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ORIGINAL ARTICLE

High plasma pentosidine level is accompanied with cardiovascular events in hemodialysis patients

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Abstract
Background Cardiovascular disease is a major complication in patients with end-stage renal disease (ESRD). The accumulation of advanced glycation end products (AGEs) is facilitated in these patients. The aim of this study was to investigate the relationship between circulating AGEs and cardiovascular events in hemodialysis patients.
Methods The plasma level of pentosidine, a well-defined AGEs, was measured in 110 hemodialysis patients who were prospectively followed for 90 months. The relationship between plasma pentosidine level and cardiovascular events was assessed using Kaplan-Meier and Cox regression analysis.
Results Thirty-nine cardiovascular events (14 coronary heart disease and 25 strokes) occurred during the follow-up period. Multivariable Cox proportional hazard analysis showed that plasma pentosidine levels (HR 1.040, 95% CI 1.022–1.058, $p < 0.01$) were correlated to increased risk for cardiovascular events. When patients were divided into four groups according to plasma pentosidine levels, Kaplan-Meier analysis revealed that cardiovascular events in the highest pentosidine group were significantly greater than in the other groups ($p < 0.01$ in lower and low, and $p < 0.05$ in high pentosidine groups).
Conclusion The plasma pentosidine level predicts cardiovascular events in hemodialysis patients. The effects of lowering circulating AGE levels on cardiovascular events should be examined in ESRD patients.

Keywords Pentosidine · Cardiovascular event · Hemodialysis

Trial registration www.umin.ac.jp/ctr/, study number UMIN000005452.

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Introduction

The leading cause of death in hemodialysis patients is cardiovascular disease. Although the traditional cardiovascular risk factors are applicable to hemodialysis patients, the high cardiovascular risk in these patients cannot be fully explained by these factors. Several non-traditional cardiovascular risk factors in hemodialysis patients are proposed.

Advanced glycation end products (AGEs) are reported to be involved in the pathogenesis of atherosclerosis in uremia [1]. In fact, the AGE level is correlated to carotid intima-media thickness in hemodialysis patients [2, 3]. Furthermore, increased AGE levels are associated with extensive coronary artery calcification in hemodialysis patients, which may predict future coronary events [4]. The accumulation of AGEs has been demonstrated as a cardiovascular risk factor in patients without end-stage renal disease (ESRD) [5, 6]. On the contrary, the roles of increased AGE levels in the development of cardiovascular events has not been well studied in ESRD patients [7].

Oxidative stress is known to be associated with cardiovascular diseases and is increased in ESRD patients [8, 9]. The oxidative stress modifies proteins either directly through the oxidation of amino acids by reactive oxygen species or indirectly by an increased generation of reactive carbonyl compounds (RCOs). The RCOs are the precursors of uremia-associated AGEs [10]. Indeed, pentosidine, a well-defined AGEs, is highly correlated with RCOs [11]. These suggest that increased pentosidine levels in ESRD patients are associated with the cardiovascular events.

Several studies were conducted to clarify the relationship between plasma AGEs and mortality in ESRD patients [12–14]. However, few clinical trials have studied the relationship between plasma AGEs and cardiovascular events in hemodialysis patients. In this study, we investigated whether the plasma pentosidine level predicted cardiovascular events in 110 hemodialysis followed for 90 months.

Methods

This study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Iwata City Hospital. Written informed consent was obtained from all patients.

Patients

Subjects were recruited from ESRD patients undergoing hemodialysis at Iwata City Hospital ($N = 146$). Study inclusion criteria were patients who had been receiving hemodialysis therapy for more than 6 months, were in stable condition, and were younger than 80 years old. Patients with a history of apparent cardiovascular diseases, such as myocardial infarction, angina pectoris and stroke, were excluded. Patients with life-threatening co-morbid conditions such as active infection, systemic vasculitis, malignant disease and end-stage cardiac/pulmonary/hepatic disease, were also excluded. Finally, 110 patients (67 men, 43 women) were enrolled in this study. The mean age of these patients was 62.9 ± 1.1 years, and the mean hemodialysis vintage was 114.4 ± 8.6 months. Primary renal diseases were chronic glomerulonephritis ($N = 69$), diabetic nephropathy ($N = 26$), polycystic kidney disease ($N = 8$), nephrosclerosis ($N = 6$) and unknown disease ($N = 1$).

A regular hemodialysis session was carried out three times per week. Each hemodialysis session lasted 4–5 h, with a blood flow rate of 200–220 ml/min and a dialysate flow rate of 500 ml/min. In all patients, single-use biocompatible synthetic high-flux polysulfone membranes were used. The dialysis fluid was bicarbonate dialysate, and the endotoxin level in the dialysate was below the detection limit (0.001 EU/l). Blood pressure was recorded by averaging three predialysis blood pressure measurements.

Laboratory examinations

Blood samples were drawn at the start of the first dialysis session of the week, and plasma was immediately separated and stored at −82°C until analyzed.

Blood urea nitrogen, creatinine, uric acid, calcium, phosphate, albumin, total cholesterol, triglyceride, CRP and blood cell counts were measured by standard laboratory technique using an automatic analyzer. Plasma β_2-microglobulin was measured by the latex agglutination method. Measurements of intact PTH was carried out in the commercial laboratory (SRL, Tokyo) using ECLIA. The plasma pentosidine level was assayed by means of high-performance liquid chromatography as previously described [15].

Dialysis adequacy was evaluated using single-pool Kt/V as follows:

$$\mathrm{spKt}/V = -\mathrm{Ln}(R - 0.008 \times t) + (4 - 3.5 \times R) \times \mathrm{UF}/\mathrm{BW}$$

where R is the ratio of postdialysis to predialysis serum urea nitrogen, t is time of dialysis in hours, UF is the amount of ultrafiltration in liters and BW is postdialysis body weight in kilograms.

Follow-up study

After the initial laboratory examinations, all patients were followed up for 90 months. The first cardiovascular event, including coronary heart disease (myocardial infarction and angina pectoris) and stroke, was regarded as an end point for each patient. Coronary heart disease (myocardial infarction and angina pectoris) was diagnosed by typical clinical symptoms and changes in ECG, UCG and laboratory findings. Stroke was diagnosed by means of CT or MRI performed within 3 days after the onset of clinical symptoms. Transient ischemic attack was excluded.

Statistical analysis

Data were expressed as mean ± SEM or percentage. Differences between groups were analyzed by Mann-Whitney U test, Kruskal-Wallis test or chi-square test as appropriate. Survival curves were estimated by the Kaplan-Meier method with log-rank test. Relative risk for a cardiovascular event was estimated by using the Cox proportional hazard model. P values <0.05 were considered statistically significant. All statistical calculations were performed with SPSS 11.0J for Windows.

Results

During the follow-up period, 39 patients suffered cardiovascular events, with coronary heart disease in 14 patients and stroke in 25 patients. Coronary heart diseases were consisted of myocardial infarction ($N = 8$) and angina pectoris ($N = 6$), and strokes were ischemic ($N = 18$) and hemorrhagic ($N = 7$), respectively.

Baseline characteristics of patients with and without cardiovascular events are listed in Table 1. Patients who suffered cardiovascular events were older than those who did not. Hemodialysis vintage was longer in patients with cardiovascular events than without. The plasma pentosidine level was significantly higher in patients who suffered cardiovascular events than in those who did not.

Table 2 shows univariate associations between cardiovascular events and other clinical parameters. Higher values for age, hemodialysis vintage, CRP and plasma pentosidine level, and lower values of BMI and albumin were associated with the subsequent development of cardiovascular events. Multivariable Cox proportional hazard analysis showed that higher levels of plasma pentosidine as well as elevated CRP levels were correlated to increase risk for cardiovascular events (Table 3).

Patients were divided into four groups according to their plasma pentosidine concentrations: 1st quartile (<24.7 pmol/mg alb, $N = 26$), 2nd quartile (24.7–32.9 pmol/mg alb, $N = 28$), 3rd quartile (32.9–40.7 pmol/mg alb, $N = 28$) and 4th quartile (>40.7 pmol/mg alb, $N = 28$), and Kaplan-Meier survival analysis was performed. Baseline characteristics of the four groups classified by pentosidine

Table 1 Baseline characteristics of patients with and without cardiovascular events

Variable	With events	Without events	*p* value
Gender (M/F)	24/15	43/28	NS
Age (years)	66.4 ± 1.8	60.9 ± 1.4	0.03
HD vintage (months)	142.9 ± 14.2	96.8 ± 10.5	<0.01
Diabetes (%)	20.5	23.9	NS
BMI (kg/m^2)	19.2 ± 0.5	20.3 ± 0.4	NS
Systolic blood pressure (mmHg)	160.5 ± 3.0	162.9 ± 3.1	NS
Diastolic blood pressure (mmHg)	83.9 ± 2.5	85.4 ± 1.9	NS
Hb (g/dl)	10.5 ± 0.2	10.3 ± 0.1	NS
Albumin (g/dl)	3.7 ± 0.1	3.8 ± 0.1	NS
CRP (mg/dl)	0.7 ± 0.3	0.4 ± 0.1	NS
Total cholesterol (mg/dl)	152.0 ± 5.5	160.5 ± 4.1	NS
Triglyceride (mg/dl)	87.8 ± 6.9	107.1 ± 8.6	NS
Blood urea nitrogen (mg/dl)	69.7 ± 2.8	73.0 ± 1.5	NS
Creatinine (mg/dl)	11.1 ± 0.4	11.0 ± 0.3	NS
Uric acid (mg/dl)	6.9 ± 0.3	7.3 ± 0.2	NS
Calcium (mg/dl)	9.3 ± 0.2	9.2 ± 0.1	NS
Phosphate (mg/dl)	5.2 ± 0.2	5.6 ± 0.2	NS
Calcium × phosphate	49.0 ± 2.5	52.7 ± 1.8	NS
Intact PTH (pg/ml)	199.4 ± 28.0	189.1 ± 28.2	NS
β_2-Microglobulin (mg/dl)	28.1 ± 0.7	28.0 ± 0.8	NS
ACEI/ARB (%)	59.0	52.1	NS
Smoking (%)	15.4	15.5	NS
Pentosidine (pmol/mg alb)	45.6 ± 2.1	28.7 ± 1.4	<0.01

Table 2 Univariate Cox proportional hazard model for cardiovascular events

Variable	HR	95% CI	*p* value
Gender (M/F)	0.992	0.520–1.891	NS
Age (years)	1.042	1.011–1.072	<0.01
HD vintage (months)	1.004	1.001–1.007	0.026
Diabetes (%)	0.922	0.422–2.016	NS
BMI (kg/m^2)	0.876	0.779–0.986	0.023
Systolic blood pressure (mmHg)	0.995	0.981–1.009	NS
Diastolic blood pressure (mmHg)	0.989	0.969–1.009	NS
Hb (g/dl)	1.175	0.872–1.583	NS
Albumin (g/dl)	0.303	0.131–0.699	<0.01
CRP (mg/dl)	1.298	1.061–1.587	0.01
Total cholesterol (mg/dl)	0.995	0.986–1.005	NS
Triglyceride (mg/dl)	0.995	0.988–1.001	NS
Blood urea nitrogen (mg/dl)	0.982	0.959–1.005	NS
Creatinine (mg/dl)	0.967	0.848–1.102	NS
Uric acid (mg/dl)	0.845	0.662–1.007	NS
Calcium (mg/dl)	1.063	0.801–1.409	NS
Phosphate (mg/dl)	0.791	0.621–1.008	NS
Calcium × phosphate	0.987	0.967–1.007	NS
Intact PTH (pg/ml)	1.000	0.999–1.001	NS
β_2-Microglobulin (mg/dl)	1.002	0.954–1.053	NS
ACEI/ARB (%)	0.843	0.445–1.596	NS
Smoking (%)	0.782	0.327–1.870	NS
Pentosidine (pmol/mg alb)	1.047	1.031–1.064	<0.01

Table 3 Multivariate Cox proportional hazard model for cardiovascular events

Variable	HR	95% CI	*p* value
Pentosidine (1.0 pmol/mg alb)	1.040	1.022–1.058	<0.01
CRP (1.0 mg/dl)	1.255	1.016–1.549	0.035
HD vintage (1 month)	1.003	0.999–1.006	0.104
Albumin (1.0 g/dl)	0.412	0.129–1.317	0.135
Age (1 year)	1.021	0.988–1.055	0.210
BMI (kg/m^2)	0.975	0.847–1.122	0.720

Table 4 Clinical variables in the four groups with differing plasma pentosidine levels

Variable	1st quartile	2nd quartile	3rd quartile	4th quartile	*p* value
Gender (M/F)	16/10	16/12	18/10	17/11	NS
Age (years)	62.7 ± 2.4	60.7 ± 2.2	61.1 ± 1.7	67.4 ± 2.5	NS
HD vintage (months)	69.8 ± 16.4	115.5 ± 17.4	138.6 ± 17.0	130.6 ± 16.1	0.001
Diabetes (%)	34.6	21.4	17.8	17.8	NS
BMI (kg/m^2)	21.1 ± 0.6	19.8 ± 0.6	19.6 ± 0.6	19.3 ± 0.6	NS
Systolic blood pressure (mmHg)	161.9 ± 6.2	166.7 ± 4.9	159.5 ± 3.7	160.3 ± 3.7	NS
Diastolic blood pressure (mmHg)	86.1 ± 3.3	86.0 ± 2.6	86.6 ± 2.8	80.3 ± 3.3	NS
Hb (g/dl)	10.3 ± 0.2	10.1 ± 0.2	10.4 ± 0.2	10.4 ± 0.2	NS
Albumin (g/dl)	3.7 ± 0.1	3.8 ± 0.1	3.8 ± 0.1	3.7 ± 0.1	NS
CRP (mg/dl)	0.4 ± 0.1	0.4 ± 0.2	0.3 ± 0.1	0.8 ± 0.4	NS
Total cholesterol (mg/dl)	166.9 ± 8.3	161.3 ± 5.4	155.8 ± 6.4	146.8 ± 5.9	NS
Triglyceride (mg/dl)	113.3 ± 14.6	108.5 ± 13.6	105.1 ± 12.0	75.3 ± 7.0	0.032
Blood urea nitrogen (mg/dl)	69.8 ± 2.2	73.4 ± 2.1	71.4 ± 2.6	72.5 ± 3.8	NS
Creatinine (mg/dl)	10.0 ± 0.5	11.1 ± 0.3	11.9 ± 0.5	11.0 ± 0.4	NS
spKt/V	1.51 ± 0.05	1.63 ± 0.07	1.57 ± 0.06	1.56 ± 0.04	NS
Uric acid (mg/dl)	7.6 ± 0.2	7.4 ± 0.2	6.7 ± 0.3	7.0 ± 0.3	NS
Calcium (mg/dl)	9.3 ± 0.2	9.2 ± 0.2	9.3 ± 0.2	9.2 ± 0.2	NS
Phosphate (mg/dl)	5.7 ± 0.2	5.7 ± 0.2	5.5 ± 0.3	5.1 ± 0.2	NS
Calcium × phosphate	53.4 ± 3.3	53.3 ± 2.4	51.9 ± 3.3	47.2 ± 2.9	NS
Intact PTH (pg/ml)	187.2 ± 37.6	165.9 ± 33.5	251.2 ± 57.4	166.5 ± 30.7	NS
β_2-Microglobulin (mg/dl)	25.3 ± 1.2	28.5 ± 1.4	28.2 ± 0.8	30.1 ± 1.2	0.053
ACEI/ARB (%)	46.2	60.7	64.3	46.5	NS
Smoking (%)	26.9	0	10.7	25.0	0.023
Pentosidine (pmol/mg alb)	18.7 ± 0.8	27.6 ± 0.5	36.8 ± 0.5	54.4 ± 2.2	<0.001

concentration are listed in Table 4. Hemodialysis vintages were longer in higher pentosidine groups than in lower groups. Although serum triglyceride levels were lower in the 4th quartile, there were no differences in serum total cholesterol, albumin, CRP, BMI, blood pressure, blood urea nitrogen, creatinine, spKt/V and diabetes prevalence among groups. Cardiovascular events did not occur in the 1st quartile. On the contrary, the incidences of cardiovascular event were 14.3, 53.6 and 71.4% in the 2nd, 3rd and 4th quartile, respectively. Cardiovascular event-free survival was significantly greater in the 1st quartile than in the other quartiles ($p < 0.05$ in the 2nd quartile, and $p < 0.01$ in the 3rd and 4th quartile) (Fig. 1).

Patients were divided into two groups according to their CRP levels. There was a weak but significant difference in cardiovascular event-free survival between groups of patients with low and high CRP levels ($p = 0.0498$).

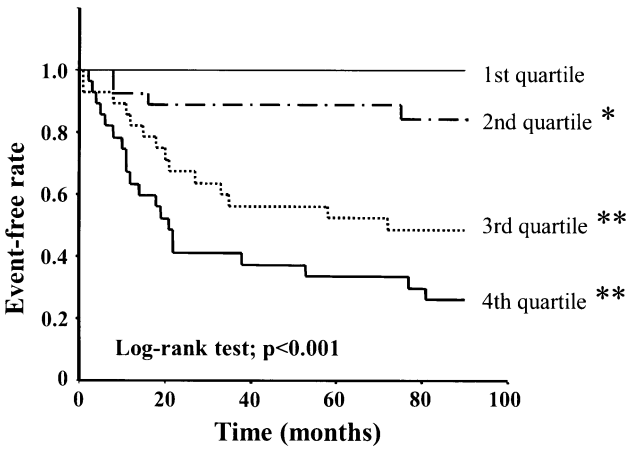

Fig. 1 Cumulating cardiovascular event-free rate in hemodialysis patients. Patients were divided into four groups according to plasma pentosidine level. First quartile (plasma pentosidine level <24.7 pmol/mg alb, $N = 26$), 2nd quartile (plasma pentosidine level 24.7–32.9 pmol/mg alb, $N = 28$), 3rd quartile (plasma pentosidine level 32.9–40.7 pmol/mg alb, $N = 28$) and 4th quartile (plasma pentosidine level >40.7 pmol/mg alb, $N = 28$). *$p < 0.0.5$ and **$p < 0.01$ compared to 1st quartile

Discussion

In this study, we demonstrated that the hemodialysis patients with higher plasma pentosidine levels had a high risk for cardiovascular events during the 90-month follow-up. In addition, a high level of CRP is associated with an increased risk of cardiovascular events.

Uremic arteriosclerosis is characterized by arterial intima and media calcification. The extent of arterial calcification is a strong predictor of cardiovascular mortality; in particular, arterial media calcification has a strong impact in uremic patients [16]. Co-localization of pentosidine and calcified deposits in the aortic media was observed in hemodialysis patients [17]. Recently, the correlation between plasma levels of pentosidine and the aortic calcification index was shown in hemodialysis patients [18]. Furthermore, Taki et al. [4] demonstrated that plasma pentosidine levels were associated with the coronary artery calcification index, a predictor of future cardiovascular events in hemodialysis patients. These support our results that high plasma pentosidine levels are strongly associated with cardiovascular events in uremic patients.

In contrast, Stein et al. [7] reported that serum pentosidine levels could not be identified as independent risk factors for cardiovascular events in hemodialysis patients. The exact reasons for the discrepancy between their result and the current ones are not known. However, it is possible that the discrepancy was caused by the differences in follow-up period and hemodialysis vintage. Since their follow-up period was short (26 months), the incidence of cardiovascular events was lower than in the current study (26 vs. 36%). In addition, we found that the hemodialysis vintage was associated with cardiovascular events in univariate analysis. The mean hemodialysis vintage in Stein's study was 37 months, which was shorter than in the current study (114 months). The same discrepancies were observed when using N^{ε}-(carboxymethyl)-lysine (CML), a well-defined AGE. Wagner et al. [13] demonstrated that serum CML levels predict cardiovascular and overall mortality in hemodialysis patients. However, Schwedler et al. [19] indicated that a high serum CML level was linked to better survival in hemodialysis patients. The discrepancies between these two studies were caused by differences in the follow-up periods and incidence of preexisting cardiovascular disease. A lower incidence of preexisting cardiovascular disease contributes to better survival in hemodialysis patients. Since the follow-up periods were 90 months and patients with a history of apparent cardiovascular diseases were excluded in the current study, the impact of the plasma pentosidine level on cardiovascular events may not be biased by these factors.

In the current study, the incidence of stroke was greater than that of coronary heart disease. We found that ischemic stroke was more common than hemorrhagic stroke. This is consistent with the results of the CHOICE study [20]. Little is known about the relationship between AGEs and stroke. Recently, it has been demonstrated that skin AGEs were increased in ischemic stroke patients without renal failure [21]. Furthermore, Ikeda et al. [22] found that the high serum pentosidine level was an independent prognostic factor for acute ischemic stroke. These findings suggest that the association of plasma pentosidine level and ischemic stroke is also indicated in uremic patients.

Bush et al. [23] demonstrated that an elevated CRP level is an independent risk factor for cardiovascular events in ESRD patients. Inflammation may have a role in the production of AGEs. Miyata et al. [24] clearly showed a positive correlation between CRP and plasma pentosidine levels in patients with rheumatoid arthritis. Recently, Suliman et al. [25] demonstrated the plasma pentosidine level is positively correlated to hs-CRP in ESRD patients. We found both plasma pentosidine level and CRP were independent risk factors for cardiovascular events in hemodialysis patients. Unfortunately, we failed to show the correlation between them (data not shown) since we did not measure hs-CRP in the current study.

Several factors that affect the plasma pentosidine levels were demonstrated. In hemodialysis patients, the dialysis membrane type and dialysate purity were reported to have a strong influence on plasma pentosidine levels. The plasma pentosidine levels were lower in patients using polysulfone membranes than in patients using other membranes [26]. Furthermore, the switch from conventional to ultrapure dialysate significantly decreased the plasma pentosidine levels in hemodialysis patients [27]. In the current study, all patients used polysulfone membranes, and the endotoxin levels in the dialysate were below the detection limit throughout the study period. Using ultrapure dialysate, there was no difference in plasma pentosidine levels among different dialysis modalities, such as hemodialysis, hemodiafiltration and hemofiltration [28]. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor antagonist (ARB) have been shown to be potent inhibitors of AGEs formation [29]; however, no difference was observed in ACEI/ARB treatment in the current study. The serum AGE level in diabetic patients with normal renal function was higher than that in non-diabetic patients. In hemodialysis patients, Makita et al. [30] demonstrated that the serum AGE level was higher in diabetic than in non-diabetic patients. In contrast, Miyata et al. [15] demonstrated that there was no difference in the plasma pentosidine levels between diabetics and non-diabetics on hemodialysis. In the current study, we found no significant difference in diabetes prevalence among four groups divided by the plasma pentosidine level.

In summary, higher levels of plasma pentosidine were associated with cardiovascular events in hemodialysis patients. This indicated that the plasma pentosidine level predicts cardiovascular events in hemodialysis patients. This study has some limitations. First, the number of patients enrolled in this study was small. Second, we

measured only pentosidine as AGEs. It is important to confirm our findings by a large study with measurements of several AGEs.

Conflict of interest None declared.

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