Renal Replacement Therapy

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Significance of nutrition in hemodialysis patients with peripheral arterial disease evaluated by skin perfusion pressure

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Abstract

Background: Peripheral artery disease (PAD) is a serious complication in hemodialysis (HD) patients. Low skin perfusion pressure (SPP) is a useful marker for detecting PAD. Malnutrition is an important cause of intractable complications. We examined the relationship between low SPP and various indicators of nutritional status.

Methods: A total of 120 patients on maintenance HD were enrolled for SPP measurement. SPP was measured at the soles of both feet during HD, and patients were divided into low SPP (L-SPP) and normal SPP (N-SPP) groups by 50 mmHg. The following values were determined by averaging four blood samples taken before SPP measurements every 3 months for one year: hemoglobin, total protein, albumin (Alb), total cholesterol, urea nitrogen, creatinine (Cr), potassium, calcium, phosphate, intact parathyroid hormone, iron (Fe), transferrin saturation (T-SAT), and C-reactive protein (CRP). We calculated the percent Cr production rate, dialysis index (Kt/V), normalized protein catabolic rate (nPCR), geriatric nutritional risk index (GNRI), and estimated salt intake using the required formulas. In addition, the age, body mass index, and presence of diabetes mellitus (DM) were compared between both groups along with all other measurements. Data were expressed as the mean ± standard deviation or median with interquartile range as appropriate. Differences in continuous variables between the two groups were analyzed by Student's t-test or Wilcoxon's rank-sum test, as appropriate. Multivariate logistic analysis and receiver operating curve (ROC) analysis were performed for significant variables. The results were expressed as odds ratios with respective 95% confidence intervals (CIs).

Results: The enrolled patients were 82 men and 38 women, with a mean age of 66.9 ± 13.3 years and HD duration of 4.76 (2.13–12.28) years (median interquartile range). Twenty patients belonged to the L-SPP group, suggesting PAD. Comparison between the L-SPP and N-SPP groups showed significant differences in age, Cr, Fe, T-SAT, CRP, nPCR, GNRI, DM, and estimated salt intake. When the GNRI, estimated salt intake, CRP, and DM were applied as independent variables for multiple logistic regression analysis, the GNRI (odds ratio: 0.857, 95% CI 0.781–0.941, $p = 0.001$), CRP (2.406, 1.051–3.980, $p = 0.035$), and DM (9.194, 2.497–33.853, $p = 0.001$) were found to be significant for L-SPP, and a cutoff level of 92.1 (sensitivity 80%, specificity 72%, AUC: 0.742, 95% CI 0.626–0.858, $p = 0.001$) in the GNRI obtained by ROC was consistent with the risk index in the elderly presented previously.

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Conclusions: SPP measurement is an essential tool for detecting high-risk PAD in maintenance HD, which is affected by malnutrition, DM, and inflammation. The GNRI is important for the determination of malnutrition.

Keywords: Hemodialysis, Peripheral artery disease, Skin perfusion pressure, Nutrition management, Geriatric nutritional risk index

Background

Peripheral arterial disease (PAD) is a disease in which systemic arteriosclerosis extends to the arteries of the lower limbs, causing various symptoms. Hemodialysis (HD) patients develop PAD as well as other arteriosclerotic diseases such as cardiovascular and cerebrovascular disorders at a significantly higher frequency than non-dialysis patients [1]. Therefore, PAD is considered an important complication in HD patients, and the prevention of PAD is important for improving their prognosis and quality of life. However, PAD in HD patients causes few symptoms in the early stages and is difficult to recognize before the advanced stage of severe lower limb ischemia. In addition, PAD is progressive and treatment-resistant [2–5].

Therefore, it is important to screen patients for PAD. The ankle-brachial systolic blood pressure ratio (ankle-brachial index; ABI) has been used as an index [6] for the assessment of PAD, but it is relatively insensitive for identifying disease progression [7]. Skin perfusion pressure (SPP) measurement is known to be highly accurate and useful for the early detection and appropriate treatment of PAD [8, 9].

Diabetes is regarded as an important factor for the onset of PAD [10]; however, deterioration of nutrition may also play a role in the development of PAD, as has been observed in elderly patients with chronic kidney disease (CKD) [11]. To investigate the role of nutrition in the development of PAD, we evaluated nutritional parameters such as the geriatric nutritional risk index (GNRI), normalized protein catabolic rate (nPCR), estimated salt intake, and various clinical and laboratory results, and compared them with the risk of PAD detected by SPP measurement.

Methods

A total of 120 patients on maintenance HD were enrolled when SPP was measured at the outpatient HD unit of the Sanko Clinic. We excluded patients with unstable dry weight and those with cancer or dialysis-related amyloidosis. Additionally, patients with an HD period of less than one year were excluded. Clinical data including age, sex, duration of HD therapy, cardiothoracic ratio (CTR), body mass index (BMI), and the underlying etiology of the end-stage renal disease were collected from the patients' clinical records. The following values were determined by the average of four blood samples, taken before the SPP measurement, every 3 months, for one year: hemoglobin (Hb), total protein (TP), albumin (Alb), total cholesterol (TC), urea nitrogen (UN), creatinine (Cr), potassium, calcium, phosphate, intact parathyroid hormone (iPTH), iron (Fe), transferrin saturation (T-SAT), and C-reactive protein (CRP). The percent Cr production rate, dialysis index (Kt/V) [12], nPCR, GNRI, and estimated salt intake were calculated using their respective formulas.

Based on a previously described method, we used a laser Doppler device, SensiLase PAD4000 (Kaneka, Osaka, Japan), to measure the SPP. The SPP was measured while the patient was in the supine position during HD via a laser Doppler probe enclosed within a cuff wrapped around the patient's forefoot. When the cuff (applied to the plantar artery) was inflated to a suprasystolic pressure and decompressed, the initial perfusion point was determined as the SPP. Each patient's SPP was expressed as the average of both limb measurements. A poor prognosis was predicted in PAD when the SPP was < 50 mmHg [8], and patients were divided into low SPP (L-SPP) and normal SPP (N-SPP) groups.

Statistical Analysis

The laboratory data, age, and body mass index (BMI) are presented as mean ± SD. Unpaired t-test was used for between-group comparison. Prevalence data of diabetes mellitus (DM) were analyzed using Fisher's exact test (Table 2). Some significant values in the univariate analysis were used as independent variables for multiple logistic regression analysis to identify the risk factors. Receiver operating curve (ROC) analysis was also performed to estimate the cutoff point, sensitivity, and specificity. Statistical analysis was performed using IBM SPSS software ver. 25 (IBM, Armonk, NY), and statistical significance was set at $p < 0.05$.

Results

The background characteristics are presented in Table 1. The subjects were 120 patients (82 men and 38 women, mean age 66.9 ± 13.3 years) with a mean HD duration of 4.76 (2.13–12.28) years. Regarding the cause of renal failure, the ratio of diabetes to non-diabetes was 49:71. The mean SPP of both legs was 76.02 ± 3.95 mmHg (Table 1).

Table 1 Baseline clinical characteristics of patients ($N=120$)

Characteristics	Numbers or mean ± SD	Characteristic	Mean ± SD
Sex (M:F)	82: 38	Cr production rate (%)	101.81 ± 25.66
Age (ys)	66.9 ± 13.3	Kt/V	1.47 ± 0.28
Duration (ys)	4.76 (2.13–12.28)	nPCR	0.88 ± 0.12
CTR (%)	49.78 ± 5.43	GNRI	93.16 ± 6.12
Values in serum or blood	Numbers or mean ± SD	BMI (kg/m^2)	21.52 ± 3.95
Hb (g/dL)	11.29 ± 0.58	Estimated salt intake (g/day)	9.03 ± 2.59
TP (g/dL)	6.62 ± 0.39	**SPP**	**Mean ± SD**
Alb (g/dL)	3.69 ± 0.29	Right (mmHg)	76.81 ± 27.75
TC (mg/dL)	162.57 ± 34.82	Left (mmHg)	75.63 ± 24.84
UN (mg/dL)	62.94 ± 9.58	Average (mmHg)	76.02 ± 27.75
Cr (mg/dL)	10.83 ± 2.58	**Causes of dialysis**	**Numbers**
K (mEq/L)	4.81 ± 0.45	CGN	32
Ca (mg/dL)	8.89 ± 0.45	Diabetes	49
P (mg/dL)	5.15 ± 0.77	Nephrosclerosis	23
iPTH (pg/mL)	174.35 ± 108.06	Others	16
Fe (μg/dL)	68.76 ± 21.30		
T-SAT (%)	28.05 ± 10.10		
CRP (mg/dL) 0.14	(0.05–0.44)		

CTR cardiothoracic ratio, *Hb* hemoglobin, *TP* total protein, *Alb* albumin, *TC* total cholesterol, *UN* urea nitrogen, *Cr* creatinine, *K* potassium, *Ca* calcium, *P* phosphate, *iPTH* intact parathyroid hormone, *Fe* iron, *T-SAT* transferrin saturation, *CRP* C-reactive protein, *Kt/v* dialysis index, *nPCR* normalized protein catabolic rate, *GNRI* geriatric nutritional risk index, *BMI* body mass index, *SPP* skin perfusion pressure, *CGN* chronic glomerulonephritis

Data are given in mean ± SD or median format

According to the diagnostic criteria of Okamoto et al. [8], we detected PAD when the SPP was less than 50 mmHg in 20 of 120 HD patients (16.71%). Comparison of the parameters between the L-SPP ($n=20$) and N-SPP ($n=100$) groups revealed that age was significantly higher in the L-SPP group ($p=0.011$), but that Alb ($p=0.001$), Cr ($p=0.037$), Fe ($p=0.004$), T-SAT ($p=0.032$), CRP ($p=0.049$), nPCR ($p=0.041$), GNRI ($p=0.001$), and estimated salt intake ($p=0.005$) were significantly lower in the L-SPP group (Table 2). Diabetes mellitus, which is regarded as an important factor for PAD, was found in 14 patients (70.0%) in the L-SPP group and 35 patients (35.0%) in the N-SPP group. Fisher's exact test showed a significant difference between the two groups ($p=0.005$).

Since CRP, GNRI, estimated salt intake, and DM were significant in univariate analysis, and seemed to be important, multivariate logistic regression analysis was performed using these four variables as independent determinants. The results showed that the GNRI (odds ratio: 0.857, 95% CI 0.781-0.941, $p=0.001$) was a significant risk factor for L-SPP as well as DM (9.194, 2.497–33.853, $p=0.001$) and CRP (2.406, 1.051–3.980, $p=0.035$) (Table 3). Additionally, ROC analysis showed an optimal cutoff level of 92.1 in the GNRI for L-SPP (sensitivity 80%, specificity 72%, AUC: 0.742, 95% CI 0.626–0.858, $p=0.001$) (Fig. 1), which was consistent with malnutrition level in hemodialysis patients shown in a previous report [13].

Although GNRI has been known as a useful tool screening malnourished patients with hemodialysis, these results show that GNRI is also a prognostic indicator of PAD.

Discussion

ABI, toe-brachial pressure index (TBI), and transcutaneous oxygen pressure (TcPO2) are noninvasive examinations that are considered useful for the early diagnosis of PAD [8]. ABI is a simple measurement method that is widely used. However, accurate measurement cannot be taken when the lower limb arteries are calcified, as observed in many HD patients [8, 14]. In these cases, TBI may be effective in assessing local blood flow because arterial calcification rarely extends to the toes. However, toe cuffs cannot be attached to patients with ulcers or necrosis in the toes. TcPO2 is also useful for evaluating local blood flow, but it lacks accuracy, and its measurement is complicated.

In 1997, Castronuovo et al. [15] found that SPP can be used to diagnose critical limb ischemia with an accuracy of approximately 80% in non-HD patients. They noted that an SPP of 30 mmHg was a predictive factor for healing of the amputation edge. However, Okamoto et al. [8] found that an SPP of 50 mmHg was a useful cutoff value

Table 2 Comparison of the parameters between L-SPP ($n=20$) and N-SPP ($n=100$) groups

	L-SPP ($n=20$)	N-SPP ($n=100$)	*p* value
Age (ys)	72.8 ± 10.0	65.7 ± 13.6	0.011
Duration (ys)	10.74 (4.92–19.67)	4.01 (1.99–11.15)	0.012
CTR (%)	50.60 ± 4.53	49.62 ± 5.60	0.404
Hb(g/dL)	11.10 ± 0.78	11.33 ± 0.53	0.224
TP (g/dL)	6.65 ± 0.43	6.61 ± 0.39	0.750
Alb (g/dL)	3.48 ± 0.27	3.73 ± 0.27	0.001
TC (mg/dL)	157.53 ± 36.40	163.58 ± 34.60	0.499
UN (mg/dL)	59.33 ± 10.20	63.66 ± 9.33	0.091
Cr (mg/dL)	9.78 ± 2.31	11.04 ± 2.59	0.037
K (mEq/L)	4.67 ± 0.35	4.84 ± 0.46	0.057
Ca (mg/dL)	9.29 ± 0.49	9.05 ± 0.55	0.242
P (mg/dL)	5.28 ± 0.64	5.12 ± 0.79	0.327
iPTH (pg/mL)	150.05 ± 66.82	179.21 ± 114.17	0.128
Fe (μg/dL)	57.65 ± 16.62	70.98 ± 21.50	0.004
T-SAT (%)	24.25 ± 7.87	28.81 ± 10.35	0.032
CRP (mg/dL)	0.55 (0.19–0.97)	0.13 (0.04–0.26)	0.000
Cr production rate (%)	100.20 ± 13.01	109.53 ± 23.86	0.120
Kt/V	1.44 ± 0.31	1.48 ± 0.27	0.599
nPCR	0.83 ± 0.12	0.89 ± 0.12	0.041
GNRI	88.71 ± 6.16	94.05 ± 5.74	0.001
BMI (kg/m^2)	20.92 ± 0.43	21.64 ± 3.88	0.496
Estimated salt intake (g/day)	7.55 ± 2.38	9.32 ± 2.53	0.005
Diabetes mellitus (n)	14 (70.0%)	35 (35.0%)	0.005

Data are given in mean ± SD or median format

L-SPP low-skin perfusion pressure, *N-SPP* normal-skin perfusion pressure, *CTR* cardiothoracic ratio, *Hb* hemoglobin, *TP* total protein, *Alb* albumin, *TC* total cholesterol, *UN* urea nitrogen, *Cr* creatinine, *K* potassium, *Ca* calcium, *P* phosphate, *iPTH* intact parathyroid hormone, *Fe* iron, *T-SAT* transferrin saturation, *CRP* C-reactive protein, *Kt/v* dialysis index, *nPCR* normalized protein catabolic rate, *GNRI* geriatric nutritional risk index, *BMI* body mass index, *SPP* skin perfusion pressure, *CGN* chronic glomerulonephritis

Table 3 Multivariate logistic regression analysis for independent determinants of L-SPP

Independent variables	*p* value	Odds ratio (95% CI)
CRP	0.035	2.046 (1.051–3.980)
GNRI	0.001	0.857 (0.781–0.941)
Estimated salt intake	0.263	0.854 (0.648–1.126)
DM	0.001	9.194 (2.497–33.853)

L-SPP low-skin perfusion pressure, *CI* confidence interval, *CRP* C-reactive protein, *GNRI* geriatric nutritional risk index, *DM* diabetes mellitus

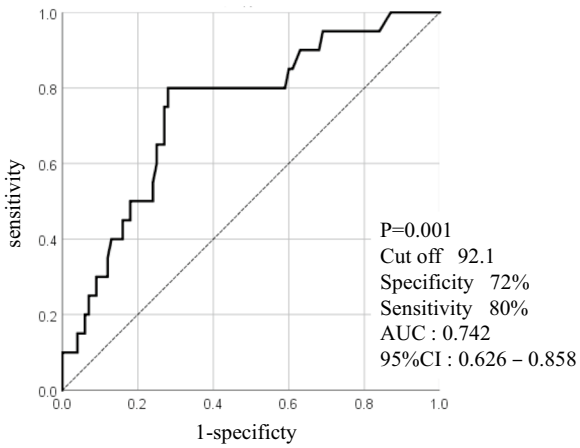

Fig. 1 Receiver operating characteristic analysis (ROC) of SPP for between GNRI and PAD. ROC analysis of PAD revealed a cutoff point of 92.1 with a specificity of 72% and a sensitivity of 80%. Area under the curve (AUC) was 0.742, 95% CI 0.626–0.858

for detecting early PAD in HD patients with high accuracy (sensitivity 84.9%, specificity 76.9%). This criterion was considered appropriate in the current study and was used to detect 20 of 120 patients with early PAD. In fact, as SPPs evaluate microcirculation in the foot, PAD can be diagnosed by low SPP levels even if the ABI is within the normal range [16]. Additionally, a recent study suggested that evaluation of PAD by SPP measurement is useful for predicting the prognosis of HD patients [17].

Malnutrition frequently occurs in elderly and complicated HD patients and is an important prognostic factor because it is directly linked to mortality [18]. There are various causes of malnutrition in patients undergoing HD. One of these is restricted eating during hemodialysis treatment [19]. Furthermore, a combination of malnutrition and chronic inflammation has been reported to increase all-cause and cardiovascular mortality in patients undergoing HD treatment [20]. PAD is a microcirculatory disorder associated with cardiovascular diseases [21], and as shown in the current study, it is reasonable that PAD may be deteriorated by malnutrition, which is closely associated with inflammatory conditions as indicated by CRP.

Protein-energy wasting (PEW) is the strongest death risk factor in CKD, and serum Alb levels have been used as the available value for PEW [22]. However, it is not always an accurate measure because many factors are involved in nutritional status. In our study, serum Alb level < 3.4 g/dL, indicating malnutrition, was identified in 22 (26.4%) of the total 120 subjects and in only 10 of the 20 L-SPP patients. In 2005, Bouillanne et al., introduced the GNRI [23] as a nutritional index for the elderly, which can be calculated from the serum Alb value, height, and weight.

In the current study, the GNRI, DM, and CRP (a marker of inflammation) were significantly related to L-SPP when investigated by multivariate logistic analysis (Table 3), and the cutoff value of 92.1 in the ROC

curve analysis was consistent with the risk index of the GNRI for malnutrition [13]. Therefore, the GNRI was confirmed to be useful for examining malnutrition as a deterioration of PAD indicating L-SPP. In patients with PAD, when the GNRI is low, it is necessary to ask in detail about the dietary contents and intake, investigate the cause of malnutrition, and consider nutritional treatment. Since the number of subjects was small, further studies with a larger population are needed to confirm this result.

Conclusions

SPP measurement is an essential important tool for evaluating a prognosis of PAD in maintenance HD, which is affected by malnutrition, DM, and inflammation. The GNRI is valuable for the determination of malnutrition even in PAD. Therefore, nutritional treatment is important when the GNRI is low in patients with PAD.

Abbreviations

PAD: Peripheral artery disease; HD: Hemodialysis; SPP: Skin perfusion pressure; ABI: Ankle-brachial index; CKD: Chronic kidney disease; GNRI: Geriatric nutritional risk index; ROC: Receiver operating curve; nPCR: Normalized protein catabolic rate; CTR: Cardiothoracic ratio; BMI: Body mass index; Alb: Albumin; UN: Urea nitrogen; TC: Total cholesterol; Cr: Creatinine; iPTH: Intact parathyroid hormone; CRP: C-reactive protein; Fe: Iron; T-SAT: Transferrin saturation; Kt/V: Dialysis index; TBI: Toe-TBI brachial pressure index; TcPO2: Transcutaneous oxygen pressure; PEW: Protein-energy wasting.

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Authors' contributions

MW and TS designed this study, analyzed the data, and prepared the manuscript. AF, ST, KU, and MU participated in SPP measurements and other aspects of data collection. YS, KI, TY, and KM provided advice for this study. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets created and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Fukuoka University (No. 2017M 070). Written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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