Research Article

Associations of Small Fiber Neuropathy with Geriatric Nutritional Risk Index and Arterial Stiffness in Hemodialysis

Mei-Chuan Kuo 1,2, Jiun-Chi Huang 1,3,4,5, Pei-Yu Wu 3,5, Hsiu-Chin Mai 6, Szu-Chia Chen 1,3,4,5, Yi-Wen Chiu 1,2, Jer-Ming Chang 1,2, and Hung-Chun Chen 1,2

1 Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan
2 Faculty of Renal Care, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
3 Department of Internal Medicine, Kaohsiung Municipal SiaoGang Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan
4 Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
5 Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
6 Department of Nursing, Kaohsiung Municipal SiaoGang Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

Correspondence should be addressed to Jiun-Chi Huang; karajan77@gmail.com and Jer-Ming Chang; jemich@kmu.edu.tw

Received 27 October 2019; Accepted 28 April 2020; Published 19 May 2020

Academic Editor: Alexandra Scholze

Copyright © 2020 Mei-Chuan Kuo et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Peripheral neuropathy is a common neurological complication in uremic patients, and quantitative sensory testing (QST) is effective for diagnosis of small fiber neuropathy. Malnutrition and arterial stiffness are prevalent in patients undergoing hemodialysis (HD). The associations of small fiber neuropathy with nutritional status and arterial stiffness remain uncertain in maintenance HD patients. Methods. A total of 152 HD patients were included. Geriatric nutritional risk index (GNRI), an indicator of nutritional status, was calculated by serum albumin and actual and ideal body weight. Arterial stiffness was defined as brachial-ankle pulse wave velocity (baPWV) > 1400 cm/s. Small fiber neuropathy was assessed by an abnormal QST threshold of cold and warm sensation in patients’ hands or feet. Multivariate forward logistic regression analysis was performed to examine the associations among abnormal QST threshold, GNRI, and arterial stiffness. Results. baPWV and prevalence of abnormal QST threshold were significantly higher in diabetic patients. Multivariable logistic analyses revealed that older age (OR, 1.081; 95% CI, 1.026–1.139; \( p = 0.003 \)) and male gender (OR, 4.450; 95% CI, 1.250–15.836; \( p = 0.021 \)) were associated with abnormal warm threshold of hands. Furthermore, diabetes (OR, 3.966; 95% CI, 1.351–11.819; \( p = 0.012 \)) and lower GNRI (per 1 unit increase, OR, 0.935, 95% CI, 0.887–0.985, \( p = 0.012 \)) were associated with abnormal cold threshold of feet. Arterial stiffness (OR, 5.479, 95% CI, 1.132–22.870, \( p = 0.020 \)) and higher calcium-phosphorus product (OR, 1.071, 95% CI, 1.013–1.081, \( p = 0.015 \)) were associated with abnormal warm threshold of feet. Conclusions. Lower GNRI and arterial stiffness were significantly associated with small fiber neuropathy in patients undergoing HD. Malnutrition risk and vascular factors might play important roles in small fiber neuropathy among patients undergoing HD.

1. Introduction

Patients with end-stage renal disease (ESRD) often suffer from neurological complications, thereby contributing to morbidity and mortality [1–3]. Peripheral neuropathy is the most commonly reported neurological complication associated with chronic renal failure [4], with an incidence rate of more than 60% in patients on dialysis. It can affect sensory, motor, and cranial nerves and is characterized by axonal degeneration and demyelination [5]. Furthermore, uremic neuropathy is typically a distal, symmetric, and predominantly axonal type which affects the legs more than the arms [1, 2]. Lindblom and Tegner reported abnormalities in thermal sensation in 30% of patients with ESRD and concluded that small fiber neuropathy may be a distinct entity [6]. Small nerve fibers were traditionally thought to be invisible as they could not be detected in routine nerve conduction studies, leading to underestimation of small fiber neuropathy and...
physicians’ overlook. Skin biopsy for detecting altered inter-
epidermal nerve fiber density remains the gold standard in
diagnosing small fiber neuropathy, but it is still an invasive
approach [7, 8]. Quantitative sensory testing (QST) is a non-
invasive, psychophysical examination of small fiber functions
through assessment of thresholds to thermal and cold signals
[9]. Furthermore, QST has been shown to be useful in diag-
nosis of small fiber neuropathy [10–12], with a reported di-
agnostic sensitivity ranging from 60% to 85% [13–16].

Small fiber neuropathy is characterized by the presence
of abnormal thermal thresholds in the distal limbs, linking
to decreased quality of life in affected individuals, and is
often neglected in clinical practice because of a paucity of
readily available diagnostic methods [17]. Nutritional
aspects and microvascular dysregulation were previously
advocated as the potential causes of small fiber neuropathy
[11, 18, 19]. In particular, arterial stiffness and malnutrition
are common among patients undergoing hemodialysis (HD)
and play their vital roles in prognostic significance [20–24].
The geriatric nutritional risk index (GNRI) is a useful and
accurate indicator for the assessment of nutritional status
in maintenance HD patients [25, 26]. Several studies have
suggested that GNRI and arterial stiffness are associated with
cognitive impairment, frailty, and inflammation [27–31].
However, the relationships of malnutrition risk and arterial
stiffness with small fiber neuropathy remain not clearly
understood and have never been investigated. Therefore,
the aim of this study is to examine the associations of nutri-
tional risk and arterial stiffness, assessed by GNRI and
brachial-ankle pulse wave velocity (baPWV), with small
fiber neuropathy in patients receiving HD.

2. Materials and Methods

2.1. Study Patients. In the present study, we enrolled all
patients (n = 170) undergoing thrice weekly maintenance
HD treatment for more than 3 months at a dialysis unit of
a regional hospital in Taiwan in April 2014. Patients who
refused to undergo QST or baPWV examinations (n = 15)
and had bilateral below knee amputations (n = 3) were
excluded from the study. This study was approved by the
Institutional Review Board of Kaohsiung Medical University
Hospital. All study participants provided their written
informed consent. The methods were carried out in accor-
dance with the approved guidelines.

2.2. Measurement of QST for Assessment of Small Fiber
Neuropathy. A Medoc TSA-II Neurosensory Analyzer was
used for the QST [32]. The patients were seated comfortably
in a quiet room with an ambient temperature of 24–25°C.
The testing areas of the QST were the dorsolateral border
of the feet for the lower limbs and the hypothenar eminence
of the thumbs for the upper limbs. Cold and warm sensations
were then tested after the test had been carefully explained
to the patients, including the need to react promptly to any
change in temperature. The test was performed by placing a
30 mm × 30 mm thermode on the testing areas of the skin.
Four threshold temperature values for each testing area
were recorded and averaged for analysis. If the sensation was iden-
tified incorrectly, this was also recorded. Based on values
obtained from a control population, the mean threshold
temperature ± 2 standard deviation (SD) for each testing area
was considered as the upper (or lower) limit of normal. Small
fiber neuropathy was defined as the abnormalities of cold or
warm threshold in one of the testing areas (either hands or
feet) using QST [9, 11].

2.3. Measurement of baPWV for Assessment of Arterial
Stiffness. The baPWV was measured 10–30 minutes before
HD session using an automatic waveform analyzer (VP-
1000, Colin, Komaki, Japan) for each patient. The baPWV
value was calculated as the transmission distance divided by
the transmission time. The highest of bilateral baPWV values
was used as the representative value for analysis. Arterial
stiffness was defined as baPWV > 1400 cm/s [33].

2.4. Calculation of the GNRI. The GNRI was calculated
according to baseline serum albumin level and body weight
as follows: GNRI = [14.89 × albumin (g/dL)] + [41.7 × (body
weight/ideal body weight)] [34]. The ideal body weight in
the present study was defined as the value calculated from
the height and a body mass index (BMI) of 22 [35]. If the
patient’s body weight was greater than the ideal body weight,
body weight/ideal body weight was set to 1 [27].

2.5. Demographic, Medical, and Laboratory Data. Each
patient’s overnight fasting blood samples were obtained
within 1 month of study enrollment for laboratory tests using
an autoanalyzer (Roche Diagnostics GmbH, D-68298 Mann-
heim COBAS Integra 400). Kt/V was evaluated based on the
Daugirdas formula to assess the efficiency of HD treatment
[36]. Demographic and medical information, including age,
gender, smoking history (ever vs. never), and comorbidity
conditions, were obtained from study patients’ medical records
and interviews.

2.6. The Primary and Secondary Outcomes. The primary
outcome of this study was to elucidate the effects of diabetes
and arterial stiffness on thermal threshold in QST among HD
patients. The secondary outcome was to identify the determi-
nants of abnormal QST threshold as well as the roles of nutri-
tional risk and arterial stiffness in small fiber neuropathy.

2.7. Statistical Analysis. Statistical analysis was performed
using SPSS for Windows version 19.0 (SPSS Inc., Chicago,
IL, USA). Data are expressed as percentage, mean ± SD, or
median (25 th–75 th percentile) for the duration of dialysis
and serum triglycerides. Between-group differences were
analyzed using the chi-square test for categorical variables
and the independent t-test for continuous variables. Multi-
variate forward logistic regression analysis was performed
to identify the factors associated with abnormal QST thresh-
old, with adjustment for age, gender, duration of dialysis,
smoking history, diabetes mellitus, baPWV > 1400 cm/s,
GNRI, hemoglobin, calcium-phosphorus (Ca × P) product,
and Kt/V. A difference was considered significant for the
p value < 0.05.
3. Results

A total of 152 patients (78 men and 74 women, mean age 60.7 ± 10.7 years) were included in the present study. The mean baPWV was 1925 ± 526 cm/s, and the mean GNRI was 103.4 ± 9.0.

3.1. Comparison of QST Threshold between Diabetic and Nondiabetic Patients. As diabetes mellitus (DM) is one of the major risk factors of neurologic complications, the comparison of baseline characteristics and thermal threshold on QST between diabetic and nondiabetic patients is summarized in Table 1. Diabetic patients were more likely to be older in age and had shorter duration of dialysis, higher baPWV, lower cold threshold, and higher warm threshold among the QST of both hands and feet. Diabetic patients significantly had higher prevalence of abnormal cold and warm threshold on QST, except for warm threshold of feet, when compared to nondiabetic patients.

3.2. Comparison of QST Threshold between Patients with baPWV ≤ 1400 cm/s and >1400 cm/s. Among QST results, patients with baPWV > 1400 cm/s had significantly lower cold threshold of the right foot (p = 0.005) and significantly higher warm threshold of the right (p = 0.002) and left feet (p = 0.049) in comparison to QST in patients with baPWV ≤ 1400 cm/s (Figure 1).

3.3. Determinants of Abnormal QST Threshold. The study patients were then stratified into two groups according to normal or abnormal QST threshold. The comparison of baseline characteristics between patients with normal or abnormal QST threshold of the hands is shown in Table 2. The prevalence of abnormal cold and warm sensation in the hands was 73.0% and 88.8%, respectively. Compared to patients with normal cold sensation, those with abnormal cold sensation in the hands had older age, shorter duration of dialysis, higher prevalence of DM, and higher baPWV. Moreover, compared to patients with normal warm sensation, patients with abnormal warm sensation in the hands had higher prevalence of male gender.

The comparison of baseline characteristics between patients with normal or abnormal QST threshold of the feet was demonstrated in Table 3. The prevalence of abnormal cold and warm sensation in the feet was 84.9% and 89.5%, respectively. Compared to patients with normal cold sensation, those with abnormal cold sensation in the feet had older age, higher prevalence of DM, and higher baPWV. Furthermore, compared to patients with normal warm sensation, patients with abnormal warm sensation in the feet had higher prevalence of male gender.

Table 4 shows the determinants of abnormal QST threshold in our study patients using multivariate forward logistic regression analysis. In the multivariate analysis (adjusted for age, gender, duration of dialysis, smoking history, DM, baPWV > 1400 cm/s, GNRI, hemoglobin, Ca × P product, and Kt/V), old age (per 1 year; odds ratio (OR), 1.083; 95% confidence interval (CI), 1.042 to 1.126; p < 0.001) was independently associated with abnormal cold threshold of the hands. Old age (per 1 year; OR, 1.081; 95% CI 1.026 to 1.139; p = 0.003) and male gender (OR, 4.450; 95% CI, 0.001).
Right foot CS (<i>p = 0.005</i>)
Right foot WS (<i>p = 0.002</i>)
Left foot CS (<i>p = NS</i>)
Left foot WS (<i>p = 0.049</i>)
Left/t hand CS (<i>p = NS</i>)
Left/t hand WS (<i>p = 0.049</i>)

Figure 1: Comparison of QST threshold between patients with baPWV > 1400 cm/s and ≤1400 cm/s. CS: cold threshold; WS: warm threshold.

Table 2: Comparison of baseline characteristics between patients with normal or abnormal QST threshold of the hands.

| Parameters                        | Normal (n = 41) | Cold threshold (n = 111) | p   | Warm threshold (n = 17) | Abnormal (n = 135) | p   |
|-----------------------------------|----------------|--------------------------|-----|-------------------------|---------------------|-----|
| Age (year)                        | 54.8 ± 10.8    | 62.9 ± 9.8               | <0.001 | 53.7 ± 8.3              | 61.6 ± 10.7         | 0.004 |
| Male gender (%)                   | 48.8           | 52.3                     | 0.704 | 23.5                    | 54.8                | 0.015 |
| Duration of dialysis (year)       | 8.8 (4.7–13.3) | 6.1 (2.0–10.3)           | 0.023 | 10.7 (5.1–13.3)         | 6.3 (2.3–10.4)      | 0.066 |
| Smoking history (%)               | 34.1           | 39.6                     | 0.536 | 17.6                    | 40.7                | 0.109 |
| Diabetes mellitus (%)             | 31.7           | 53.2                     | 0.019 | 17.6                    | 51.1                | 0.009 |
| Coronary artery disease (%)       | 2.4            | 11.7                     | 0.114 | 0                       | 10.4                | 0.369 |
| baPWV (cm/s)                      | 1766 ± 406     | 1982 ± 553               | 0.027 | 1672 ± 367              | 1956 ± 535          | 0.041 |
| Body mass index (kg/m²)           | 24.4 ± 4.6     | 23.9 ± 3.5               | 0.495 | 23.6 ± 3.6              | 24.1 ± 3.9          | 0.603 |
| GNRI                              | 104.9 ± 11.0   | 102.8 ± 8.1              | 0.217 | 101.9 ± 9.9             | 103.6 ± 8.9         | 0.480 |
| Laboratory parameters             |                |                          |      |                         |                     |     |
| Albumin (g/dL)                    | 3.9 ± 0.4      | 3.9 ± 0.3                | 0.155 | 3.8 ± 0.4               | 3.9 ± 0.3           | 0.552 |
| Triglycerides (mg/dL)             | 125 (94–273)   | 139 (91–217)             | 0.340 | 149 (90–249)            | 131 (91–219)        | 0.707 |
| Total cholesterol (mg/dL)         | 185.3 ± 34.6   | 179.7 ± 41.1             | 0.439 | 190.9 ± 40.0            | 180.0 ± 39.4        | 0.284 |
| Hemoglobin (g/dL)                 | 10.7 ± 1.0     | 10.6 ± 1.3               | 0.828 | 10.5 ± 1.3              | 10.7 ± 1.2          | 0.685 |
| Total calcium (mg/dL)             | 9.5 ± 1.1      | 9.3 ± 1.0                | 0.362 | 9.0 ± 1.2               | 9.4 ± 1.0           | 0.241 |
| Phosphorus (mg/L)                 | 4.6 ± 1.2      | 4.5 ± 1.0                | 0.846 | 4.7 ± 1.6               | 4.5 ± 1.0           | 0.490 |
| Ca × P product (mg²/dL²)          | 43.2 ± 11.7    | 42.2 ± 11.1              | 0.624 | 43.3 ± 15.4             | 42.4 ± 10.7         | 0.755 |
| Kt/V (Daugirdas)                  | 1.6 ± 0.3      | 1.6 ± 0.3                | 0.695 | 1.7 ± 0.3               | 1.6 ± 0.3           | 0.070 |

Abbreviations: baPWV: brachial-ankle pulse wave velocity; GNRI: geriatric nutritional risk index; Ca × P product: calcium-phosphorus product.
Table 3: Comparison of baseline characteristics between patients with normal or abnormal QST threshold of the feet.

| Parameters                        | Normal (n = 23) | Abnormal (n = 129) | p     | Normal (n = 16) | Abnormal (n = 136) | p     |
|-----------------------------------|-----------------|--------------------|-------|-----------------|--------------------|-------|
| Age (year)                        | 55.6 ± 10.5     | 61.7 ± 10.5        | 0.011 | 56.6 ± 12.7     | 61.2 ± 10.4        | 0.100 |
| Male gender (%)                   | 65.2            | 48.8               | 0.148 | 23.5            | 54.8               | 0.242 |
| Duration of dialysis (year)       | 9.0 (3.4–11.8)  | 6.5 (2.3–10.8)     | 0.614 | 9.9 (2.9–12.6)  | 6.4 (2.4–10.6)     | 0.218 |
| Smoking history (%)               | 47.8            | 36.4               | 0.300 | 31.3            | 39.0               | 0.548 |
| Diabetes mellitus (%)             | 21.7            | 51.9               | 0.008 | 25.0            | 50.0               | 0.068 |
| Coronary artery disease (%)       | 0               | 10.9               | 0.130 | 0               | 10.3               | 0.364 |
| baPWV (cm/s)                      | 1691 ± 352      | 1966 ± 541         | 0.023 | 1876 ± 711     | 1931 ± 502         | 0.694 |
| Body mass index (kg/m²)           | 25.9 ± 6.1      | 23.7 ± 3.2         | 0.011 | 24.3 ± 3.5     | 24.0 ± 3.9         | 0.797 |
| GNRI                              | 107.9 ± 12.6    | 102.6 ± 7.9        | 0.008 | 103.7 ± 9.3    | 103.3 ± 9.0        | 0.873 |

Laboratory parameters

| Albumin (g/dL)                    | 3.9 ± 0.3       | 3.9 ± 0.3          | 0.242 | 3.9 ± 0.3      | 3.9 ± 0.3          | 0.919 |
| Triglycerides (mg/dL)             | 125 (87–304)    | 139 (92–219)       | 0.309 | 108.5 (88–229) | 143 (91.3–219)     | 0.928 |
| Total cholesterol (mg/dL)         | 182.4 ± 27.3    | 181.1 ± 41.3       | 0.885 | 171.7 ± 34.8   | 182.4 ± 39.9       | 0.307 |
| Hemoglobin (g/dL)                 | 10.9 ± 1.2      | 10.6 ± 1.2         | 0.208 | 10.9 ± 1.5     | 10.6 ± 1.2         | 0.435 |
| Total calcium (mg/dL)             | 9.3 ± 1.1       | 9.3 ± 1.0          | 0.844 | 9.1 ± 1.1      | 9.3 ± 1.0          | 0.371 |
| Phosphorus (mg/dL)                | 4.7 ± 1.4       | 4.5 ± 1.0          | 0.625 | 4.1 ± 1.0      | 4.6 ± 1.1          | 0.058 |
| Ca × P product (mg²/dL²)          | 43.1 ± 13.0     | 42.3 ± 11.0        | 0.753 | 37.0 ± 9.6     | 43.1 ± 11.3        | 0.041 |
| Kt/V (Daugirdas)                  | 1.6 ± 0.3       | 1.6 ± 0.3          | 0.557 | 1.6 ± 0.3      | 1.6 ± 0.3          | 0.857 |

Abbreviations: baPWV: brachial-ankle pulse wave velocity; GNRI: geriatric nutritional risk index; Ca × P product: calcium-phosphorus product.

Table 4: Determinants of abnormal QST threshold using multivariate forward logistic regression analysis.

| Parameters                                      | OR (95% CI) | Multivariate (forward) | p  |
|------------------------------------------------|-------------|------------------------|----|
| Abnormal cold threshold of the hands            |             |                        |    |
| Age (per 1 year)                                | 1.083 (1.042–1.126) | <0.001                |    |
| Abnormal warm threshold of the hands             |             |                        |    |
| Age (per 1 year)                                | 1.081 (1.026–1.139) | 0.003                  |    |
| Male gender (vs. female)                        | 4.450 (1.250–15.836) | 0.021                  |    |
| Abnormal cold threshold of the feet              |             |                        |    |
| Diabetes mellitus                               | 3.996 (1.351–11.819) | 0.012                  |    |
| GNRI (per 1 unit)                                | 0.935 (0.887–0.985) | 0.012                  |    |
| Abnormal warm threshold of the feet              |             |                        |    |
| baPWV > 1400 cm/s                               | 5.479 (1.312–22.870) | 0.020                  |    |
| Ca × P product (per 1 mg²/dL²)                   | 1.071 (1.013–1.132) | 0.015                  |    |

Values expressed as odds ratio (OR) and 95% confidence interval (CI). Adjusted for age, gender, duration of dialysis, smoking history, diabetes mellitus, baPWV > 1400 cm/s, GNRI, hemoglobin, Ca × P product, and Kt/V.

1.250 to 15.836; p = 0.021) were significantly associated with abnormal warm threshold of the hands. Furthermore, DM (OR, 3.996; 95% CI, 1.351 to 11.819; p = 0.012) and low GNRI (per 1 unit; OR, 0.935; 95% CI, 0.887 to 0.985; p = 0.012) were significantly associated with abnormal cold threshold of the feet. Finally, baPWV > 1400 cm/s (OR, 5.479; 95% CI, 1.312 to 22.870; p = 0.020) and high Ca × P product (per 1 mg²/dL²; OR, 1.071; 95% CI, 1.013 to 1.132; p = 0.015) were independently associated with abnormal warm threshold of the feet.

4. Discussion

In this study, we found that the prevalence of abnormal QST threshold and baPWV were significantly higher in diabetic HD patients. Furthermore, we examined factors associated with small fiber neuropathy. In multivariate analysis, older age was associated with abnormal cold and warm threshold of the hands; DM and lower GNRI were significantly associated with abnormal cold threshold of the feet, whereas baPWV > 1400 cm/s and higher Ca × P product were
significantly associated with abnormal warm threshold of the feet in HD patients.

The first important finding of this study is that patients undergoing HD with baPWV > 1400 cm/s had significant higher warm threshold and lower cold threshold in the feet on QST. In addition, patients with abnormal thermal threshold in the hands and abnormal cold threshold in the feet had significantly higher baPWV level than those with normal QST threshold. This suggests that arterial stiffness might be an important factor contributed to abnormalities of small fiber function in HD patients. Our findings are in line with previous studies showing an independent association between pulse wave velocity and peripheral neuropathy in patients with DM [37–39]. Elevated baPWV evinces structural changes of the arterial wall, medial smooth muscle calcification, and breaks in elastic fibers in ESRD [40]. Increased arterial stiffness might lead to damage of the microcirculation, such as vasa nervorum, through increasing the transmission of detrimental pulsatile pressure waves [41]. Furthermore, emerging evidence suggests independent association of arterial stiffness with galectin-3 among HD patients [42]. Galectin-3 has been recently considered as a key molecule in the neural functions and nerve regeneration, and inhibition of galectin-3 could attenuate neuropathic pain after peripheral nerve injury [43, 44]. Our results may bring additional insight into the role of arterial stiffness in small fiber neuropathy in maintenance HD patients.

Another important finding of this study is a low GNRI was associated with an abnormal QST threshold. The pathogenesis of small fiber neuropathy in patients with ESRD is complex and remains not fully understood. Malnutrition is associated with increased level of tumor necrosis factor-α (TNF-α) in patients undergoing dialysis [45]. TNF-α has been shown to act a central role in the development of inflammatory demyelination [46]. Moreover, uremic toxins, combined with oxidative stress-related free radical activity and hyperkalemia, have been reported to cause motor, sensory, and autonomic nerve damage, making these as potentially causative factors in the development of uremic neuropathy [4]. Therefore, malnutrition risk might be involved in the pathogenesis of small fiber neuropathy in this patient population.

Abnormalities of homeostasis among calcium, phosphate, and parathyroid hormone are quite common in patients with ESRD, and increased Ca × P product promotes vascular calcification [47]. Recent studies demonstrated that impaired intracellular calcium balance is implicated in the development of diabetic polyneuropathy [48], while calcimimetic can deter the progression of neuropathy by ameliorating inflammation, apoptosis, and autophagy through increased expression of the calcium-sensing receptors [49]. In this study, we found that a higher level of Ca × P product was associated with an abnormal QST threshold, suggesting that vascular calcification and homeostasis of calcium and phosphate may have their roles mediating functional abnormalities in small nerve fibers in patients undergoing HD.

Maintenance HD patients often have certain neurological complications, including small fiber neuropathy, which can be linked to frailty and decreased quality of life. To the best of our knowledge, this is the first study to investigate the associations of GNRI and baPWV with small fiber neuropathy in HD patients. Nonetheless, there are several limitations in the present study. First, the number of study patients is relatively small. Second, this study was cross-sectional in design; therefore, the causal relationship and long-term clinical outcomes could not be confirmed. Further prospective studies and more participants are warranted to examine the impacts of nutrition and vascular factors as well as their involving roles in small fiber neuropathy. Third, confirmation of small fiber neuropathy using skin biopsy was lacking. Although skin biopsy is able to detect altered interepidermal nerve fiber density, it remains an invasive approach.

5. Conclusion

Our results demonstrated that small fiber neuropathy was associated with a lower GNRI and baPWV > 1400 cm/s. Furthermore, older age, DM, and a higher level of Ca × P product were associated with an abnormal QST threshold. Physicians should devote more attention toward maintenance HD patients with malnutrition risk and arterial stiffness to early diagnose small fiber neuropathy, prevent serious neurological complications, and improve quality of life.

Data Availability

The data supporting the findings of the present study are available within the article or are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors’ Contributions

The research idea and study design were from M.C.K., J.C.H., and J.M.C.; data acquisition was performed by P.Y.W., H.C.M., J.C.H., and S.C.C.; data analysis/interpretation was performed by M.C.K., J.C.H., P.Y.W., S.C.C., and Y.W.C.; statistical analysis was performed by J.C.H., S.C.C., J.M.C., and H.C.C.; supervision or mentorship was done by J.C.H., J.M.C., and H.C.C. All authors contributed important intellectual content during manuscript drafting or revision and approved the final version of the manuscript.

Acknowledgments

The research presented in this article is supported by the grants from Kaohsiung Municipal Siaogang Hospital (kmhk-102-003), Kaohsiung Medical University, Kaohsiung, Taiwan.

References

[1] B. Jabbari and N. D. Vaziri, “The nature, consequences, and management of neurological disorders in chronic kidney
disease,” *Hemodialysis International*, vol. 22, no. 2, pp. 150–160, 2018.

[2] A. V. Krishnan and M. C. Kiernan, “Neurological complications of chronic kidney disease,” *Nature Reviews Neurology*, vol. 5, no. 10, pp. 542–551, 2009.

[3] M. Stosovic, A. Nikolic, M. Stanojevic et al., “Nerve Conduction Studies and Prediction of Mortality in Hemodialysis Patients,” *Renal Failure*, vol. 30, no. 7, pp. 695–699, 2008.

[4] A. V. Krishnan and M. C. Kiernan, “Uremic neuropathy: clinical features and new pathophysiological insights,” *Muscle & Nerve*, vol. 35, no. 3, pp. 273–290, 2007.

[5] A. V. Krishnan, B. A. Pussell, and M. C. Kiernan, “Neuromuscular disease in the dialysis patient: an update for the nephrologist,” *Seminars in Dialysis*, vol. 22, no. 3, pp. 267–278, 2009.

[6] U. Lindblom and R. Tegner, “Thermal sensitivity in uremic neuropathy,” *Acta Neurologica Scandinavica*, vol. 71, no. 4, pp. 290–294, 1985.

[7] T. Mainka, C. Maier, and E. K. Enax-Krumova, “Neuropathic pain assessment,” *Current Opinion in Anaesthesiology*, vol. 28, no. 5, pp. 537–545, 2015.

[8] G. Lauria and R. Lombardi, “Small fiber neuropathy: is skin biopsy the holy grail?,” *Current Diabetes Reports*, vol. 12, no. 4, pp. 384–392, 2012.

[9] A. C. Y. Chan and E. P. Wilder-Smith, “Small fiber neuropathy: Getting bigger!,” *Muscle & Nerve*, vol. 53, no. 5, pp. 671–682, 2016.

[10] J. G. Hoeijmakers, C. G. Faber, G. Lauria, I. S. Merkies, and S. G. Waxman, “Small-fibre-neuropathies-advances in diagnosis, pathophysiology and management,” *Nature Reviews Neurology*, vol. 8, no. 7, pp. 369–379, 2012.

[11] G. Devigili, V. Tugnoli, P. Penza et al., “The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology,” *Brain*, vol. 131, Part 7, pp. 1912–1925, 2008.

[12] G. Shukla, M. Bhatia, and M. Behari, “Quantitative thermal sensory testing - value of testing for both cold and warm sensation detection in evaluation of small fiber neuropathy,” *Clinical Neurology and Neurosurgery*, vol. 107, no. 6, pp. 486–490, 2005.

[13] M. Voortman, D. Fritz, O. J. M. Vogels et al., “Small fiber neuropathy: a disabling and underrecognized syndrome,” *Current Opinion in Pulmonary Medicine*, vol. 23, no. 5, pp. 447–457, 2017.

[14] P. Hansson, M. Backonja, and D. Bouhassira, “Usefulness and limitations of quantitative sensory testing: clinical and research application in neuropathic pain states,” *Pain*, vol. 129, no. 3, pp. 256–259, 2007.

[15] M. M. Backonja, N. Attal, R. Baron et al., “Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus,” *Pain*, vol. 154, no. 9, pp. 1807–1819, 2013.

[16] M. E. Shy, E. M. Frohman, Y. T. So et al., “Quantitative sensory testing: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology,” *Neurology*, vol. 60, no. 6, pp. 898–904, 2003.

[17] M. Bakkers, C. G. Faber, J. G. Hoeijmakers, G. Lauria, and I. S. Merkies, “Small fibers, large impact: quality of life in small-fiber neuropathy,” *Muscle & Nerve*, vol. 49, no. 3, pp. 329–336, 2014.

[18] S. Khan and L. Zhou, “Characterization of non-length-dependent small-fiber sensory neuropathy,” *Muscle & Nerve*, vol. 45, no. 1, pp. 86–91, 2012.

[19] G. Lauria, I. S. Merkies, and C. G. Faber, “Small fibre neuropathy,” *Current Opinion in Neurology*, vol. 25, no. 5, pp. 542–549, 2012.

[20] J. Chen, X. Qin, Y. Li et al., “Comparison of three nutritional screening tools for predicting mortality in maintenance hemodialysis patients,” *Nutrition*, vol. 67-68, article 110532, 2019.

[21] L. Koppe, D. Fouque, and K. Kalantar-Zadeh, “Kidney cachexia or protein-energy wasting in chronic kidney disease: facts and numbers,” *Journal of Cachexia, Sarcopenia and Muscle*, vol. 10, no. 3, pp. 479–484, 2019.

[22] S. C. Chen, J. C. Huang, H. M. Su et al., “Prognostic cardiovascular markers in chronic kidney disease,” *Kidney and Blood Pressure Research*, vol. 43, no. 4, pp. 1388–1407, 2018.

[23] P. Georgianos, P. Sarafidis, and A. Lasaridis, “Arterial stiffness: a novel cardiovascular risk factor in kidney disease patients,” *Current Vascular Pharmacology*, vol. 13, no. 2, pp. 229–238, 2015.

[24] U. Feroze, N. Noori, C. P. Kovesdy et al., “Quality-of-life and mortality in hemodialysis patients: roles of race and nutritional status,” *Clinical Journal of the American Society of Nephrology*, vol. 6, no. 5, pp. 1100–1111, 2011.

[25] I. Kobayashi, E. Ishimura, Y. Kato et al., “Geriatric nutritional risk index, a simplified nutritional screening index, is a significant predictor of mortality in chronic dialysis patients,” *Nephrology Dialysis Transplantation*, vol. 25, no. 10, pp. 3361–3365, 2010.

[26] K. Yamada, R. Furuya, T. Takita et al., “Simplified nutritional screening tools for patients on maintenance hemodialysis,” *The American Journal of Clinical Nutrition*, vol. 87, no. 1, pp. 106–113, 2008.

[27] S. C. Chen, W. S. Chung, P. Y. Wu et al., “Associations among geriatric nutrition risk index, bone mineral density, body composition and handgrip strength in patients receiving hemodialysis,” *Nutrition*, vol. 65, pp. 6–12, 2019.

[28] J. Xiong, M. Yang, Y. Zhang et al., “Association of geriatric nutritional risk index with mortality in hemodialysis patients: a meta-analysis of cohort studies,” *Kidney and Blood Pressure Research*, vol. 43, no. 6, pp. 1878–1889, 2018.

[29] S. Angermann, M. Baumann, S. Wasertheurer et al., “Pulse wave velocity is associated with cognitive impairment in hemodialysis patients,” *Clinical Science*, vol. 131, no. 13, pp. 1483–1493, 2017.

[30] H. Ishii, H. Takahashi, Y. Ito et al., “The association of ankle brachial index, protein-energy wasting, and inflammation status with cardiovascular mortality in patients on chronic hemodialysis,” *Nutrients*, vol. 9, no. 4, p. 416, 2017.

[31] S. C. Chen, M. Y. Lee, J. C. Huang et al., “Platelet to lymphocyte percentage ratio is associated with brachial-ankle pulse wave velocity in hemodialysis,” *Medicine*, vol. 95, no. 6, article e2727, 2016.

[32] D. Yarnitsky, “Quantitative sensory testing,” *Muscle & Nerve*, vol. 20, no. 2, pp. 198–204, 1997.

[33] A. Yamashina, H. Tomiyama, T. Arai et al., “Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk,” *Hypertension Research*, vol. 26, no. 8, pp. 615–622, 2003.

[34] O. Bouillanne, G. Morineau, C. Dupont et al., “Geriatric nutritional risk index: a new index for evaluating at-risk elderly medical patients,” *The American Journal of Clinical Nutrition*, vol. 82, no. 4, pp. 777–783, 2005.
B. Shah, K. Sucher, and C. B. Hollenbeck, “Comparison of ideal body weight equations and published height-weight tables with body mass index tables for healthy adults in the United States,” Nutrition in Clinical Practice, vol. 21, no. 3, pp. 312–319, 2006.

J. T. Daugirdas, T. A. Depner, F. A. Gotch et al., “Comparison of methods to predict equilibrated Kt/V in the HEMO Pilot Study,” Kidney International, vol. 52, no. 5, pp. 1395–1405, 1997.

K. Yeboah, J. A. Agyekum, R. N. A. Owusu Mensah et al., “Arterial stiffness is associated with peripheral sensory neuropathy in diabetes patients in Ghana,” Journal of Diabetes Research, vol. 2018, 8 pages, 2018.

A. Tentolouris, I. Eleftheriadou, P. Grigoropoulou et al., “The association between pulse wave velocity and peripheral neuropathy in patients with type 2 diabetes mellitus,” Journal of Diabetes and its Complications, vol. 31, no. 11, pp. 1624–1629, 2017.

S. Szczyrba, G. M. Kozera, J. Neubauer-Geryk, B. Wolnik, W. M. Nyka, and L. Bieniaszewski, “Diabetic symmetric polyneuropathy is associated with increased aortal stiffening but not cerebral angiopathy in type 1 diabetes,” Journal of Diabetes and its Complications, vol. 29, no. 1, pp. 73–76, 2015.

G. M. London, M. E. Safar, and B. Pannier, “Aortic aging in ESRD: structural, hemodynamic, and mortality implications,” Journal of the American Society of Nephrology, vol. 27, no. 6, pp. 1837–1846, 2016.

J. L. Cavalcante, J. A. Lima, A. Redheuil, and M. H. Al-Mallah, “Aortic stiffness: current understanding and future directions,” Journal of the American College of Cardiology, vol. 57, no. 14, pp. 1511–1522, 2011.

Q. Zhang, K. Yin, M. Zhu et al., “Galectin-3 is associated with arterial stiffness among hemodialysis patients,” Biomarkers in Medicine, vol. 13, no. 6, pp. 437–443, 2019.

Z. Ma, Q. Han, X. Wang, Z. Ai, and Y. Zheng, “Galectin-3 inhibition is associated with neuropathic pain attenuation after peripheral nerve injury,” PLoS One, vol. 11, no. 2, article e0148792, 2016.

K. Mostacada, F. L. Oliveira, D. M. Villa-Verde, and A. M. Martinez, “Lack of galectin-3 improves the functional outcome and tissue sparing by modulating inflammatory response after a compressive spinal cord injury,” Experimental Neurology, vol. 271, pp. 390–400, 2015.

G. Pertosa, G. Grandaliano, L. Gesualdo, and F. P. Schena, “Clinical relevance of cytokine production in hemodialysis,” Kidney International, vol. 58, pp. S104–S111, 2000.

B. C. Kieseier, R. Kiefer, R. Gold, B. Hemmer, H. J. Willison, and H. P. Hartung, “Advances in understanding and treatment of immune-mediated disorders of the peripheral nervous system,” Muscle & Nerve, vol. 30, no. 2, pp. 131–156, 2004.

A. B. Reiss, N. Miyawaki, J. Moon et al., “CKD, arterial calcification, atherosclerosis and bone health: inter-relationships and controversies,” Atherosclerosis, vol. 278, pp. 49–59, 2018.

E. Zherebitskaya, J. Schapansky, E. Akude et al., “Sensory neurons derived from diabetic rats have diminished internal Ca2+ stores linked to impaired re-uptake by the endoplasmic reticulum,” ASN Neuro, vol. 4, no. 1, p. AN20110038, 2012.

Y. C. Chung, J. H. Lim, H. M. Oh et al., “Calcimimetic restores diabetic peripheral neuropathy by ameliorating apoptosis and improving autophagy,” Cell Death & Disease, vol. 9, no. 12, p. 1163, 2018.