Research Article

Hyperhomocysteinemia Associated with Low Muscle Mass, Muscle Function in Elderly Hemodialysis Patients: An Analysis of Multiple Dialysis Centers

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Received 22 March 2019; Accepted 23 May 2019; Published 9 June 2019

Academic Editor: Germán Vicente-Rodriguez

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Background. The hyperhomocysteinemia was with high prevalence and has been considered as a risk factor for cardiovascular disease in hemodialysis patients. These patients also experienced a high risk of muscle wasting caused by the comorbidity, malnutrition, and low physical activity. We investigated the associations of homocysteinemia with muscle mass, muscle function in elderly hemodialysis patients. Methods. A clinical cross-sectional study was conducted on 138 hemodialysis patients aged 65 years and above in seven hospital-based hemodialysis centers in Taiwan. The data on anthropometry, laboratory, and 3-day dietary intake was examined. The skeletal muscle mass (SMM) was measured by the bioelectrical impedance analysis; the SMM was adjusted by height or weight as SMM_btw (kg/m²) and SMM_wt (%). Muscle function was defined as handgrip strength (HGS) (kg) measured by handgrip dynamometer. Statistical analyses were conducted using simple regression and multivariable stepwise regression analysis. Results. In the total sample, 74.6 % of hemodialysis patients were hyperhomocysteinemia (≥ 15 μmol/L). The means of SMM_btw, SMM_wt, arm lean mass, hand grip strength, and muscle quality were 8.7 ± 1.2, 37.7 ± 5.6, 1.7 ± 0.5, 21.1 ± 7.4, and 10.0 ± 3.0, respectively. The multivariable stepwise regression analysis showed that homocysteinemia level was significantly inversely associated with SMM_wt (B-coeff. = -0.03, p = 0.02) in hemodialysis patients above 65 years old, but not with muscle function. Conclusions. Hyperhomocysteinemia is common and associated with decreased muscle mass in the elderly hemodialysis patients. Future studies are suggested to explore the impact of the homocysteine-lowering therapy on muscle decline.
1. Introduction

The United States Renal Data System reported that the prevalence of treated end-stage renal disease (ESRD) was highest for individuals aged 65-74 years in Taiwan [1]. The elderly hemodialysis patients experienced the high risk for muscle wasting, which was related to higher morbidity and mortality [2]. Muscle wasting was the most common condition in elderly people, especially those undergoing hemodialysis with a high prevalence of decreased muscle mass and muscle function, varying from 12.7% to 45.1% in hemodialysis patients [3], the declines in muscle mass and function caused by age [3], comorbidity like diabetes mellitus and infections [4], malnutrition [5], and physical inactivity [6]. In addition, physicians prescribed exercise restrictions in those patients with complications during the treatment [7]. Furthermore, declines of muscle mass and function were exaggerated due to the long bedridden time for the dialysis, low physical function [8], low exercise capacity [9], and increased muscle atrophy [6].

The hyperhomocysteinemia was presented in 80% to 90% of hemodialysis cases [10]. Homocysteine (Hcy) has been considered an important cardiovascular risk factor [11]. Moreover, studies have established an association between high levels of homocysteine and a decline in physical function in elderly populations [12]. The lower muscle mass was observed in higher plasma homocysteine group in ≥ 65 years adults [13]. The effects of hyperhomocysteinemia in vascular and myocyte function leading to impaired muscle function were summarized as follows: (i) oxidative defense reduced and production of reactive oxygen species enhanced, (ii) inhibition of nitric oxide (NO) signaling, (iii) inflammation and its associated changes, and (vi) endoplasmic reticulum (ER) stress enhanced [14]. Previous empirical studies have shown elevated Hcy associated with the decline of muscle strength and physical function in the older adults [15,16].

Since hemodialysis patients are with a high prevalence of hyperhomocysteinemia and in a high-risk group of muscle wasting, however, there are a limited number of studies that discussed this issue in hemodialysis patients, especially in the elderly. Therefore, we aim to investigate the association between homocysteine level and muscle mass, muscle function in elderly hemodialysis patients.

2. Materials and Methods

2.1. Study Design and Patients. A clinical cross-sectional design was conducted from September 2013 to April 2017 in seven hospital-based hemodialysis centers in Taiwan. The study was approved by the Taipei Medical University Joint Institutional Review Board (no. TMU-JIRB 201302024) for conducting in Taipei Medical University Hospital, Taipei Medical University-Wan Fang Hospital, Taipei Medical University-Shuang Ho Hospital, Wei Gong Memorial Hospital, and Lotung Poh-Ai Hospital, the institutional Ethics Committee from Cathay General Hospital (no. CGH-OP104001), and Taipei Tzu-Chi Hospital (no. 04-M11-090). All patients signed written informed consent forms before their participation.

The total sample of 138 patients aged 65 years and above and undergoing hemodialysis was recruited for the study. Patients who received stable hemodialysis treatment in the previous 3 months with equilibrated Kt/V of 1.2 and higher were included. Patients with obvious edema, hyperthyroidism, hypothyroidism, amputation, malign tumor, pregnancy, or hospitalization for renal disease reason were excluded.

2.2. Data Collection

2.2.1. Demographics Data. We conducted chart reviews to collect the data related to age, gender, dialysis vintage, diabetes mellitus (DM), hypertension, cardiovascular disease (CVD), and the anthropometry data including dry weight, height, and interdialytic weight gain.

2.2.2. Physical Activity. Patients’ physical activity was assessed using the short version of the International Physical Activity Questionnaire (IPAQ) [17]. Interviewers recorded the average number of days per week and the average time per day that patient spent on exercising (vigorous, moderate, or walking exercise) in the past 7 days. The value of metabolic equivalent (MET in kcal/day) value was used to examine the levels of physical activity [17].

2.2.3. Dietary Intake Data. All patients wrote down a three-day dietary record, including one dialysis day, one nondialysis day, and one day during the weekend. The data collection of dietary intake was also mentioned in our previous publication [18]. In brief, qualified dietitians taught patients how to fill in the record. To assure the record, the well-trained dietitians contacted with all patients and conducted the interviews by face-to-face, or by telephone. Next, the dietitians used the 24 h recall to confirm the data provided by patients using the common utensils in the household as the means. The nutrients were then analyzed using nutrients analysis software (e-Kitchen, Taichung, Taiwan) based on Taiwanese nutrition compositions as the nutrient database.

2.2.4. Biochemical Values. We collected the 8-hour fasting and predialysis blood samples and sent to the Laboratory Department in Taipei Medical University Hospital for analyzing the biochemical parameters. The following parameters were collected by reviewing patient medical charts: total cholesterol, creatinine, and fasting blood glucose.

2.3. Measurements

2.3.1. Homocysteine Measurements. Homocysteine was measured used in the enzymatic method. 8-hour fasting and predialysis blood samples were withdrawn and collected in EDTA blood collection tubes keep tube cold at 4°C and centrifuged within 1-2 hour, then plasma was assessed using the Roche Cobas c702 automatic analyzer (Rui An international
2.3.3. Anthropometry Measurements. Skeletal muscle mass (SMM) and body fat are measured by using the bioelectrical impedance analysis (InBody S10, Biospace, Seoul, Korea) after the hemodialysis session (sitting position). The eight surface electrodes are placed on the thumbs, middle fingers, and either side of the ankles of the patients using multiple operating frequencies of 1, 5, 50, 250, 500, and 1,000 kHz. Moreover, SMM was normalized for weight as SMM/W (kg/m²), and height as SMM/H (kg/m²), which are indicators of muscle mass. Muscle quality (MQ) is an important determinant of muscle function, defined as muscle strength or power per unit of muscle mass and calculated as the ratio of hand grip strength (kg) to arm lean mass (kg) [21]. The handgrip strength (HGS) was measured before a hemodialysis session using grip strength dynamometer (Jamar, Sammons Preston, Bolingbrook, IL) with a precision of 0.5 kg. During the measurement, patients were asked to stand straight with arm and hands being neutrally hung beside the body and then use maximum effort to squeeze the dynamometer with nonfistula hand for at least 3 seconds, and each time was provided at least 10 seconds for recovery. Patient performed the handgrip for 3 times and the pick performance was noted as the final result.

2.4. Statistical Analyses. The sample of 138 patients with data of muscle mass and a sample of 87 patients with the data of muscle function were analyzed. The descriptive analyses were used to illustrate the mean ± standard deviation, percentage of social demographics, biochemical parameters, dietary intake, and patients’ characteristics. Simple regression was used to identify the predictors of muscle mass and muscle function which were known as prognostic factors, statistical significance when p < 0.05. Multivariate linear regression models were performed to investigate the associations of Hcy and the muscle mass and muscle function. The variables showed the associations with muscle mass and function at p < 0.2 in the simple regression analyses which were kept in the multivariate models. Variables such as age, gender, and energy intake were also included in the analysis. The unstandardized regression coefficient (B), 95% confidence interval, and adjusted R square values were presented appropriately. Statistical analyses were performed using SAS software (ver. 9.4; SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Characteristics of Hemodialysis Patients. Demographics, anthropometrics, biochemical parameters, and clinical information are shown in Table 1. In 138 hemodialysis patients, 63.0% are men; 47.1%, 51.5%, and 43.5% of the hemodialysis patients had DM, hypertension, and a history of CVD, respectively. The means of age and hemodialysis vintage were 73.1 ± 6.4 years and 4.5 ± 3.4 years, respectively. The plasma Hcy level was 19.7 ± 6.0 μmol/L; 74.6% of hemodialysis patients present in hyperhomocysteinemia (≥ 15 μmol/L). The serum folate and vitamin B12 were 18.1 ± 4.5 mg/mL and 1416.8 ± 582.6 pg/mL, respectively. Hemodialysis patients were in a healthier and had good nutritional status, according to the GNRI 98.6 ± 7.1, serum albumin 3.9 ± 0.4 g/dL, and nPNA 1.3 ± 0.4 g/day, respectively (Table 1).

3.2. Associated Factors of Muscle Mass and Muscle Function. The SMM, SMM/H, and SMM/W were positively correlated with creatinine and height and were negatively correlated with age, gender, and body fat. HGS was positively associated with creatinine and height and was negatively correlated with gender. Muscle quality (MQ) was negatively correlated with body weight and BMI (Table 2).

The results stepwise regressions show that SMM was significant associations with energy intake (regression coefficient, B = < 0.01), BMI (B = 1.03), and body fat (B = -0.37) (adjusted R² = 0.82), SMM/H was significant associations with creatinine (B = 0.23) and body fat (B = -0.04) (adjusted R² = 0.50), SMM/W was significant associations with Hcy (B = -0.03), creatinine (B = 0.13), and body fat (B = -0.57) (adjusted R² = 0.97) (Table 3). In muscle function, HGS was significant associations with creatinine (B = 0.93) (adjusted R² = 0.35); MQ was significant associations with creatinine (B = 0.45) and BMI (B = -0.58) (adjusted R² = 0.18). Plasma Hcy level was the independent risk determinants of SMM/W in hemodialysis patients ≥ 65 years old (adjusted R² = 0.97, p = 0.02).

After controlling the analysis subgroup of hyperhomocysteinemia hemodialysis patients, Hcy was significantly associated with SMM/W (B = -0.03, p = 0.027) (adjusted R² = 0.99), HGS (B = -0.41, p = 0.058) (adjusted R² = 0.35), and MQ (B = -0.18, p = 0.071) (adjusted R² = 0.19) in hyperhomocysteinemia hemodialysis patients (Table 4).

4. Discussion

The current study found that Hcy was significantly inversely associated with muscle mass in hemodialysis patients aged 65
The previous studies showed that elevated Hcy is associated with muscle function decline in hyperhomocysteinemia hemodialysis patients aged 65 years and above. A previous longitudinal study has confirmed the association between higher homocysteine lower muscle strength in a general population aged 50 years or older [22]. Contributing factors such as age, low physical performance, and the presence of comorbidities were associated with muscle wasting [23].

In our study, Kt/V was significantly associated with muscle function declined in hyperhomocysteinemia impaired muscle function concluded by Veeranki and Tyagi [14], Hcy thiolactone reacts with proteins by a mechanism involving homocysteinyltation of protein lysine residues in human serum and leads to protein damage and atrophy of skeletal muscle [24], the phenomenon called protein homocysteinyltation [24]. Protein homocysteinyltation is the post-translational acylation of free amino groups (e.g., protein-N-homocysteinyltation) or formation of a covalent–S–S–bond (protein-S-homocysteinyltation) mediated by Hcy thiolactone [24], which potentially causes significant alterations in the protein function. A study reported that protein-N-homocysteinyltation and protein-S-homocysteinyltation were significantly higher in hemodialysis patients, and the significant association between plasma Hcy and protein-S-homocysteinyltation was also found [25]. This indicated that hyperhomocysteinemia may cause the toxicity via the oxidative damage to proteins [26] and may result in muscle weakness and atrophy [24].

In our study, Kt/V was significantly associated with the lower SMM in hemodialysis patients. The negative association between Kt/V and muscle mass was also demonstrated in 34 Japanese hemodialysis patients [27]. The result indicated that patients with lower muscle mass may require a higher dialysis clearance. Therefore, muscle mass should be addressed while evaluating the hemodialysis adequacy.

The present study showed that dialysis vintage, creatinine, and BMI were independently associated with muscle mass and/or muscle function. The predialysis serum creatinine level will be proportional to dietary protein intake and the SMM that lower muscle mass may indicate the lower creatinine excretion [28]. The previous study showed that
Table 2: Associated factors of muscle mass and muscle function via simple linear regression analyses.

| Variables                  | SMM | SMM Ht | SMM Wt | Hand grip strength | Muscle quality |
|----------------------------|-----|--------|--------|-------------------|---------------|
| Age (years)                | -0.123 (-0.244 to -0.003) | 0.045 | -0.045 (-0.077 to -0.004) | 0.005 | -0.177 (-0.326 to -0.029) | 0.020 | -0.311 (-0.651 to 0.029) | 0.072 | -0.090 (-0.244 to 0.064) | 0.243 |
| Male, n (%)                | -6.222 (-7.426 to -5.017) | < 0.001 | -1.274 (-1.637 to -0.912) | < 0.001 | -5.449 (-7.209 to -3.689) | < 0.001 | -6.228 (-10.669 to -1.786) | 0.007 | 0.966 (1.180 to 3.113) | 0.367 |
| Dialysis vintage (year)    | -0.001 (-0.230 to 0.229) | 0.997 | 0.012 (-0.048 to 0.073) | 0.688 | 0.170 (-0.113 to 0.453) | 0.237 | -0.179 (-0.829 to 0.472) | 0.580 | -0.013 (-0.301 to 0.275) | 0.929 |
| eKt/V                      | -5.448 (-7.742 to -3.153) | < 0.001 | -1.94 (-1.719 to -0.470) | 0.001 | -2.657 (-5.691 to 0.378) | 0.086 | 3.500 (2.446 to 4.546) | 0.240 | 2.188 (0.378 to 3.754) | 0.092 |
| Albumin (g/dL)             | 1.441 (0.726 to 3.337) | 0.115 | 0.354 (-0.139 to 0.808) | 0.165 | 0.070 (-2.175 to 2.314) | 0.951 | 3.270 (-3.909 to 10.443) | 0.361 | 0.248 (-2.950 to 3.447) | 0.876 |
| Creatinine (mg/dL)         | 1.158 (0.784 to 1.531) | < 0.001 | 0.325 (0.215 to 0.410) | < 0.001 | 0.531 (-0.003 to 1.030) | 0.051 | 1.161 (0.065 to 2.257) | 0.039 | -0.042 (-0.556 to 0.472) | 0.869 |
| FPG (mg/dL)                | -0.005 (-0.007 to 0.007) | 0.494 | -0.002 (-0.005 to 0.001) | 0.231 | -0.008 (-0.023 to 0.007) | 0.291 | -0.015 (-0.083 to 0.053) | 0.663 | -0.005 (-0.035 to 0.025) | 0.725 |
| Insulin (μU/mL)            | -0.005 (-0.039 to 0.030) | 0.779 | -0.003 (-0.022 to 0.007) | 0.587 | -0.045 (-0.087 to 0.003) | 0.037 | -0.066 (-0.168 to 0.036) | 0.186 | -0.002 (-0.048 to 0.044) | 0.925 |
| HOMA-IR                    | -0.019 (-0.082 to 0.044) | 0.552 | -0.007 (-0.023 to 0.010) | 0.413 | -0.072 (-0.149 to 0.005) | 0.066 | -0.198 (-0.481 to 0.084) | 0.162 | -0.010 (-0.138 to 0.118) | 0.872 |
| Homocysteine (μmol/L)      | -0.008 (-0.138 to 0.122) | 0.908 | -0.009 (-0.043 to 0.025) | 0.592 | 0.060 (-0.101 to 0.221) | 0.463 | 0.385 (-0.080 to 0.853) | 0.101 | -0.025 (-0.238 to 0.188) | 0.816 |
| Folate (ng/mL)             | 0.040 (-0.131 to 0.211) | 0.648 | 0.001 (-0.003 to 0.005) | 0.635 | -0.001 (-0.213 to 0.211) | 0.991 | -0.164 (-0.358 to 0.209) | 0.378 | 0.049 (-0.116 to 0.215) | 0.548 |
| Vitamin B12 (μg/mL)        | 0.001 (-0.001 to 0.002) | 0.594 | 0.0001 (-0.001 to 0.000) | 0.809 | -0.001 (-0.002 to 0.001) | 0.386 | -0.001 (-0.005 to 0.003) | 0.739 | 0.001 (-0.002 to 0.002) | 0.853 |
| Energy (kcal/day)          | 0.003 (-0.001 to 0.004) | 0.001 | 0.001 (-0.001 to 0.000) | 0.333 | 0.001 (-0.001 to 0.003) | 0.371 | 0.003 (-0.001 to 0.008) | 0.887 | 0.001 (-0.002 to 0.002) | 0.914 |
| Height (cm)                | 0.454 (-0.393 to 0.515) | < 0.001 | 0.067 (-0.044 to 0.090) | < 0.001 | 0.278 (-0.166 to 0.391) | < 0.001 | 0.392 (0.141 to 0.643) | 0.003 | -0.042 (-0.166 to 0.083) | 0.504 |
| Body weight (kg)           | 0.316 (0.257 to 0.375) | < 0.001 | 0.067 (-0.050 to 0.085) | < 0.001 | -0.100 (-0.898 to -0.033) | 0.044 | 0.393 (-0.050 to 0.436) | 0.116 | -0.127 (-0.229 to -0.025) | 0.016 |
| BMI (kg/m²)                | 0.388 (0.127 to 0.634) | 0.004 | 0.146 (0.082 to 0.210) | < 0.001 | -0.982 (-1.259 to -0.706) | < 0.001 | -0.135 (-0.897 to 0.627) | 0.721 | -0.373 (-0.684 to -0.062) | 0.020 |
| Body fat (%)               | -0.244 (-0.317 to -0.172) | < 0.001 | -0.065 (-0.084 to -0.046) | < 0.001 | -0.591 (-0.612 to -0.570) | < 0.001 | -0.171 (-0.441 to 0.100) | 0.209 | -0.019 (-0.141 to 0.031) | 0.752 |
| MET (kcal/day)             | 0.004 (-0.002 to 0.007) | < 0.001 | 0.005 (0.001 to 0.002) | 0.004 | 0.003 (-0.001 to 0.006) | 0.002 | 0.001 (-0.008 to 0.011) | 0.791 | -0.001 (-0.005 to 0.003) | 0.660 |

FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment-estimated insulin resistance; BMI, body mass index; MET, metabolic equivalent; SMM, skeletal muscle mass; Ht, height; Wt, weight.
the hemodialysis vintage was negatively associated with the loss of SMM and muscle function. In addition, BMI was positively associated with SMM [27]. The possible reason for the negative correlation between BMI and MQ was supposed to be the calculation formula, BMI would be increase, and MQ would be decreased when skeletal muscle mass increases.

Our study shows that body fat was an independent determinant of muscle mass and muscle function among hemodialysis patients. A previous study was conducted using the computed tomography (CT) to take mid-thigh muscle cross-sectional area in a 36-year-old hemodialysis patient and an 80-year-old hemodialysis patient. Results showed that the fat accumulated in the striated muscle cells and intermuscular adipose tissue in older hemodialysis patients. Besides, the results also reveal that reduced muscle cross-sectional area, increased intermuscular adipose tissue, and/or intramuscular lipid were independently associated with aging and indices of maximal strength and physical performance [29].

Our study was with a number of strengths and limitations. The plasma homocysteine was analyzed by the international standard protocol in the hospital. We used the bioelectrical impedance analysis (BIA) as body composition measurement. The BIA is inexpensive, portable, and easy-to-use as compared with others devices. The measurement conducted by BIA might be minor differences as compared with other methods such as the dual-energy X-ray absorptiometry (DEXA), CT, and magnetic resonance imaging (MRI). However, the examination of total-body muscle mass using the BIA was highly correlated with estimation using the MRI in hemodialysis patients [30]. Finally, the basis of a cross-sectional design cannot provide the causal evidence between plasma Hcy and muscle mass. Therefore, the results must be interpreted with caution. Future cohort designs or control trials are suggested.

5. Conclusion

The current study revealed that hyperhomocysteinemia is high prevalence in hemodialysis patients. Elevated homocysteine level is associated with lower muscle mass in hemodialysis patients aged 65 years and above. Thus, the homocysteine-lowering therapy might have a positive impact on muscle mass. The longitudinal studies are suggested to provide a deeper understanding of the association. Randomized control trials are needed for evaluating the effectiveness of therapy.

Data Availability

Data is available upon request to corresponding author of this article.
Table 4: Stepwise regression analyses for determining muscle mass and muscle function in hemodialysis patients with hyperhomocysteinemia.

| Variables                  | B (95% CI) | p    | adjusted R² |
|----------------------------|------------|------|-------------|
| SMM                        |            |      | 0.84        |
| Creatinine (mg/dL)         | 0.23 (0.01 to 0.45) | 0.042 |             |
| BMI (kg/m²)                | 1.02 (0.86 to 1.18) | < 0.001 |             |
| Body fat (%)               | -0.36 (-0.41 to -0.30) | < 0.001 |             |
| SMM(Ht)                    |            |      | 0.47        |
| Creatinine (mg/dL)         | 0.18 (0.07 to 0.29) | 0.002 |             |
| Body fat (%)               | -0.04 (-0.06 to -0.02) | < 0.001 |             |
| MET (kcal/day)             | 0.0006 (-0.0001 to 0.0012) | 0.084 |             |
| SMM(Wt)                    |            |      | 0.99        |
| Homocysteine (µmol/L)      | -0.03 (-0.05 to -0.01) | 0.027 |             |
| Creatinine (mg/dL)         | 0.17 (0.09 to 0.25) | < 0.001 |             |
| Body fat (%)               | -0.55 (-0.56 to -0.53) | < 0.001 |             |
| Hand grip strength         |            |      | 0.35        |
| Homocysteine (µmol/L)      | -0.41 (-0.83 to 0.01) | 0.058 |             |
| Dialysis vintage (year)    | -0.40 (-0.93 to 0.14) | 0.143 |             |
| eKt/V                      | 6.65 (1.39 to 11.91) | 0.014 |             |
| Creatinine (mg/dL)         | 1.34 (0.37 to 2.32) | 0.008 |             |
| Energy (kcal/day)          | 0.0042 (0.0008 to 0.0075) | 0.015 |             |
| Body fat (%)               | -0.19 (-0.40 to 0.02) | 0.079 |             |
| Muscle quality²            |            |      | 0.19        |
| Homocysteine (µmol/L)      | -0.18 (-0.37 to 0.02) | 0.071 |             |
| Dialysis vintage (year)    | -0.22 (-0.46 to 0.02) | 0.068 |             |
| eKt/V                      | 3.14 (0.76 to 5.53) | 0.011 |             |
| Creatinine (mg/dL)         | 0.54 (0.08 to 1.01) | 0.023 |             |
| Energy (kcal/day)          | 0.0015 (0.00005 to 0.0031) | 0.045 |             |
| BMI (kg/m²)                | -0.47 (-0.73 to -0.21) | < 0.001 |             |

*The significance levels of any potential factor for entry (SLE) and for stay (SLS) in the stepwise variable selection were set to 0.2. Age and gender were adjusted. Variables retained in the model are presented in the table.

BMI, body mass index; MET, metabolic equivalent; SMM, skeletal muscle mass; Ht, height; Wt, weight.

Disclosure

The funder had no role in the decision to collect data, data analysis, or reporting of the results.

Conflicts of Interest

The authors had no conflicts of interest relevant to this article to be disclosed.

Authors’ Contributions

Chi-Sin Wang and Tuyen Van Duong contributed equally to this paper.

Acknowledgments

The authors express the appreciation to medical staff and patients from Taipei Medical University Hospital, Wan-Fang Hospital, Shuang Ho Hospital, Cathay General Hospital, and Taipei Tzu-Chi Hospital, Wei-Gong Memorial Hospital, and Lutong Poh-Ai Hospital. The research was funded by Ministry of Science and Technology in Taiwan (NSC-102-2320-B-038-026; MOST 105-2320-B-038-033-MY3).

References

[1] United States Renal Data System, "2014 USRDS annual data report: Epidemiology of kidney disease in the United States," National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2014.

[2] A. J. Cruz-Jentoft, J. P. Baeyens, J. M. Bauer et al., "Sarcopenia: European consensus on definition and diagnosis," Age and Ageing, vol. 39, no. 4, Article ID afg034, pp. 412–423, 2010.

[3] F. Lamarca, J. J. Carrero, J. C. D. Rodrigues, F. G. Bigogno, R. L. Fetter, and C. M. Avesani, "Prevalence of sarcopenia in elderly maintenance hemodialysis patients: The impact of different diagnostic criteria," The Journal of Nutrition, Health & Aging, vol. 18, no. 7, pp. 710–717, 2014.

[4] M.-T. Liao, C.-C. Sung, K.-C. Hung, C.-C. Wu, L. Lo, and K.-C. Lu, "Insulin resistance in patients with chronic kidney disease," Journal of Biomedicine & Biotechnology, 2012.

[5] T. A. Ikizler, N. J. Cano, H. Franch et al., "Prevention and treatment of protein energy wasting in chronic kidney disease patients: A consensus statement by the International Society of
Renal Nutrition and Metabolism,” *Kidney International*, vol. 84, no. 6, pp. 1096–1107, 2013.

[6] K. M. Majchrzak, L. B. Pupim, K. Chen et al., “Physical activity patterns in chronic hemodialysis patients: comparison of dialysis and nondialysis days,” *Journal of Renal Nutrition*, vol. 15, no. 2, pp. 217–224, 2005.

[7] H. Nishiwaki, T. Hasegawa, M. Shintji et al., “Practice pattern of physician’s directions of exercise restriction in patients with chronic kidney disease: results from the Chronic Kidney Disease Japan Cohort study,” *Clinical and Experimental Nephrology*, vol. 22, no. 5, pp. 1108–1115, 2018.

[8] K. Hiraki, T. Yasuda, C. Hotta et al., “Decreased physical function in pre-dialysis patients with chronic kidney disease,” *Clinical and Experimental Nephrology*, vol. 17, no. 2, pp. 225–231, 2013.

[9] E. Sterky and B. G. Stegmayr, “Elderly patients on haemodialysis have 50% less functional capacity than gender- and age-matched healthy subjects,” *Scandinavian Journal of Urology*, vol. 39, no. 5, pp. 423–430, 2005.

[10] U. V. Kharlamova and O. E. Illyicheva, “Effect of homocysteine on left ventricular structural and functional parameters in patients on programmed hemodialysis,” *Terapevticheskii Arkhiv*, vol. 85, no. 3, pp. 90–93, 2013.

[11] M. Sagheb, M. Ostovan, Z. Sohrabi, E. Atabati, G. Raisjilai, and J. Roozbeh, “Hyperhomocysteinemia and cardiovascular risks in hemodialysis patients,” *Saudi Journal of Kidney Diseases and Transplantation*, vol. 21, no. 5, pp. 863–866, 2010.

[12] K. M. A. Swart, N. M. Van Schoor, M. W. Heymans, L. A. Schaap, M. Den Heijer, and P. Lips, “Elevated homocysteine levels are associated with low muscle strength and functional limitations in older persons,” *The Journal of Nutrition, Health & Aging*, vol. 17, no. 6, pp. 578–584, 2013.

[13] K. M. A. Swart, A. W. Enneman, I. P. van Wijngaarden et al., “Homocysteine and the methylenetetrahydrofolate reductase 677C–>T polymorphism in relation to muscle mass and strength, physical performance and postural sway,” *European Journal of Clinical Nutrition*, vol. 67, no. 7, pp. 743–748, 2013.

[14] S. Veeranki and S. C. Tyagi, “Defective homocysteine metabolism: Potential implications for skeletal muscle malfunction,” *International Journal of Molecular Sciences*, vol. 14, no. 7, pp. 15074–15091, 2013.

[15] H.-K. Kuo, K.-C. Liao, S. G. Leveille et al., “Relationship of homocysteine levels to quadriiceps strength, gait speed, and late-life disability in older adults,” *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, vol. 62, no. 4, pp. 434–439, 2007.

[16] T.-P. Ng, K. C. Y. Aung, L. Feng, S. C. Scherer, and K. B. Yap, “Homocysteine, folate, vitamin B-12, and physical function in older adults: Cross-sectional findings from the Singapore longitudinal ageing study,” *American Journal of Clinical Nutrition*, vol. 96, no. 6, pp. 1362–1368, 2012.

[17] Y. M. Liou, C. J. C. Jwo, K. G. Yao, L.-C. Chiang, and L.-H. Huang, “Selection of appropriate Chinese terms to represent intensity and types of physical activity terms for use in the Taiwan version of IPAQ,” *Journal of Nursing Research*, vol. 16, no. 4, pp. 252–263, 2008.

[18] T. Wong, Y. Chen, P. Wu et al., “Ratio of dietary n-6/n-3 polyunsaturated fatty acids independently related to muscle mass decline in hemodialysis patients,” *PLoS ONE*, vol. 10, no. 10, p. e0140402, 2015.

[19] M. F. Crutchlow, B. Robinson, B. Pappachen et al., “Validation of steady-state insulin sensitivity indices in chronic kidney disease,” *Diabetes Care*, vol. 30, no. 7, pp. 1813–1818, 2007.

[20] K/DOQI Workgroup, “K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure,” *American Journal of Kidney Diseases*, vol. 35, no. 6, pp. SI–S140, 2000.

[21] S. Barbat-Artigas, Y. Rolland, M. Zamboni, and M. Aubertin-Leheudre, “How to assess functional status: A new muscle quality index,” *The Journal of Nutrition, Health & Aging*, vol. 16, no. 1, pp. 67–77, 2012.

[22] M. L. Vidoni, K. Pettee Gabriel, S. T. Luo, E. M. Simonsick, and R. S. Day, “Relationship between homocysteine and muscle strength decline: the Baltimore longitudinal study of aging,” *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, vol. 73, no. 4, pp. 546–551, 2018.

[23] S. Ohkawa, M. Odamaki, N. Ikegaya, I. Hibi, K. Miyaji, and H. Kumagai, “Association of age with muscle mass, fat mass and fat distribution in non-diabetic haemodialysis patients,” *Nephrology Dialysis Transplantation*, vol. 20, no. 5, pp. 945–951, 2005.

[24] H. Jakubowski, “Homocysteine thiolactone: Metabolic origin and protein homocysteinylation in humans,” *Journal of Nutrition*, vol. 130, no. 5, pp. 377S–381S, 2000.

[25] A. F. Perna, E. Satta, F. Acanfora, C. Lombardi, D. Ingrosso, and N. G. De Santo, “Increased plasma protein homocysteinylation in hemodialysis patients,” *Kidney International*, vol. 69, no. 5, pp. 869–876, 2006.

[26] D. Xu, R. Neville, and T. Finkel, “Homocysteine accelerates endothelial cell senescence,” *FEBS Letters*, vol. 470, no. 1, pp. 20–24, 2000.

[27] Y. Morishita, K. Kubo, Y. Haga et al., “Skeletal Muscle Loss Is Negatively Associated With Single-Pool Kt/V and Dialysis Duration in Hemodialysis Patients,” *Therapeutic Apheresis and Dialysis*, vol. 18, no. 6, pp. 612–617, 2014.

[28] L. H. Oterdoom, R. T. Gansveevoet, J. P. Schouten, P. E. de Jong, R. O. B. Gans, and S. J. L. Bakker, “Urinary creatinine excretion, an indirect measure of muscle mass, is an independent predictor of cardiovascular disease and mortality in the general population,” *Atherosclerosis*, vol. 207, no. 2, pp. 534–540, 2009.

[29] B. Cheema, H. Abas, B. Smith et al., “Investigation of skeletal muscle quantity and quality in end-stage renal disease,” *Nephrology*, vol. 15, no. 4, pp. 454–463, 2010.

[30] G. A. Kaysen, F. Zhu, S. Sarkar et al., “Estimation of total-body and limb muscle mass in hemodialysis patients by using multifrequency bioimpedance spectroscopy,” *American Journal of Clinical Nutrition*, vol. 82, no. 5, pp. 988–995, 2005.