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A Novel Risk Factor of Aggravating Atherosclerosis in Hemodialysis Patients; the Decreased Platelet Counts

Hidekazu Takeuchi*

Nagasaki-ken Tomie Hospital 499 Tomie-chou, Gotou-city, Nagasaki 853-0205, Japan

Abstract

Introduction: Hemodialysis patients cause coronary artery diseases to a higher rate and have a poor survival prognosis. Brachial ankle pulse wave velocity (baPWV) is a reliable measurement of arterial stiffness, and could predict mortality in patients with end-stage renal diseases. It is generally thought that atherosclerosis is not improved by hemodialysis treatments. We retrospectively examined whether hemodialysis treatments improved atherosclerosis or not, using the value of baPWV/systolic blood pressure (SBP) as an arteriosclerotic index.

Methods: We examined the relationship between the value of baPWV, SBP and platelet counts of 14 hemodialysis patients and assessed the change of baPWV for 13 patients who were measured baPWV more than twice.

Results: The value of baPWV and SBP showed the significant positive correlation ($r=0.62$, $p<0.001$), so the value of baPWV/SBP was used as an arteriosclerotic index. Value of 10 hemodialysis patients showed the improvement of the value of baPWV/SBP, and three patients showed the exacerbation of the value of baPWV/SBP. Three patients whose baPWV/SBP were not improved had the significant lower platelet counts (<90,000/μl) than the improved group ($n=10$; $p<0.001$).

Conclusion: This is the first reported case to demonstrate that hemodialysis treatments improved baPWV/SBP of some hemodialysis patients, which might represent hemodialysis treatments alleviated atherosclerosis, and decreased platelet counts (<90,000/μl) was associated with the exacerbation of the value of baPWV/SBP. The mechanisms of this relationship were elusive.

Keywords: Atherosclerosis; Hemodialysis; Decreased platelets count; Klotho gene

Introduction

Patients receiving maintenance hemodialysis for end stage renal disease have a worse survival and morbidity prognosis. The number of hemodialysis patients is annually increasing worldwide. Cardiovascular mortality rates among hemodialysis patients are approximately from 40% to 50% of deaths [1,2]. The cardiovascular mortality rates of the hemodialysis patients are higher than those of the general population by at least 10 times to 20 times. When a hemodialysis period becomes longer, the atherosclerosis is accelerated and patients develop cardiovascular diseases to a higher rate [1,3,4].

Patients with chronic kidney diseases died from much higher CVD than renal disease itself [5]. It is generally thought that atherosclerosis is not improved by hemodialysis treatments. Patients with CKD usually have traditional cardiovascular risk factors such as hypertension, hypercholesterolemia and diabetes mellitus.

Arterial stiffness can be assessed by noninvasive measurement of brachial ankle pulse wave velocity (baPWV), which is a simple and reproducible method [6,7]. baPWV reflects arterial wall structural components such as collagen and elastin, transmural pressure and smooth muscle tone, which mainly regulates arterial vessel distensibility and function [8,9]. baPWV is reported to be a crucial independent determinant of cardiovascular risk [10,11]. And baPWV could predict mortality in patients with hypertension [12], type 2 diabetes [13], and end-stage renal diseases [14].

The objective of the present study was retrospectively to elucidate whether hemodialysis treatments improve atherosclerosis or not, using the value of baPWV/systolic blood pressure (SBP) as an arteriosclerotic index and to clarify what the essential factor is.

Methods

Study participants

We investigated 14 patients with end-stage renal diseases, who were undertook the hemodialysis treatment. The average age of 14 patients was 67 ± 14 years, and 64% were male. They received hemodialysis treatments for 4.0–5.0 hour during each hemodialysis treatment. The frequency of hemodialysis treatments was three times a week, and their average hemodialysis periods were 4.3 years at the time of enrollment in the present study. The present study was just retrospective study and there was no necessity to get informed consents from the patients.

Protocol

The patients were measured baPWV at least once, and we evaluated the value of baPWV, SBP, hemoglobin and platelet counts. We assessed the change of baPWV for 13 hemodialysis patients who were measured baPWV more than twice. baPWV and SBP were measured in the supine position at about two hours after starting the hemodialysis treatments. Cuffs were wrapped around the arm opposite to the arterio-venous fistula arm and around both ankles. Although baPWV measurements were reported to have the validity, reproducibility and clinical

***Corresponding author:** Hidekazu Takeuchi, Nagasaki-ken Tomie Hospital 499 Tomie-chou, Gotou-city, Nagasaki 853-0205, Japan, Tel: +81-959-86-1121; E-mail: takeuch-h@r8.dion.ne.jp

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significance [14], we used the value of baPWV/SBP to evaluate arterial stiffness as an index of atherosclerosis for the purpose of decreasing the effects of highly varied SBP values with wide range.

Statistical analysis

Continuous data were expressed as mean values ± standard deviation (SD). The relationship between baPWV and SBP was analyzed by Pearson's correlation coefficient. Linear regression was used to investigate the relationship between the two parametric variables. The two groups were compared by using the unpaired t-test for continuous variables. A probability value less than 0.05 was accepted as statistically significant. Statistical analyses were done with the statistical package for social sciences software for Windows (SPSS, version 19.0, SPSS Japan, Tokyo, Japan).

Results

The clinical data of the two groups including biochemistry were summarized in Table 1. The detailed clinical personal data were shown in Table 2. baPWV and SBP were measured 1 to 3 times for each patient and the total measurement number was 40 times and they showed the significant positive correlation (Figure 1; r=0.62, p<0.001), which suggested that patients with hypertension had higher values of baPWV. baPWV was significantly affected by hypertension, so baPWV/SBP was used as an arteriosclerotic index to decrease the effect of changed SBP, which had from lower SBP to higher SBP.

10 hemodialysis patients (77%) showed the improvement of the value of baPWV/SBP. The change was shown in Table 3. Among three patients (23%) who were not improved, the value of baPWV/SBP of two patients (Table 3; No.11 and No.12) was exacerbated slightly, but the baPWV/SBP value of the third patient (Table 3; No.13) was aggravated largely.

Among 10 patients with improved baPWV/SBP values, their platelet counts were more than 100,000/μl. However, three patients whose baPWV/SBP values were not improved had the platelet counts less than 90,000/μl. And there was statistically significant difference between their platelet counts of the two groups (Figure 2; p<0.001). The three worsened patients were not infected by hepatitis C virus or hepatitis B virus.

Discussion

According to the results of the present study, hemodialysis treatments improved atherosclerosis of 10 hemodialysis patients, but atherosclerosis of three hemodialysis patients (23%) were not improved. When atherosclerosis of hemodialysis patients was evaluated, it was proper to consider the influence of hypertension on arterial wall and to use the value of baPWV/SBP as an arteriosclerotic index for hemodialysis patients.

Cardiovascular risk factors such as hypertension, inflammation, oxidative stress have been studied intensely [15]. In addition to these common cardiovascular risk factors, other factors such as uramic milieu and hemodialysis procedure itself such as heparin and dialysis

	Improved Group (No.1~No.10; n=10)	Worsened Group (No.11~No.13; n=3)	P value
Age (years)	64.7 ± 15.3	75.0 ± 2.0	0.067
Male n (%)	6 (60%)	3 (100%)	0.188
Plt (15~35 ×10*4/μl)	17.41 ± 5.06	7.70 ± 0.85	<0.001
TP (6.5-8.2 g/dl)	6.72 ± 0.58	6.87 ± 0.42	0.65
Alb (3.9-4.9 g/dl)	3.64 ± 0.43	3.77 ± 0.32	0.608
Hb (11.5-14.5 g/dl)	9.47 ± 0.55	9.93 ± 0.45	0.214
WBC (4,000-9,000 /μl)	5,73 ± 2,593	5,023 ± 1,208	0.453
Ca (8.8-10.1 mg/dl)	9.07 ± 1.64	9.53 ± 0.47	0.446
P (2.4-4.6 mg/dl)	4.39 ± 1.14	4.37 ± 0.81	0.97
HbA1c (4.3-5.8 %)	5.39 ± 1.07	5.10 ± 0.56	0.553
SBP (mmHg)	147.3 ± 25.5	121.0 ± 14.8	0.066

Plt, platelet; TP, total protein; Alb, albumin; Hb, hemoglobin; WBC, white blood cell; Ca, calcium; P, phosphate; HbA1c, hemoglobin A1c; SBP, systolic blood pressure

Table 1: Baseline Charateristics of the Study Groups.

No.	y.o.	Sex	Year HD	WBC	Hb	Plt	Ca	P	TP	Alb	HbA1c	SBP
1	77	M	6.6	4,750	10.6	10	7.9	4.3	6.2	3.6	4.8	146
2	57	M	2	6,560	9.8	16.5	10.2	2.6	7.7	3.9	5.7	146
3	85	M	3.7	2,720	9.2	12.8	5.1	2.7	7.5	3.2	4.2	151
4	76	F	5.2	3,280	9.2	24.7	8.8	5	6.7	2.8	6.9	183
5	76	F	5.2	3,280	9.2	24.7	8.8	5	6.7	2.8	6.9	183
6	68	M	4.8	6,180	9.2	12.2	9.7	4.8	6.1	3.8	7	192
7	66	F	2.2	5,450	8.7	19.9	9.8	4.4	6.8	4.1	5	131
8	34	M	4.3	7,360	9.4	14	9	4.2	6.1	3.6	4.1	114
9	54	F	4.5	12,090	9	23.6	10.8	4.5	6.2	3.3	6.4	157
10	53	F	2.8	5,090	10.1	21	10.4	6.6	7.1	4	5.2	137
11	73	M	6.7	3,870	9.5	6.9	9	3.9	6.4	3.4	5	128
12	77	M	6.5	6,280	10.4	8.6	9.7	3.9	7.2	4	4.6	131
13	75	M	3	4,919	9.9	7.6	9.9	5.3	7	3.9	5.7	104

Year HD, Year of hemodialysis; WBC, white blood cell; Hb, hemoglobin; Plt, platelet; Ca, calcium; P, phosphate; TP, total protein; Alb, albumin; HbA1c, hemoglobin A1c; SBP, systolic blood pressure (No.1~No.10 patients are Improved Group. No.11~No.13 patients are Worsened Group).

Table 2: Laboratory Data of the Patients.

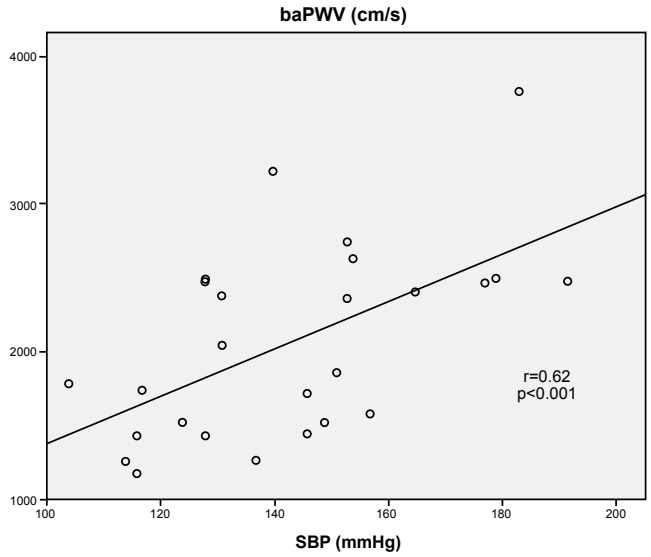

Figure 1: The brachial ankle pulse wave velocity (baPWV) (cm/s) had the significant positive correlation with systolic blood pressure (SBP) (mmHg).

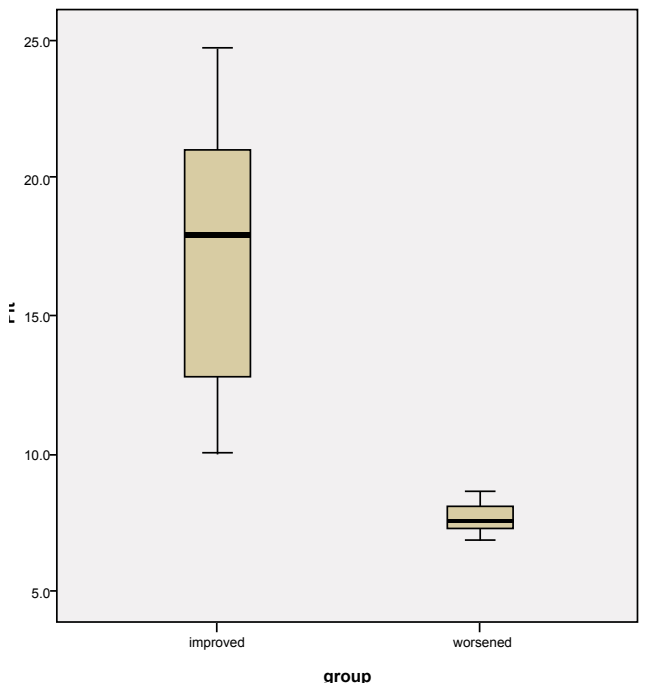

Figure 2: Box plot showed the mean and the distribution. Comparison of platelet numbers between the improved and the worsened groups. The worsened group showed the significantly (p<0.001) reduced number in platelet count; 17.4 ± 5.1 to 7.7 ± 0.9 (×10,000/μl).

membrane are known to be possible risk factors for hemodialysis patients [16,17].

As far as we know, this is the first report to demonstrate that the decreased platelet counts (<90,000/μl) were associated with the exacerbation of atherosclerosis in hemodialysis patients. In Figure 2, the box plot showed that the worsened group (No.11~No.13) had the significantly (p<0.001) lower values in the serum level of platelet counts than those of the improved group (No.1~No.10) and the least platelet counts of the improved group (Table 3; No.1; 100,000/μl) were larger than the largest platelet counts of the worsened group (Table 3; No.11; 86,000/μl).

Presently, although the hemodialysis patients were treated with medical interventions such as beta-blockers, statins and erythropoietin [4], decreased platelet counts (<90,000/μl) were not the target of the treatment. The decreased platelet counts may have been implicated in exacerbating atherosclerosis in patients with hemodialysis treatments and they may predict the bad prognosis.

The reason why platelet counts in the worsened group were less than those of the improved group remains elusive.

Patients with chronic kidney disease (CKD) have higher risks of cardiovascular disease and mortality than the normal population [18]. Klotho is the gene associated with attenuating the progression of hypertension, anti-aging, mineral metabolism, and vitamin D metabolism and encodes a single-pass transmembrane protein that forms a complex with multiple fibroblast growth factor receptors, and is most abundant in the renal tubules [19]. A defect in Klotho gene expression in mice results in shortened lifespan and aging-like phenotypes [20-23]. Recent studies also showed that Klotho functions as a renoprotective factor [24,25]. Klotho expression is decreased in patients with acute or chronic kidney diseases in response to reactive oxygen species [26].

Previous studies indicated that uremic toxins increased the oxidative stress and reduced cell viability [27,28]. An animal study showed that

No.	baPWV (cm/s)	SBP (mmHg)	baPWV/ SBP	Change	Plt x10,000/ μl
No.1 first	2,494	179	13.93		
No.1 last	1,438	146	9.85	4.08	10
No 2. first	1,733	117	14.81		
No.2 last	1,708	146	11.7	3.11	16.5
No.3 first	2,352	153	15.37		
No.3 last	1,855	151	12.28	3.09	12.8
No.4. first	3,206	140	22.9		
No.4 last	3,763	183	20.56	2.34	24.7
No.5 first	3,206	140	22.9		
No.5 last	3,763	183	20.56	2.34	24.7
No.6. first	2,401	165	14.55		
No.6 last	2,469	192	12.86	1.69	12.2
No.7 first	2,628	154	17.06		
No.7 last	2,041	131	15.58	1.48	19.9
No.8. first	1,428	116	12.31		
No.8 last	1,254	114	11	1.31	14
No.9 first	1,430	128	11.17		
No.9 last	1,570	157	10	1.17	23.6
No.10. first	1,525	149	10.23		
No.10 last	1,266	137	9.24	0.99	21
No.11 first	2,468	128	19.28		
No.11 last	2,481	128	19.38	-0.1	6.9
No.12 first	2,739	153	17.9		
No.12 last	2,379	131	18.16	-0.26	8.6
No.13 first	2,458	177	13.89		
No.13 last	1,779	104	17.11	-3.21	7.6
Average				1.37	

baPWV, brachial ankle pulse wave velocity; SBP, systolic blood pressure; Plt, platelet
No.1~No.10 patients are Improved Group. No.11~No.13 patients are Worsened Group

Table 3: The change of baPWV/SBP and platelet count.

treatment with the uremic toxin sorbent, AST-120, increased Klotho expression and inhibited cell senescence in the kidneys of uremic rats [29]. Epigenetic modification of specific genes by uremic toxins might be an important pathological mechanism in uremic milieu.

A malfunction of Klotho gene induces the progression of atherosclerosis [30-33].

Before the induction of hemodialysis, uremia suppresses the Klotho gene regulation via hypermethylation of the CpG islands in promoter and may promote atherosclerosis. In the present case, hemodialysis can't improve the baPWV/SBP values of three patients (23%). Although we have the model that hemodialysis improves the expression of Klotho gene, we don't have the model that hemodialysis can't improve the baPWV/SBP, in which hemodialysis may not attenuate the suppression of the Klotho gene. Some candidate of new models is hypermethylation of CpG islands shore or non-coding RNA, which regulates of Klotho gene.

In Klotho-deficient mice, suicidal erythrocyte death was reported to accelerate [34]. This decrease of platelets may be caused by severe damage of Klotho gene. Much more studies are desirable.

The present study had several potential limitations because of retrospective study nature and the number of enrolled patients was very small, so that it might not be representative of all hemodialysis patients. It is important to confirm the relationship between decreased baPWV/SBP and decreased platelet counts for more hemodialysis patients, to elucidate the mechanisms and to improve decreased platelet counts by some methods to avoid aggravating atherosclerosis in the hemodialysis patients.

Conclusion

This is the first to show that the hemodialysis treatment improved the values of baPWV/SBP as an index of atherosclerosis in some hemodialysis patients and that the decreased platelet counts (<90,000/μl) were associated with the aggravation of atherosclerosis in the hemodialysis patients.

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Competing interests: None.

Patient consent: Consent was not obtained but the presented data are anonymised and risk of identification is low.

Ethics approval: Ethics approval was not provided because the present study was just retrospective study.

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