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Changes in the ankle-brachial blood pressure index among hemodialysis patients

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Abstract

Background: The ankle-brachial blood pressure index (ABI) is an independent predictor of mortality in hemodialysis patients. In the present study, we investigated the factors that predict changes in the ABI in hemodialysis patients.

Methods: A total of 61 consecutive patients receiving maintenance hemodialysis who successfully underwent ABI examinations in 2005 and 2011 were enrolled in this study. The change in the ABI (2011 measurement versus 2005 measurement) was estimated. We set the baseline at 2011 and investigated the patient outcomes. Furthermore, we compared the change in the ABI and several clinical factors observed in 2005.

Results: The mean follow-up period was 3.1 ± 0.7 years. In the univariate Cox proportional hazard analysis, predictive variables for mortality included ABI (0.43 [0.25–0.64]; [per 0.1 increase]) and the change in the ABI (0.62 [0.49–0.79]; [per 0.1 increase]). Patient age was negatively correlated and the serum creatinine level was positively correlated with the change in the ABI ($P = 0.030$ and 0.022, respectively).

Conclusions: We confirmed that not only the value of the ABI itself but also the change in the ABI was a risk factor for mortality among hemodialysis patients. The change in the ABI was negatively correlated with age and was positively correlated with the serum creatinine level. Careful observation of the ABI is needed for old patients and patients with a low serum creatinine level.

Keywords: Ankle-brachial index, Hemodialysis, Peripheral artery disease

Background

Epidemiological and clinical studies of the general population have demonstrated that the presence of peripheral artery disease (PAD) is associated with an increased risk of myocardial infarction and stroke [1, 2]. PAD is a regular complication of hemodialysis patients [3, 4] and is associated with poor outcomes [4–9]. Clinically, the ankle-brachial blood pressure index (ABI) is highly correlated with PAD of the lower extremities [10], and ABI is an independent predictor of all-cause mortality in hemodialysis patients [6–9]. A recent study also revealed that not only the value of the ABI itself but also the rate of the reduction in the ABI was a risk factor for cardiovascular mortality [11]. In the present study, we investigated the effect of changes in the ABI on mortality and the factors that predict changes in the ABI in hemodialysis patients.

Methods

A total of 61 consecutive patients receiving maintenance hemodialysis who successfully underwent ABI examinations in both 2005 and 2011 were retrospectively enrolled in this study. All patients were not treated by interventional or surgical repair for PAD during 2005 and 2011. Clinical data including age, sex, durations of hemodialysis therapy, presence of diabetes mellitus and/or hypertension complications, and biological examinations were collected from the patient's records. Hypertension was defined as a systolic blood pressure of 140 mmHg or higher, a diastolic blood pressure of

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90 mmHg or higher, and/or the current use of antihypertensive drugs. Diabetes mellitus was defined as fasting glucose ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, or the use of medication. A peripheral blood sample was obtained before hemodialysis on a Monday or a Tuesday. The ABI was determined in all the patients using an ABI form (Colin, Japan), which simultaneously measures bilateral arm and ankle blood pressures (brachial and posterior tibial arteries, respectively) using an oscillometric method. The blood pressure was measured after the patients had rested in a supine position for at least 5 min. The ABI was calculated using the ratio of the ankle systolic pressure divided by the arm systolic pressure. Blood pressure measurement in the arm with blood access is not desirable. So, the systolic pressure of the arm without dialysis access was used for the calculation. Patients who failed to measure ABI of either side of the legs were excluded from the study. The change in the ABI (2011 measurement versus 2005 measurement) was estimated. Delta ABI was defined and estimated as the following formula.

$$\text{Delta ABI} = \text{ABI in 2011} - \text{ABI in 2005}$$

We set the baseline at 2011 and investigated the patient outcomes. The clinical endpoints were defined as cardiovascular disease (CVD) events and death from any cause. CVD events include cardiac events (angina pectoris, hospitalization for heart failure, percutaneous coronary intervention, coronary artery bypass surgery, or acute myocardial infarction), cerebral events (hospitalization for cerebral infarction or bleeding), aortic dissection (hospitalization for aortic dissection), and PAD events (hospitalization for PAD including intervention, graft bypass surgery, or amputation). The smaller values for either ABI or delta ABI among the two values of both legs were adopted and incorporated into the analysis. Averages of ABI and delta ABI values for both legs were also examined.

Furthermore, we compared the change in the ABI (including both legs) and several clinical factors observed in 2005. Oral informed consent was obtained from the subjects. This study was conducted in accordance with the principles of the Declaration of Helsinki and permitted by the research ethics committee of the Tokyo Women's Medical University (Approved No. 3601).

The data were expressed as means ± SD or median (interquartile range, IQR). A univariate Cox proportional hazard model was used to examine the predictors of the overall outcomes. A simple regression analysis was used to examine the relationship between two continuous variables. All the statistical calculations were performed using JMP 5.1 software. *P* values less than 0.05 were considered statistically significant.

Results

The mean follow-up period was 3.1 ± 0.7 years. The patient background characteristics are shown in Table 1. The mean age was 57.2 ± 13.2 years, and the mean duration of hemodialysis therapy was 19.3 ± 8.7 years. The results of the biochemistry analyses and the primary causes of end-stage kidney disease are also shown in Table 1. Chronic glomerulonephritis was the major cause of end-stage kidney disease in this study. Hypertension and diabetes mellitus were observed in 59.0 and 14.8 % of the study participants, respectively.

During the follow-up period, seven deaths were recorded. The causes of death were infection in five cases, cerebrovascular disease in one case, and unknown in one case. Table 2 shows the Cox proportional hazard analysis of the covariates for predicting mortality. In the univariate analysis, predictive variables for mortality included old age (HR, 1.06 [1.00–1.13]; $P = 0.048$ [per 1 year increase]), low level of serum albumin (HR, 0.12 [0.02–0.82]; $P = 0.032$ [per 1 g/dL increase]), creatinine (HR, 0.49 [0.32–0.71]; $P < 0.001$ [per 1 mg/dL increase]), uric acid (HR, 0.42 [0.20–0.80]; $P = 0.008$ [per 1 mg/dL

Table 1 Background characteristics of the study participants

	All patients ($n = 61$)
Age (year)	57.2 ± 13.2
Gender (M/F)	33/28
Duration of HD (year)	19.8 (11.1–28.1)
Albumin (g/dL)	3.7 ± 0.3
Creatinine (mg/dL)	11.8 ± 2.3
Uric acid (mg/dL)	7.7 ± 1.4
Corrected calcium (mg/dL)	9.4 ± 0.8
Phosphate (mg/dL)	5.4 ± 1.4
Ca × P $(mg/dL)^2$	50.6 ± 12.2
Total cholesterol (mg/dL)	159 ± 36
Triglyceride (mg/dL)	102 ± 41
C-reactive protein (mg/dL)	0.07 (0.05–0.16)
Hemoglobin (g/dL)	10.7 ± 0.8
Primary Cause of ESKD, *n* (%)	
Chronic glomerulonephritis	43 (70.5)
Diabetic nephropathy	5 (8.2)
Polycystic kidney disease	3 (4.9)
Chronic pyelonephritis	1 (1.7)
Post transplantation	8 (13.1)
Unknown and others	1 (1.7)
Complication, *n* (%)	
Hypertension	36 (59.0)
Diabetes mellitus	9 (14.8)

Mean ± SD, median (interquartile range: IQR)
HD hemodialysis, *Ca* calcium, *P* phosphate, *ESKD* end-stage kidney disease

Table 2 Cox proportional hazard analysis of the covariates for predicting mortality (univariate analysis)

Parameters ($n = 61$)	Hazard ratio (95 % CI)	P value
Age (per 1 year)	1.06 (1.00 to 1.13)	0.048
Gender (M)	0.77 (0.34 to 1.64)	0.493
Duration of HD (per 1 year)	1.00 (0.91 to 1.09)	0.969
Albumin (per 1 g/dL)	0.12 (0.02 to 0.82)	0.032
Creatinine (per 1 mg/dL)	0.49 (0.32 to 0.71)	<0.001
Uric acid (per 1 mg/dL)	0.42 (0.20 to 0.80)	0.008
Corrected calcium (per 1 mg/dL)	1.14 (0.42 to 2.81)	0.789
Phosphate (per 1 mg/dL)	0.26 (0.09 to 0.65)	0.002
Ca × P (per 1 $(mg/dL)^2$)	0.98 (0.92 to 1.03)	0.446
Total cholesterol (per 1 mg/dL)	1.00 (0.98 to 1.02)	0.919
Triglyceride (per 1 mg/dL)	1.00 (0.98 to 1.02)	0.916
C-reactive protein (per 1 mg/dL)	1.04 (0.29 to 1.75)	0.912
Hemoglobin (per 1 g/dL)	0.60 (0.25 to 1.44)	0.250
Hypertension (Y)	2.15 (0.89 to 9.36)	0.095
Diabetes mellitus (Y)	0.95 (0.22 to 2.29)	0.918
ABI (per 0.1)[a]	0.43 (0.25 to 0.64)	<0.0001
ΔABI (per 0.1)[a]	0.62 (0.49 to 0.79)	<0.001

ΔABI = ABI in 2011 − ABI in 2005
HD hemodialysis, *Ca* calcium, *P* phosphate, *ABI* ankle-brachial blood pressure index
[a]ABI and ΔABI: smaller values among both legs

Table 3 Cox proportional hazard analysis of the covariates for predicting composite endpoints including cardiovascular events and mortality (univariate analysis)

Parameters ($n = 61$)	Hazard ratio (95 % CI)	P value
Age (per 1 year)	1.04 (1.00 to 1.09)	0.044
Gender (M)	1.25 (0.73 to 2.25)	0.419
Duration of HD (per 1 year)	1.03 (0.97 to 1.09)	0.357
Albumin (per 1 g/dL)	0.16 (0.05 to 0.64)	0.011
Creatinine (per 1 mg/dL)	0.67 (0.52 to 0.86)	0.001
Uric acid (per 1 mg/dL)	0.80 (0.51 to 1.21)	0.294
Corrected calcium (per 1 mg/dL)	1.68 (0.74 to 3.64)	0.211
Phosphate (per 1 mg/dL)	0.60 (0.34 to 0.96)	0.033
Ca × P (per 1 $(mg/dL)^2$)	0.96 (0.91 to 1.01)	0.084
Total cholesterol (per 1 mg/dL)	0.99 (0.97 to 1.00)	0.141
Triglyceride (per 1 mg/dL)	1.01 (1.00 to 1.02)	0.153
C-reactive protein (per 1 mg/dL)	1.44 (0.84 to 2.05)	0.154
Hemoglobin (per 1 g/dL)	0.52 (0.27 to 0.98)	0.042
Hypertension (Y)	1.40 (0.81 to 2.67)	0.239
Diabetes mellitus (Y)	0.62 (0.15 to 1.40)	0.299
ABI (per 0.1)[a]	0.65 (0.50 to 0.86)	0.025
ΔABI (per 0.1)[a]	0.73 (0.61 to 0.90)	0.005

ΔABI = ABI in 2011 − ABI in 2005
HD hemodialysis, *Ca* calcium, *P* phosphate, *ABI* ankle-brachial blood pressure index
[a] ABI and ΔABI: smaller values among both legs

increase]), phosphate (HR, 0.26 [0.09–0.65]; $P = 0.002$ [per 1 mg/dL increase]), ABI (smaller values among both legs) (HR, 0.43 [0.25–0.64]; $P < 0.0001$ [per 0.1 increase]), and delta ABI (smaller values among both legs) (HR, 0.62 [0.49–0.79]; $P < 0.001$ [per 0.1 increase]). The average values of ABI and delta ABI among both legs were also risk factors for mortality (HR, 0.47 [0.29–0.71]; $P < 0.001$ [per 0.1 increase], HR, 0.49 [0.31–0.74]; $P < 0.001$ [per 0.1 increase], respectively).

Table 3 shows the Cox proportional hazard analysis of the covariates for predicting composite endpoints including CVD events and mortality. Nine CVD events were observed during the follow-up period including three in cardiac events (two angina pectoris, one acute myocardial infarction), three in cerebral events (one cerebral infarction, one acute subdural hematoma, one chronic subdural hematoma), two in PAD events (interventional therapy for PAD), and one in aortic dissection. In the univariate analysis, predictive variables for the composite endpoints included old age (HR, 1.04 [1.00–1.09]; $P = 0.044$ [per 1 year increase]), low level of serum albumin (HR, 0.16 [0.05–0.64]; $P = 0.011$ [per 1 g/dL increase]), creatinine (HR, 0.67 [0.52–0.86]; $P = 0.001$ [per 1 mg/dL increase]), and phosphate (HR, 0.60 [0.34–0.96]; $P = 0.033$ [per 1 mg/dL increase]), low level of hemoglobin (HR, 0.52 [0.27–0.98]; $P = 0.042$ [per 1 g/dL increase]), ABI (smaller values among both legs) (HR, 0.65 [0.50–0.86]; $P = 0.025$, [per 0.1 increase]), and delta ABI (smaller values among both legs) (HR, 0.73 [0.61–0.90]; $P = 0.005$, [per 0.1 increase]). The average values of ABI and delta ABI among both legs were also risk factors for composite endpoints including CVD events and mortality (HR, 0.68 [0.50–0.92]; $P = 0.014$ [per 0.1 increase], HR, 0.01 [0.00–0.33]; $P = 0.001$ [per 0.1 increase], respectively).

Table 4 shows the relationships between the change in the ABI (2005 to 2011) and other clinical parameters observed in 2005. Patient age was negatively correlated and the serum creatinine level was positively correlated with the change in the ABI ($P = 0.030$ and 0.022, respectively).

Discussion

We confirmed that not only the value of the ABI itself but also the change in the ABI was a risk factor for mortality among hemodialysis patients. The change in the ABI was negatively correlated with patient age and was positively correlated with the serum creatinine level.

PAD is a regular complication of hemodialysis patients, and the HEMO study reported a prevalence of 23.0 % [12]. In addition, we previously reported a high prevalence (22.1 %) of PAD among hemodialysis patients [7]. PAD is recognized as a polyvascular disease because of the frequent coexistence of coronary artery and

Table 4 The relationship between the change of ABI (2005 to 2011) and other clinical parameters of 2005

	r	*P* value
Age (year)	-0.1968	0.030
Duration of HD (year)	0.0762	0.404
Albumin (g/dL)	0.0490	0.592
Creatinine (mg/dL)	0.2079	0.022
Corrected calcium (mg/dL)	0.0783	0.391
Phosphate (mg/dL)	−0.0371	0.685
Ca × P $(mg/dL)^2$	0.0542	0.553
Total cholesterol (mg/dL)	−0.1385	0.128
Triglyceride (mg/dL)	−0.0002	0.998
C-reactive protein (mg/dL)	0.1233	0.176
Hemoglobin (g/dL)	−0.0134	0.884

fABI ankle-brachial blood pressure index, *HD* hemodialysis, *Ca* calcium, *P* phosphate

cerebrovascular atherosclerosis [13]. Moreover, we recently showed that, in a study examining 117 hemodialysis patients, infection was significantly more prevalent in the PAD group than in the non-PAD group [8]. Both the short-term and long-term outcomes of hemodialysis patients with PAD have been reported to be poor [6–9]. The ABI is a simple, reliable diagnostic tool that can be used to define the existence and severity of PAD. We also confirmed that a low ABI was a risk factor for mortality.

Recently, Kuwahara et al. estimated 300 hemodialysis patients and showed that a higher rate of ABI decline was a prominent predictor of survival among patients receiving hemodialysis therapy (HR, 4.044; $P < 0.001$ [per 0.1/year decrease]) in multivariate Cox analysis [11]. We also showed that the change in the ABI was a risk factor for mortality, but it was a univariate analysis because of the small sample size. Their observation period for the change in the ABI was 1 year, which was 6 years in our study. We conformed that the change in the ABI in a relatively long period was also a risk factor for mortality. We added analysis of CVD events and conformed that not only the low level of the ABI itself but also the reduction of the ABI were both significant risk factors for CVD events and mortality.

Another recent study reported that a high fasting glucose level and old age were independent determinants of the accelerated progression of the ABI [14]. We also observed a negative correlation between age and the change in the ABI. We could not examine the fasting glucose level. However, we did observe that the serum creatinine level was positively correlated with the change in the ABI. We previously compared PAD patients and non-PAD patients and found that the serum albumin and creatinine levels were lower, the serum C-reactive protein level was higher, and the hemoglobin level was lower among PAD hemodialysis patients than non-PAD patients [8]. A low serum creatinine level is not only correlated with a low ABI but also predicts further reductions in the ABI. Serum creatinine is a marker of nutrition [15], and malnutrition and atherosclerosis are well known to affect each other in a condition known as malnutrition inflammation atherosclerosis (MIA) syndrome [16]. A malnutrition status is correlated with a low serum creatinine level and causes atherosclerosis, which reduces the ABI. The reason why other markers of malnutrition, such as the serum albumin level, did not predict the change in the ABI remained unclear. A relatively long-term observation period may be one of the reasons.

Our study had several limitations. The study was a retrospective examination of patients evaluated at a single institution, and differences in care, including medications, occurred over the course of the study. The prevalence of diabetes mellitus and nephrosclerosis was relatively low because of our institution's specialty. But we first revealed that low serum level of creatinine predict reduction of ABI.

Conclusions

We confirmed that not only the value of the ABI itself but also the change in the ABI was a risk factor for mortality among hemodialysis patients. Careful attention should be given to changes in the ABI as well as the value of the ABI itself. The change in the ABI was negatively correlated with age and was positively correlated with the serum creatinine level. Careful observation of the ABI is needed for old patients and patients with a low serum creatinine level.

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Authors' contributions

TAbe planned the study, searched the literature, assessed the studies, extracted the data, analyzed the data, and prepared the article. SO and NK searched the literature, assessed the studies, and assisted in the article preparation. NK and NM assessed the data extraction. TAbe, TO, and YO performed the ABI measurement. JM, IK, MM, KT, KN, and TAki assisted in the article preparation. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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References

1. Papamichael CM, Lekakis JP, Stamatelopoulos KS, Papaioannou TG, Alevizaki MK, Cimponeriu AT, et al. Ankle-brachial index as a predictor of the extent of coronary atherosclerosis and cardiovascular events in patients with coronary artery disease. Am J Cardiol. 2000;86:615–8.
2. Murabito JM, Evans JC, Larson MG, Nieto K, Levy D, Wilson PW. The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: the Framingham Study. Arch Intern Med. 2003;163:1939–42.
3. O'Hare AM, Johansen KL. Lower-extremity peripheral arterial disease among patients with end-stage renal disease. J Am Soc Nephrol. 2001;12:2838–47.
4. Fishbane S, Youn S, Flaster E, Adam G, Maesaka JK. Ankle-arm blood pressure index as a predictor of mortality in hemodialysis patients. Am J Kidney Dis. 1996;27:668–72.
5. Itaya H, Shiba M, Joki N, Nakamura M. Combined assessment of chronic kidney disease and subclinical peripheral artery disease used to predict future cardiac events. Nephrology (Carlton). 2010;15:230–5.
6. Ono K, Tsuchida A, Kawai H, Matsuo H, Wakamatsu R, Maezawa A, et al. Ankle-brachial blood pressure index predicts all-cause and cardiovascular mortality in hemodialysis patients. J Am Soc Nephrol. 2003;14:1591–8.
7. Otsubo S, Kitamura M, Wakaume T, Yajima A, Ishihara M, Takasaki M, et al. Association of peripheral artery disease and long-term mortality in hemodialysis patients. Int Urol Nephrol. 2012;44:569–73.
8. Takano M, Otsubo S, Kimata N, Oda Y, Abe T, Okajima T, et al. Influence of ankle-brachial blood pressure index on mortality and cause of death. J Jpn Soc Dial Ther. 2012;45:567–70.
9. Otani Y, Otsubo S, Kimata N, Takano M, Abe T, Okajima T, et al. Effects of the ankle-brachial blood pressure index and skin perfusion pressure on mortality in hemodialysis patients. Intern Med. 2013;52:2417–21.
10. Smith FB, Lee AJ, Price JF, van Wijk MC, Fowkes FG. Changes in ankle brachial index in symptomatic and asymptomatic subjects in the general population. J Vasc Surg. 2003;38:1323–30.
11. Kuwahara M, Hasumi S, Mandai S, Tanaka T, Shikuma S, Akita W, et al. Rate of ankle-brachial index decline predicts cardiovascular mortality in hemodialysis patients. Ther Apher Dial. 2014;18:9–18.
12. Cheung AK, Sarnak MJ, Yan G, Dwyer JT, Heyka RJ, Rocco MV, et al. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int. 2000;58:353–62.
13. Ouriel K. Peripheral arterial disease. Lancet. 2001;358:1257–64.
14. Hsu SR, Su HM, Hsieh MC, Su SL, Chen SC, Chen HC. Risk factors of accelerated progression of peripheral artery disease in hemodialysis. Kaohsiung J Med Sci. 2013;29:82–7.
15. Moreau-Gaudry X, Jean G, Genet L, Lataillade D, Legrand E, Kuentz F, et al. A simple protein-energy wasting score predicts survival in maintenance hemodialysis patients. J Ren Nutr. 2014;24:395–400.
16. Pecoits-Filho R, Lindholm B, Stenvinkel P. The malnutrition, inflammation, and atherosclerosis (MIA) syndrome—the heart of the matter. Nephrol Dial Transplant. 2002;17 Suppl 11:28–31.