function

|                          | Univariate             |         | Multivariate <sup>a)</sup> |         |
|--------------------------|------------------------|---------|----------------------------|---------|
|                          | Coefficient (95% CI)   | p-value | Coefficient (95% CI)       | p-value |
| SMM/height <sup>2</sup>  | 0.42 (0.23 to 0.85)    | 0.001   | 0.29 (0.11 to 0.25)        | 0.016   |
| ASM/height <sup>2</sup>  | 0.27 (0.02 to 0.59)    | 0.036   | 0.08 (−0.13 to 0.28)       | 0.454   |
| LESM/height <sup>2</sup> | 0.27 (0.01 to 0.42)    | 0.040   | 0.05 (−0.10 to 0.20)       | 0.485   |
| HGS                      | 0.51 (2.12 to 5.61)    | < 0.001 | 3.11 (1.57 to 4.64)        | 0.000   |
| LMS                      | 0.34 (0.92 to 6.33)    | 0.010   | 2.40 (−0.24 to 5.03)       | 0.074   |
| Gait speed               | 0.30 (0.02 to 0.18)    | 0.022   | 0.06 (−0.02 to 0.15)       | 0.129   |
| TUG                      | −0.39 (−2.61 to −0.59) | 0.002   | −1.30 (−2.32 to −0.27)     | 0.015   |

PhA, phase angle; SMM, skeletal muscle mass; ASM, appendicular skeletal muscle mass; LESM, lower extremity skeletal muscle mass; HGS, handgrip strength; LMS, leg muscle strength; TUG, timed up-and-go test; CI, confidence interval.

<sup>a)</sup> Adjusted for age, sex, diabetes, and body mass index.



**Fig. 1.** Changes in the PhA and TUG results according to the PhA slope. (A) PhA trajectories (PhA slope <0° vs. ≥0°). (B) TUG results according to PhA slope. Values are presented as mean ± standard error. PhA, phase angle; TUG, timed up-and-go test.

and NMES + P groups ( $p = 0.012$  and  $p = 0.038$ ) and the PhA levels increased in the NMES + P group ( $p = 0.032$ ). The PhA values during the study period are described for the intervention groups (Fig. 2A). Although the initial PhA levels differed between the groups ( $p = 0.032$ ), this difference was not observed at the follow-up visits ( $p = 0.617$  at 4 weeks,  $p = 0.346$  at 8 weeks, and  $p = 0.133$  and 12 weeks). Additionally, the PhA slopes in the P, NMES, and NMES + P groups did not differ from those in the control group ( $p = 0.858$ ,  $p = 0.608$ , and  $p = 0.168$ , respectively).

The PhA patterns were further compared according to the NMES and P interventions (Fig. 2B, 2C). The initial PhA values were lower in patients with protein supplementation than in those without ( $p = 0.049$ ), and there was a trend of protein supplementation increasing the PhA levels over time, although not significant ( $p = 0.138$ ) (Fig. 2B). In contrast, participants who received NMES had slightly higher PhA values at baseline and 12 weeks,

compared with those who did not receive NMES ( $p = 0.108$  and  $p = 0.088$ , respectively); however, NMES did not alter the PhA trajectory over time ( $p = 0.624$ ) (Fig. 2C). The PhA slope was also compared between the two subgroups divided by the median NMES intensity value; however, the PhA change was independent of the NMES intensity ( $p = 0.497$ ).

## DISCUSSION

This study aimed to identify the impact of intradialytic NMES and protein supplementation on the PhA using data from a randomized controlled trial. It revealed that PhA is associated with muscle mass, strength, and physical performance in patients with ESKD undergoing chronic hemodialysis. In particular, the pattern of PhA over time reflected the change in TUG results. Although an insignificant association between protein supplementation and PhA in-

**Table 3.** Change in muscle mass, strength, function, and PhA levels across the different intervention groups

|                                               | Control group    | P group          | NMES group       | NMES + P group   | p-value <sup>a)</sup> |
|-----------------------------------------------|------------------|------------------|------------------|------------------|-----------------------|
| SMM/height <sup>2</sup> (kg/m <sup>2</sup> )  |                  |                  |                  |                  |                       |
| Baseline                                      | 9.0 (8.3–9.8)    | 8.5 (7.7–9.7)    | 10.0 (8.8–10.6)  | 9.3 (8.7–10.4)   | 0.116                 |
| After 12 weeks                                | 9.1 (8.4–9.9)    | 8.4 (7.7–10.0)   | 10.0 (8.9–10.5)  | 8.9 (8.3–10.3)   | 0.170                 |
| p-value <sup>b)</sup>                         | 0.053            | 0.198            | 0.733            | 0.053            |                       |
| ASM/height <sup>2</sup> (kg/m <sup>2</sup> )  |                  |                  |                  |                  |                       |
| Baseline                                      | 6.9 (6.0–7.7)    | 6.2 (5.9–7.3)    | 7.3 (6.6–8.3)    | 7.3 (6.7–8.0)    | 0.103                 |
| After 12 weeks                                | 7.1 (6.1–8.1)    | 6.1 (5.8–7.5)    | 7.4 (6.6–8.3)    | 7.3 (6.3–7.8)    | 0.191                 |
| p-value <sup>b)</sup>                         | 0.011            | 0.099            | 0.478            | 0.035            |                       |
| LESM/height <sup>2</sup> (kg/m <sup>2</sup> ) |                  |                  |                  |                  |                       |
| Baseline                                      | 4.9 (4.5–5.6)    | 4.5 (4.4–5.5)    | 5.2 (4.8–6.0)    | 5.5 (5.1–5.8)    | 0.120                 |
| After 12 weeks                                | 5.0 (4.6–6.1)    | 4.5 (4.3–5.6)    | 5.3 (4.8–6.1)    | 5.5 (4.8–5.8)    | 0.194                 |
| p-value <sup>b)</sup>                         | 0.004            | 0.272            | 0.754            | 0.201            |                       |
| HGS (kg)                                      |                  |                  |                  |                  |                       |
| Baseline                                      | 21.3 (15.8–31.3) | 22.4 (17.9–28.0) | 30.4 (21.5–35.4) | 27.4 (20.7–30.7) | 0.213                 |
| After 12 weeks                                | 20.6 (16.7–29.4) | 19.7 (17.0–31.1) | 31.9 (26.2–37.0) | 27.1 (21.8–33.6) | 0.068                 |
| p-value <sup>b)</sup>                         | 0.753            | 0.875            | 0.331            | 0.798            |                       |
| LMS (kg)                                      |                  |                  |                  |                  |                       |
| Baseline                                      | 24.1 (20.8–43.0) | 28.0 (17.8–33.4) | 37.0 (24.3–42.0) | 31.1 (28.0–39.9) | 0.235                 |
| After 12 weeks                                | 28.0 (19.9–44.4) | 27.4 (19.9–35.0) | 39.8 (27.8–51.9) | 36.3 (26.0–46.5) | 0.130                 |
| p-value <sup>b)</sup>                         | 0.187            | 0.572            | 0.414            | 0.233            |                       |
| Gait speed (m/s)                              |                  |                  |                  |                  |                       |
| Baseline                                      | 1.2 (0.9–1.6)    | 1.2 (0.8–1.4)    | 1.2 (0.9–1.3)    | 1.3 (1.0–1.4)    | 0.701                 |
| After 12 weeks                                | 1.1 (0.9–1.5)    | 1.2 (0.7–1.3)    | 1.4 (1.1–1.6)    | 1.3 (1.1–1.4)    | 0.189                 |
| p-value <sup>b)</sup>                         | 0.955            | 0.220            | 0.012            | 0.038            |                       |
| TUG (s)                                       |                  |                  |                  |                  |                       |
| Baseline                                      | 7.0 (5.6–9.9)    | 9.4 (7.4–11.2)   | 7.3 (6.4–9.6)    | 7.3 (6.2–8.6)    | 0.185                 |
| After 12 weeks                                | 8.3 (5.6–10.0)   | 8.2 (7.0–12.5)   | 6.9 (5.8–9.0)    | 6.7 (6.3–8.4)    | 0.360                 |
| p-value <sup>b)</sup>                         | 0.910            | 0.730            | 0.910            | 0.496            |                       |
| PhA (°)                                       |                  |                  |                  |                  |                       |
| Baseline                                      | 4.9 (4.1–5.2)    | 4.5 (3.8–5.3)    | 5.4 (5.0–6.0)    | 4.7 (4.3–5.8)    | 0.056                 |
| After 12 weeks                                | 4.9 (4.4–5.1)    | 4.8 (3.6–5.3)    | 5.1 (4.6–5.9)    | 4.8 (4.4–5.9)    | 0.252                 |
| p-value <sup>b)</sup>                         | 0.461            | 0.964            | 0.972            | 0.032            |                       |

Values are presented as the median (interquartile range).

PhA, phase angle; P, protein supplementation; NMES, neuromuscular electrical stimulation; NMES + P, neuromuscular electrical stimulation combined with protein supplementation; SMM, skeletal muscle mass; ASM, appendicular skeletal muscle mass; LESM, lower extremity skeletal muscle mass; HGS, handgrip strength; LMS, leg muscle strength; TUG, timed up-and-go test.

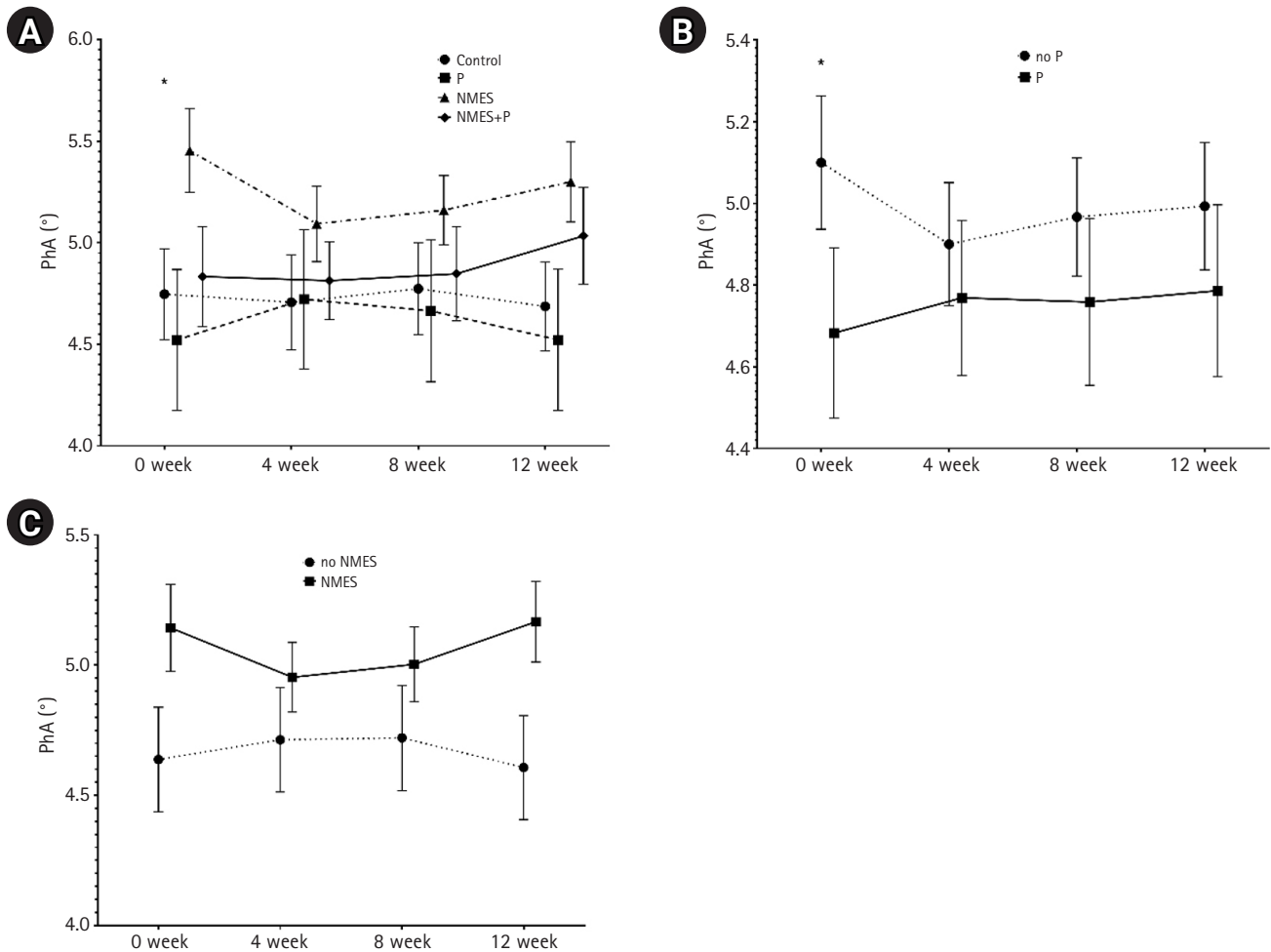
<sup>a)</sup>p<0.05 between groups at the same time point, <sup>b)</sup>p<0.05 compared to the baseline value.

crease was observed, this study did not identify a positive effect of NMES and protein supplementation on the PhA levels.

The PhA has been shown to predict nutritional status and prognosis, including mortality.<sup>13–15</sup> Moreover, the association between the PhA and parameters reflecting muscle health have been reported in studies involving patients with ESKD undergoing hemodialysis.<sup>16–18</sup> Hence, the PhA is associated with muscle mass and function, and can be used as a convenient tool to diagnose sarcopenia, as confirmed by the current study's results. However, most of previous studies have relied on cross-sectional data. Therefore, the

utility of longitudinal PhA measurements must be verified. Additionally, reflecting nutritional status, inflammatory conditions, and muscle health, the PhA can serve as a surrogate marker for examining the effects of various interventions. In this study, we explored the utility of PhA by using serial measurements to determine whether interventions to improve muscle health, such as intradialytic NMES and protein supplementation, improved PhA over time.

We evaluated the correlation between the PhA and various parameters reflecting muscle quantity and quality. We found that



**Fig. 2.** The effects of NMES and protein supplementation on the PhA values. (A) The PhA patterns based on the intervention groups. (B) Trend of PhA according to the protein supplementation. (C) Trend of PhA according to the NMES. Values are presented as mean±standard error. NMES, neuromuscular electrical stimulation; P, protein supplementation; NMES + P, neuromuscular supplementation combined with protein supplementation; PhA, phase angle.

PhA was associated with  $\text{SMM}/\text{height}^2$ , HGS, and TUG test results, which were independent of age, sex, diabetes, and BMI. The correlation with  $\text{ASM}/\text{height}^2$ ,  $\text{LESM}/\text{height}^2$ , LMS, and gait speed disappeared after adjustment. Sarcopenia can be diagnosed by muscle mass loss plus low muscle strength and/or impaired physical performance.<sup>19)</sup> Estimating these three categories is essential to determine the presence of sarcopenia. The PhA levels may reflect all aspects of muscle mass and function; thus, it seems to be a convenient indicator for identifying patients with sarcopenia. Previous studies are congruent with our results, although there is a gap according to the population and included diseases. However, the techniques for estimating muscle quantity and quality must be validated. With respect to estimating muscle mass, this study used a multifrequency BIA; however, some studies have raised concerns about the accuracy of BIA, comparing to dual-energy X-ray absorptiometry.<sup>22,23)</sup> Further studies are required to validate the tech-

niques for assessing muscle health, and the correlation with PhA needs to be clarified.

This study investigated longitudinal changes in muscle mass, strength, and physical performance during the study period, based on the PhA slope. We found that TUG results worsened in the patients with a PhA slope  $< 0^\circ$  over 12 weeks than in those with a PhA slope  $\geq 0^\circ$  over 12 weeks. There is a paucity of studies exploring temporal measurements of muscle parameters and PhA values, especially prospective ones. A previous study conducted over 48 weeks in patients with CKD analyzed changes in  $\text{SMM}/\text{height}^2$ , HGS, and gait speed according to the PhA slope and found that  $\text{SMM}/\text{height}^2$  increased in participants with an increasing PhA pattern and HGS decreased in participants with a decreasing PhA pattern.<sup>24)</sup> Despite the short duration, this study suggested that the PhA trajectory indicates longitudinal changes in muscle health-related parameters, particularly in the TUG test.

Given the evidence supporting a strong association between the PhA levels and muscle strength and function, PhA measurement can be an appropriate metric for assessing the effects of interventions in older patients and patients with diseases.<sup>25)</sup> Several studies have examined the role of PhA in older adults and patients with cancer, and a meta-analysis including these studies have advocated the role of PhA by revealing that exercise programs promoted PhA elevation.<sup>26,27)</sup> Another meta-analysis of randomized controlled trials also identified that resistance training promoted an increase in PhA in older adults.<sup>28)</sup> In this study, we evaluated the effect of intradialytic NMES on PhA in patients with ESKD receiving chronic hemodialysis; however, there was no significant change in PhA according to the intervention. This is consistent with the results of a previous study,<sup>20)</sup> wherein intradialytic NMES did not significantly change muscle strength or function. However, in another trial by Marini et al.,<sup>29)</sup> 21 Brazilian individuals with ESKD on hemodialysis were administered NMES for 4 weeks; the results showed that NMES improved the PhA ( $0.71^\circ \pm 0.27^\circ$  in the NMES group vs.  $-0.46^\circ \pm 0.23^\circ$  in the control group;  $p = 0.004$ ) but did not change the leg lean mass. It is important to note that this pilot randomized clinical trial included fewer participants and was performed for a shorter duration than our study. The discrepancy between the results of our study and those of Marini et al.'s study<sup>29)</sup> may be attributed to the differences in baseline patient characteristics. Our study included older and more comorbid patients, i.e., the mean age of the patients in our study was 61.5 years, with 61.0% of the patients having diabetes, compared with that of the patients in Marini et al.'s study<sup>29)</sup> (41.8 years). More studies with larger sample sizes are needed to evaluate whether NMES has beneficial effects on muscle mass and function and PhA.

Recent guidelines recommend prescribing a dietary protein intake of 1.0–1.2 g/kg/day for patients with ESKD on maintenance hemodialysis.<sup>30)</sup> However, most populations with this disease have insufficient protein intake, with the reported mean protein intake being less than 1.0 g/kg/day.<sup>31,32)</sup> Protein supplements may help replenish the required daily protein amount for malnourished individuals. Fouque et al.<sup>33)</sup> suggested the use of a renal-specific oral protein supplement to improve the nutritional index of these patients. The current study found a trend of increasing PhA with protein supplementation; however, it did not improve muscle strength and physical performance.<sup>20)</sup> On the other hand, PhA was used as a nutritional marker in a trial examining the effect of intradialytic parenteral nutrition in patients undergoing maintenance hemodialysis.<sup>34)</sup> Although most studies, including this study, could not identify the beneficial effect of interventions on PhA, it is noteworthy to verify if the PhA, as an indicator of nutrition and muscle health, can serve as a guide after therapeutic interventions.

This study has some limitations. First, as a secondary analysis of a randomized controlled trial that investigated the effects of NMES and protein supplementation on muscle strength and physical performance, a selection bias could have occurred. Indeed, there were intergroup differences in PhA and muscle mass indices, such as SMM/height<sup>2</sup> and ASM/height<sup>2</sup>. Other confounding factors may have been overlooked. Additionally, the sample size estimation was originally intended to detect intergroup differences in LMS; therefore, it would be inappropriate for comparing the PhA between the groups, potentially underestimating the statistical power. Second, the small sample size and short study duration may have limited the power and ignored some intergroup differences. Studies with substantial sample sizes and extended durations will be helpful in assessing the therapeutic effect on parameters indicative of muscle health, including PhA, to enable a sensitivity analysis to validate the efficacy of interventions. The small sample size also limited the number of variables that could be included in the multivariate analysis, potentially lead to overfitting or reduce the statistical power. Although we carefully selected covariates based on their clinical relevance to ensure the model remained as parsimonious as possible, this limitation may affect the robustness of the results. Third, the findings obtained from this study cannot be generalized because this study only included Korean patients with ESKD undergoing hemodialysis; body mass, composition, and PhA values differ depending on ethnicity.

In conclusion, this study revealed that the PhA reflects muscle parameters, such as muscle mass, strength, and physical performance, in patients with ESKD undergoing chronic hemodialysis. There was a strong relationship between the PhA values and TUG results. However, this study did not identify a favorable effect of NMES or protein supplementation on the PhA levels over time. Based on our results, PhA can be a valuable surrogate marker of muscle health in individuals with ESKD undergoing chronic hemodialysis. Further clinical trials are necessary to confirm the practical use of PhA measurements.

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## CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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## AUTHOR CONTRIBUTIONS

Conceptualization, JS, RhC; Data curation, JHP, RhC; Investigation, JYP; Methodology, JHP, JYP, RhC; Formal analysis, JS; Writing\_ original draft, JS, RhC. All the authors have proofread the final version.

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