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Low serum sodium concentration is a prognostic factor related to current blood glucose level in stable hemodialysis patients: an observational study

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Abstract

Background: A lot of risk factors for mortality have been proposed in hemodialysis patients. However, most of the findings were derived from the analyses using all of the hemodialysis patients. What we really want to know is the prognostic factor in stable hemodialysis patients who have good activities of daily living, because it is difficult to estimate their prognosis by physical appearance.

Methods: This is a 7-year observational study. The study involved registering 631 patients who had undergone hemodialysis for more than 1 year at enrollment and were still alive more than 1 year after it. Demographic and clinical data were collected to analyze the relationship with mortality. Moreover, the patients were age-stratified to investigate age-dependent prognostic factors.

Results: Low serum sodium concentration is an independent risk factor for all-cause and cardiovascular mortality common to a wide range of ages in stable hemodialysis patients. Causes of hyponatremia included the predialysis blood glucose level as well as the variables related to nutrition, inflammation, and fluid overload.

Conclusions: Low serum sodium concentration is a significant prognostic factor in stable hemodialysis patients. Low serum sodium concentration can be a clue to finding current poor glucose control in stable hemodialysis patients. Predialysis blood glucose level is one of the representative factors correlated with serum sodium concentration.

Keywords: Serum sodium concentration, Hemodialysis, Mortality, Diabetes, Blood glucose level

Background

To date, a lot of demographic characteristics and clinical data have been proposed as prognostic factors in hemodialysis (HD) patients. Diabetic patients have an increased mortality compared to non-diabetic patients. The variables related to nutrition and inflammation are also representative risk factors [1]. The dialysis prescription is important to control small- and middle-weight-protein uremic toxins, anemia, and mineral-bone disorder that are associated with the prognosis of HD patients [2]. However, most of these findings were derived from the analyses including all of the HD patients. There are few reports that focus on stable maintenance HD patients who have good activities of daily living (ADLs). In reality, clinicians and medical staff can easily predict the prognosis of patients in poor condition from their age, appearance, and behavior. Conversely, it is difficult to estimate the prognosis of stable HD patients with good ADLs. Consequently, what we really want to know is a common risk factor in such stable HD patients.

Low serum sodium concentration is related to mortality in not only HD patients [3], but also chronic kidney disease (CKD) [4, 5] and peritoneal dialysis patients [6, 7]. However, the reason why hyponatremia induces an increased mortality has yet to be fully examined [8]. Intervention to hyponatremia is challenged by individualized

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dialysate sodium prescription [9]. To date, dialysate sodium prescription has an effect on blood pressure and recovery time, while the relationship between dialysate sodium prescription and mortality remains uncertain [10, 11]. There is no solution to preventing a hyponatremia-related mortality risk without unveiling the hidden contributors to hyponatremia.

In this study, we investigated the risk factor for all-cause and cardiovascular mortality in stable HD patients who had undergone HD for more than 1 year at enrollment and were still alive more than 1 year after it, because HD patients have a higher mortality within a year after dialysis initiation [12] and our purpose is to seek for the prognostic marker in stable HD patients with good ADLs. Moreover, we stratified the patients according to their age to clarify the risk factor for mortality common to a wide range of ages. In addition, causes of low serum sodium concentration were evaluated, because low serum sodium was a common risk factor in our analysis.

Methods

Design and subjects

Seven hundred and forty patients received HD at Kawashima Hospital in April 2005. Of these, patients (i) who were visitors and (ii) who had acute illness, significant infection, or malignancy were initially excluded. Because our purpose of this study is to seek for the risk factor in stable maintenance HD patients who have good ADLs, the patients who had less than 1 year dialysis duration in April 2005 or who died before the end of March 2006 were also excluded, because the death rate is high in the first year after the initiation of dialysis treatment [12] and we wanted to avoid including the patients who had an unrevealed serious disease related to short life span.

Finally, 631 patients were included in the first crude analysis. Every patient received HD three times a week. In most patients, high-flux membranes with surface area of 1.4–2.2 m^2 were used according to clinical conditions. The ultrapure dialysate flow was fixed at 500 mL/min. The blood flow rate was between 220 and 280 mL/min, and the length of each HD session was between 3.5 and 5 h. Definition of cardiovascular mortality is deaths by ischemic heart disease, congestive heart failure, cerebrovascular disease, and sudden death used in the previous reports [13, 14]. This observational study was conducted for 7 years ending March 2012.

Next, we stratified the patients according to their age. We excluded 34 patients younger than 40 years old, because no one died within the 7-year observation period. We also excluded 12 patients older than or equal to 85 years old, because life expectancy is short. In fact, among the above mentioned 12 participants, 11 died within 7 years, and one moved 3 years later. The other patients were dichotomized between 40 and 64 years and 65 and 84 years old and defined as "middle-aged" and "older" patients, because the median age for prevalent HD patients was around 65 years old [12]. As a result, 341 patients were included in the middle-aged patient group, and 244 were involved in the older patient group in the second, age-stratified analysis.

Demographic and clinical characteristics were collected in April 2005. Blood samples for biochemical data were obtained from arteriovenous shunt just before starting the first HD session of the week. Cumulative mean predialysis β_2-microglobulin was the average value of serum β_2-microglobulin concentration taken every 6 months. Sodium concentration and interdialytic weight gain (the percentage of body weight gain/dry weight) were the average of the values in the first HD session of the first week in April, May, and June 2005. Kt/V, normalized protein catabolic rate (n-PCR) and creatinine generation rate (CGR) were calculated according to the formula of Shinzato [15, 16]. Serum calcium concentration was adjusted for serum albumin according to the equation: corrected Ca = measured Ca + (4.0 - serum albumin in g/dL) [17].

Statistical analysis

All values are expressed as mean ± SD. Spearman's coefficients are denoted by r_s. Statistical analysis was performed using SPSS for Windows version 13.0 (SPSS, Inc., Chicago, IL, USA). The variables related to patients' survival were initially examined by univariate Cox proportional hazards method. Urea nitrogen, creatinine, and hematocrit were deleted from the analysis because of a strong association ($r_s > 0.7$) with n-PCR, CGR, and hemoglobin, respectively. Multivariate Cox proportional hazards analysis were performed to identify the independent risk factor associated with mortality. In multivariate analysis, age, gender, HD duration, and diabetic nephropathy as the primary disease were unconditionally chosen in both full and final model analysis. The other possible factors associated with mortality that showed P less than 0.15 in univariate analysis were chosen in full model analysis. Variables that showed P less than 0.1 in full model analysis were used in final model analysis. The difference between groups was analyzed using Student's t test or Welch's t test. F test was used for comparing the factors of the total deviation. Categorical data were compared by the chi-square test. Correlation was analyzed by Spearman's rank correlation. Single and multiple regression analyses were also performed to explain serum sodium concentration using the variables above. Predialysis blood glucose level was added instead of diabetic nephropathy as the primary disease. The variables that showed P less than 0.05 in single regression analysis were used as possible factors in multiple regression analysis. Significance was defined by P less than 0.05.

Initially, the analysis was done using sodium concentration in April 2005. To confirm the results, the analysis was re-examined using average sodium concentration. The results were similar so the data obtained using average sodium concentration are shown in this manuscript.

Results

Low serum sodium concentration is a risk factor for 7-year all-cause and cardiovascular mortality of patients enrolled in crude analysis

Six hundred and thirty-one patients undergoing stable maintenance HD in April 2005 were enrolled in the first crude analysis. They were aged 24 to 94 years (mean ± SD, 61.1 ± 12.2 years). There were 395 men and 236 women. The clinical diagnoses of primary renal disease included chronic glomerulonephritis ($n = 286$), diabetic nephropathy ($n = 126$), nephrosclerosis ($n = 22$), polycystic kidney disease ($n = 17$), toxemia of pregnancy ($n = 18$), and others/unknown ($n = 162$). In the following 7-year observation period (actual follow-up period: 68.3 ± 23.3 months), 194 patients (30.7%) died. Among the 194 patients who died, 72 patients (11.4%) died from cardiovascular events. These events consisted of ischemic heart disease ($n = 17$), congestive heart failure ($n = 23$), cerebrovascular disease ($n = 19$), and sudden death ($n = 13$). Non-cardiovascular deaths suffered from infectious disease ($n = 64$), malignancy ($n = 13$), and the others/unknown ($n = 45$) (Table 1). To examine the influential factor for all-cause mortality, univariate analysis with Cox proportional hazard model was performed. The variables analyzed were shown in Table 1. Urea nitrogen, creatinine, and hematocrit were excluded because of a strong correlation with the other variable as described in the "Methods" section. Among them, we found that increased age, male sex, diabetic nephropathy as the primary disease, higher β_2-microglobulin, calcium, lower Kt/V, n-PCR, CGR, hemoglobin, platelet, albumin, uric acid, mean sodium, potassium, phosphate, and smaller interdialytic weight gain were related to mortality which have P less than 0.15 in univariate analysis. Multivariate analysis with Cox proportional hazard model (full model analysis) was performed using the variables above extracted in univariate analysis to identify the independent factor for mortality. As shown in Table 2, increased age, male sex, diabetic nephropathy as the primary disease, longer duration of HD, higher β_2-microglobulin, calcium, and phosphate, lower CGR, hemoglobin, and mean sodium were the possible factors with P less than 0.1 in full-model analysis. Finally, we performed multivariate analysis with Cox proportional hazard model (final model analysis) again with the possible factors. It revealed that all of the factors were the independent predictors of mortality in the final model analysis (P less than 0.05). Concerning cardiovascular mortality, increased age, male sex, diabetic nephropathy as the primary disease, and lower n-PCR, CGR, hemoglobin, albumin, uric acid, mean sodium, and phosphate were related to mortality which have P less than 0.15 in univariate analysis. As shown in Table 3, full and final model analysis revealed that increased age, male sex, diabetic nephropathy as the primary disease, lower hemoglobin, and mean sodium were the independent prognostic factors of mortality. Consequently, hyponatremia was chosen as a risk factor for both all-cause and cardiovascular mortality in the first crude analysis.

Table 1 Demographic and clinical characteristics of stable hemodialysis patients enrolled in crude analysis

Number of patients	631
Deaths during follow-up, *n* (%)	194 (30.7%)
Deaths in cardiovascular disease, *n* (%)	72 (11.4%)
Age, years	61.1 ± 12.2
Female, *n* (%)	236 (37.4%)
Diabetic nephropathy, *n* (%)	126 (20.0%)
Hemodialysis duration, months	110.1 ± 86.2
Body mass index, kg/m^2	22.2 ± 3.2
Kt/V	1.51 ± 0.26
Cumu. mean predia. β_2-M, mg/L	28.7 ± 5.3
Normalized PCR, g/kg/day	1.01 ± 0.18
Creatinine generation rate, %	100.7 ± 22.2
WBC count, 10^3/μL	6.09 ± 1.81
Hemoglobin, g/dL	10.6 ± 1.1
Hematocrit, %	32.4 ± 3.6
Platelet count, 10^3/μL	192.6 ± 56.8
Albumin, g/dL	3.66 ± 0.34
Urea nitrogen, mg/dL	75.3 ± 15.9
Uric acid, mg/dL	7.72 ± 1.18
Creatinine, mg/dL	11.4 ± 2.8
Mean predialysis sodium, mEq/L	139.9 ± 2.8
Potassium, mEq/L	4.86 ± 0.69
Calcium, mg/dL	9.83 ± 0.79
Phosphate, mg/dL	5.16 ± 1.12
Mean interdialytic weight gain, % of DW	4.52 ± 1.31
Actual follow-up period, months	68.3 ± 23.3

Calcium was adjusted for serum albumin according to the equation: corrected Ca = measured Ca + (4.0 - serum albumin in g/dL)
Urea nitrogen, creatinine, and hematocrit were excluded in crude analysis because of a strong association with normalized PCR, creatinine generation rate, and hemoglobin, respectively
Cumu. mean predia. β_2-M cumulative mean predialysis β_2-microglobulin, *PCR* protein catabolic rate. *WBC* white blood cell, *DW* dry weight

Characteristics of stable middle-aged and older patients undergoing HD

Next, we wonder whether hyponatremia is a risk factor common to a wide range of ages or not. Therefore, we

Table 2 Significant independent factors associated with all-cause mortality in stable hemodialysis patients

	Univariate			Multivariate (full model)			Multivariate (final model)		
Variable	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age (per 1 year)	1.089	1.074–1.104	< 0.001	1.100	1.081–1.119	< 0.001	1.098	1.081–1.116	< 0.001
Gender (vs. female)	1.768	1.289–2.425	< 0.001	1.702	1.172–2.471	0.005	1.759	1.264–2.449	0.001
DN (vs. non-DN)	2.149	1.583–2.915	< 0.001	1.687	1.190–2.392	0.003	1.673	1.184–2.363	0.004
HD duration (per 1 month)	0.999	0.997–1.001	0.269	1.003	1.001–1.005	0.002	1.003	1.001–1.005	0.002
β_2M (per 1 mg/L)	1.049	1.023–1.076	< 0.001	1.061	1.033–1.089	< 0.001	1.063	1.037–1.089	< 0.001
CGR (per 1%)	0.979	0.973–0.985	< 0.001	0.980	0.973–0.988	< 0.001	0.980	0.973–0.987	< 0.001
Hemoglobin (per 1 g/dL)	0.803	0.711–0.908	< 0.001	0.866	0.760–0.987	0.032	0.852	0.753–0.964	0.011
Mean sodium (per 1 mEq/L)	0.863	0.822–0.907	< 0.001	0.929	0.885–0.974	0.002	0.919	0.878–0.963	< 0.001
Calcium (per 1 mg/dL)	1.202	0.991–1.457	0.062	1.190	0.983–1.439	0.074	1.236	1.028–1.486	0.024
Phosphate (per 1 mg/dL)	0.771	0.672–0.886	< 0.001	1.213	1.035–1.422	0.017	1.181	1.022–1.365	0.024

In addition to age, gender, hemodialysis duration, and diabetic nephropathy, possible factors that showed *P* less than 0.15 in univariate analysis such as Kt/V, β_2-microglobulin, protein catabolic rate, creatinine generation rate, hemoglobin, platelet, albumin, uric acid, mean sodium, potassium, calcium, phosphate, and mean interdialytic weight gain were chosen in full-model analysis

Final model analysis was done with age, gender, hemodialysis duration, diabetic nephropathy, and the variables with *P* less than 0.1 in full-model analysis such as β_2-microglobulin, creatinine generation rate, hemoglobin, mean sodium, calcium, and phosphate

DN diabetic nephropathy, *HD duration* hemodialysis duration, *β_2M* cumulative mean predialysis β2-microglobulin, *CGR* creatinine generation rate, *HR* hazard ratio, *95% CI* 95% confidence interval

divided the stable HD patients into middle-aged and older patients. As shown in Additional file 1: Table S1, as expected, older patients had a higher mortality. Causes of death were shown in Additional file 2: Table S2. Older patients included a larger percentage of ones diagnosed with diabetic nephropathy and had shorter HD duration, lower n-PCR, CGR, hemoglobin, platelet, albumin, potassium, phosphate, and smaller interdialytic weight gain, suggesting older patients had lower activity and nutrient intake than middle-aged patients.

Low serum sodium concentration was selected as a prognostic factor for 7-year survival of stable middle-aged patients in age-stratified analysis

In stable middle-aged patients, using the same series of analysis, increased age, male sex, longer duration of HD, higher β_2-microglobulin, white blood cell (WBC) count, lower CGR, and mean sodium were the risk factors for mortality as shown in Additional file 3: Table S3. Moreover, higher WBC count and lower mean sodium were chosen as the prognostic factors for cardiovascular mortality as well as increased age and male sex (Additional file 4: Table S4). Therefore, hyponatremia was associated with poor prognosis in stable middle-aged patients.

Low serum sodium concentration was also selected as a prognostic factor for 7-year survival of stable older-aged patients in age-stratified analysis

In stable older patients, increased age, male sex, diabetic nephropathy as the primary disease, higher β_2-microglobulin, WBC count, lower CGR, hemoglobin, and mean sodium were the risk factors for mortality as shown in Additional file 5: Table S5. Moreover, lower hemoglobin and mean sodium as well as increased age and diabetic nephropathy as the primary disease were chosen as the prognostic factors for cardiovascular

Table 3 Significant independent factors associated with cardiovascular mortality in stable hemodialysis patients

	Univariate			Multivariate (Full model)			Multivariate (Final model)		
Variable	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*
Age (per 1 year)	1.086	1.061–1.111	< 0.001	1.089	1.060–1.117	< 0.001	1.087	1.061–1.114	< 0.001
Gender (vs. female)	2.148	1.246–3.700	0.006	2.028	1.151–3.572	0.014	1.984	1.131–3.479	0.017
DN (vs. non-DN)	2.546	1.565–4.142	< 0.001	2.050	1.169–3.595	0.012	2.008	1.178–3.423	0.010
HD duration (per 1 month)	0.999	0.996–1.001	0.349	1.001	0.998–1.004	0.425	1.001	0.998–1.004	0.409
Hemoglobin (per 1 g/dL)	0.737	0.608–0.893	0.002	0.752	0.618–0.915	0.004	0.750	0.620–0.906	0.003
Mean sodium (per 1 mEq/L)	0.789	0.731–0.851	< 0.001	0.830	0.768–0.896	< 0.001	0.826	0.767–0.890	< 0.001

In addition to age, gender, hemodialysis duration, and diabetic nephropathy, possible factors that showed *P* less than 0.15 in univariate analysis such as protein catabolic rate, creatinine generation rate, hemoglobin, albumin, uric acid, mean sodium, and phosphate were chosen in full model analysis

Final model analysis was done with age, gender, hemodialysis duration, diabetic nephropathy and the variables with *P* less than 0.1 in full model analysis such as hemoglobin, and mean sodium

DN diabetic nephropathy, *HD duration* hemodialysis duration, *HR* hazard ratio, *95% CI* 95% confidence interval

mortality (Additional file 6: Table S6). Therefore, hyponatremia was also associated with poor prognosis in stable older patients.

Causes of hyponatremia

Causes of hyponatremia were unclear, so we divided patients by average mean sodium concentration. Then, as shown in Table 4, the low sodium group consisted of larger percentages of male sex, patients diagnosed with diabetic nephropathy, and had higher WBC count, platelet count, potassium, larger interdialytic weight gain, lower CGR, albumin, and uric acid. Concerning age-stratified analysis, in stable middle-aged patients, the low sodium group consisted of a larger percentage of patients diagnosed with diabetic nephropathy and had higher platelet, calcium, larger interdialytic weight gain, and lower albumin (Additional file 7: Table S7). In stable older patients, the low sodium group consisted of larger percentages of male sex, patients diagnosed with diabetic nephropathy, and had higher potassium, larger interdialytic weight gain, lower body mass index, and uric acid (Additional file 8: Table S8). Thus, low sodium concentration was especially detected in patients diagnosed with diabetic nephropathy and/or with larger interdialytic weight gain common to a wide range of ages.

Table 4 Demographic and clinical characteristics of low sodium or high sodium patients

	Low < 139.9	High ≥ 139.9	*P*
Number of patients	274	357	N/A
Deaths during follow-up, *n* (%)	108 (39.4%)	86 (24.1%)	< 0.001
Deaths in cardiovascular disease, *n* (%)	49 (17.9%)	23 (6.4%)	< 0.001
Age, years	60.6 ± 12.7	61.5 ± 11.7	0.387
Female, *n* (%)	89 (32.5%)	147 (41.2%)	0.025
Diabetic nephropathy, *n* (%)	80 (29.2%)	46 (12.9%)	< 0.001
Hemodialysis duration, months	107.4 ± 83.8	112.3 ± 88.0	0.480
Body mass index, kg/m^2	21.9 ± 3.3	22.4 ± 3.2	0.114
Kt/V	1.50 ± 0.24	1.51 ± 0.27	0.887
Cumu. mean predia. β_2-M, mg/L	29.1 ± 5.4	28.4 ± 5.2	0.113
Normalized PCR, g/kg/day	1.01 ± 0.19	1.01 ± 0.17	0.688
Creatinine generation rate, %	97.7 ± 21.8	103.0 ± 22.2	0.003
WBC count, 10^3/μL	6.32 ± 1.86	5.92 ± 1.75	0.006
Hemoglobin, g/dL	10.5 ± 1.2	10.6 ± 1.1	0.239
Hematocrit, %	32.2 ± 3.8	32.6 ± 3.4	0.111
Platelet count, 10^3/μL	199.8 ± 61.7	187.2 ± 52.1	0.006
Albumin, g/dL	3.62 ± 0.36	3.70 ± 0.32	0.003
Urea nitrogen, mg/dL	75.1 ± 17.1	75.4 ± 15.0	0.834
Uric acid, mg/dL	7.59 ± 1.25	7.83 ± 1.11	0.011
Creatinine, mg/dL	11.2 ± 2.7	11.6 ± 2.9	0.064
Mean predialysis sodium, mEq/L	137.3 ± 1.9	141.9 ± 1.3	< 0.001
Potassium, mEq/L	4.93 ± 0.74	4.80 ± 0.66	0.020
Calcium, mg/dL	9.89 ± 0.86	9.78 ± 0.73	0.073
Phosphate, mg/dL	5.11 ± 1.21	5.20 ± 1.05	0.298
Interdialytic weight gain, % of DW	4.81 ± 1.32	4.29 ± 1.26	< 0.001

Calcium was adjusted for serum albumin according to the equation: corrected Ca = measured Ca + (4.0 - serum albumin in g/dL)
Cumu. mean predia. β_2-M cumulative mean predialysis β_2-microglobulin, *PCR* protein catabolic rate, *WBC* white blood cell, *DW* dry weight, *N/A* not applicable

Non-fasting predialysis blood glucose level was inversely correlated with serum sodium concentration

The low sodium group consisted of a larger percentage of patients diagnosed with diabetic nephropathy. Therefore, we investigated the relationship between non-fasting predialysis blood glucose level and serum sodium concentration. Then, we found a weak inverse correlation between non-fasting predialysis blood glucose level and serum sodium concentration (r_s = – 0.209, 0.204, and 0.237 in crude analysis, middle-aged patients, and older patients, respectively) (Fig. 1a–c). Next, we divided the patients with blood glucose level greater than or equal to 140 mg/dL from those with blood glucose level less than 140 mg/dL. We decided the cutoff value according to the diagnostic criteria of diabetes mellitus [18]. Then, as shown in Fig. 1d–f, we found a better correlation between blood glucose level and serum sodium concentration in the patients with blood glucose level greater than or equal to 140 mg/dL (r_s = – 0.296, 0.392, and 0.157 in crude analysis, middle-aged patients, and older patients, respectively) than that in the patients with blood glucose level less than 140 mg/dL (r_s = – 0.036, 0.054, and 0.048 in crude analysis, middle-aged patients, and older patients, respectively. Data not shown.).

The correlation of interdialytic weight gain and the other variables with serum sodium concentration

The low sodium group had a larger interdialytic weight gain common to a wide range of ages. Therefore, we also investigated the correlation of interdialytic weight gain with serum sodium concentration. As shown in Fig. 2, interdialytic weight gain had a weak inverse correlation with serum sodium concentration especially in older patients. The other variables shown in Table 1 were not correlated with serum sodium concentration in all of the crude analysis, middle-aged patients, and older patients (r_s < 0.2).

Single and multiple regression analysis to explain serum sodium concentration

Single and multiple regression analyses were performed to explain serum sodium concentration. However, we could only find low coefficient of determination (at most

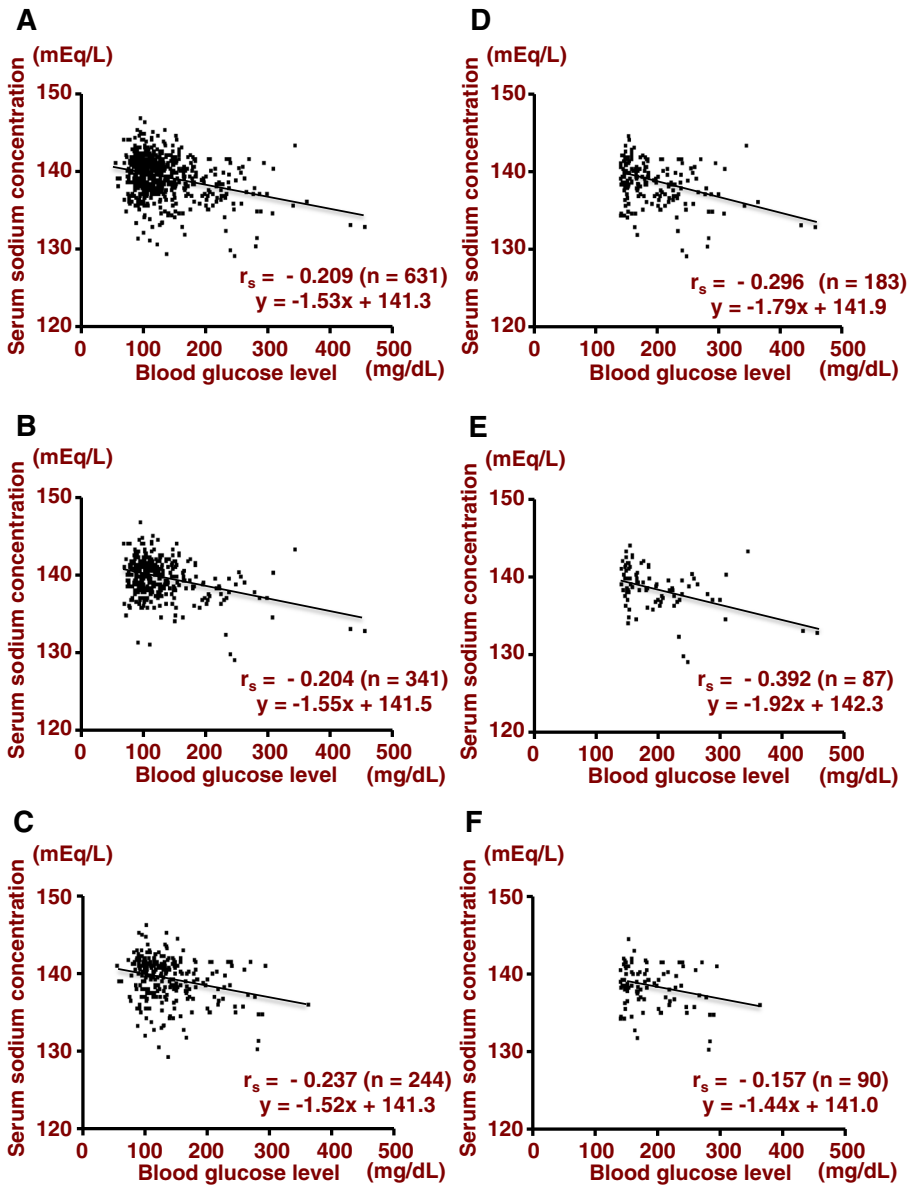

Fig. 1 Non-fasting predialysis blood glucose level was inversely related to serum sodium concentration. **a**–**c** Non-fasting predialysis blood glucose level was inversely related to serum sodium concentration in crude analysis (**a**), middle-aged patients (**b**), and older patients (**c**). **d**–**f** The relationship between serum sodium concentration and non-fasting predialysis blood glucose level in the patients with blood glucose level greater than or equal to 140 mg/dL in crude analysis (**d**), middle-aged patients (**e**), and older patients (**f**). Spearman's coefficients are denoted by r_s. The regression equation was shown in each graph

0.165 in older patients) in all of the crude analysis, middle-aged patients, and older patients (data not shown).

Discussion

In this study, we demonstrated that low serum sodium concentration is related to poor prognosis in stable HD patients. The low sodium group had a larger percentage of patients diagnosed with diabetic nephropathy and with larger interdialytic weight gain common to a wide range of ages. Predialysis blood glucose level affected serum sodium concentration.

The first finding of this study is that hyponatremia is confirmed as an independent prognostic factor for all-cause and cardiovascular mortality in stable HD patients common to a wide range of ages. HD-related guidelines were established based on the data obtained from all of the HD patients. What we really need is to find out the hidden risk factor in stable HD patients with good ADLs and look for the solution to preventing poor prognosis.

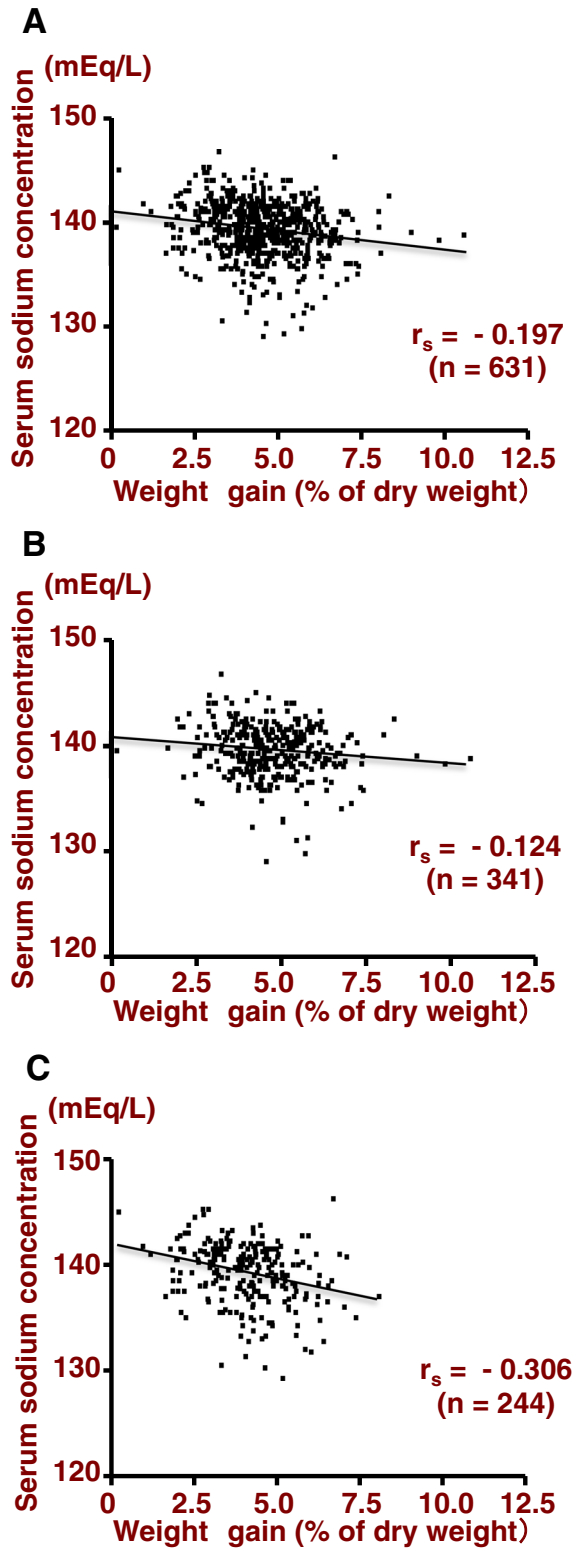

Fig. 2 The relationship between interdialytic weight gain and serum sodium concentration. Interdialytic weight gain was inversely related to serum sodium concentration especially in older patients. **a** crude analysis, **b** middle-aged patients, and **c** older patients

Serum sodium concentration is a widely available blood test item, evaluated on a daily basis. Our study clearly showed that low serum sodium concentration is important to forecast the prognosis in stable HD patients, common to a wide range of ages.

The reason why hyponatremia is associated with poor prognosis was unknown. Hyponatremia is recognized as a risk factor in CKD patients [3–8]. However, is hyponatremia a direct cause of death in HD patients? Chawla et al. discussed the role of hyponatremia in mortality in hospitalized patients [19]. The authors found that more than two thirds of patients who died after a sodium concentration less than 120 mEq/L had acute severe progressive illnesses and only 5.6% of the dead patients could plausibly be related to adverse consequences of hyponatremia. They concluded that the nature of underlying illness, rather than the severity of hyponatremia, best explains mortality associated with hyponatremia. In our study, relatively low sodium concentration within normal range was related to a higher mortality. Therefore, we also assume that hyponatremia is an indirect prognostic factor. We need to find out underlying causes of hyponatremia.

More important findings of this study were the analyses concerning causes of hyponatremia. It is noteworthy that no correlation was found between serum sodium concentration and the variables shown in Table 1 ($r_s < 0.2$) except interdialytic weight gain in older patients (Fig. 2). Next, the low sodium group in our study consisted of more patients diagnosed with diabetic nephropathy than the high sodium group. Actually, serum sodium concentration had a weak inverse correlation with non-fasting predialysis blood glucose level (Fig. 1). Katz et al. described theoretical considerations about hyperglycemia-induced hyponatremia–calculation of expected serum sodium depression, demonstrating the serum sodium concentration decreases by 1.6 mEq/l for every 100 mg/dl increase in glucose concentration due to water shifts from the intracellular to the extracellular compartment [20]. Penne et al. validated the correction factor in HD patients and reported that the mean slope for the relation between serum sodium and glucose concentration – 1.47 ± 0.82 mEq/l per 100 mg/dl increase in glucose level [21]. In our study, the regression equations in Fig. 1 were consistent with the previous report, and higher glucose level had better correlation with serum sodium concentration (Fig. 1d–f), suggesting serum sodium concentration was affected by glucose-induced serum osmolarity. Therefore, when we see the HD patients with low serum sodium concentration, it can be a promising clue to diagnosing diabetes newly, because HbA1c and glycated albumin are influenced by alterations in hemoglobin and albumin metabolism, which makes it difficult to interpret these values in HD patients [22]. However, the impact of low serum sodium on

survival cannot be explained only by diabetic status, because hyponatremia is an independent risk factor after adjustment of the existence of diabetic nephropathy as the primary disease. Coefficient of determination to explain serum sodium concentration was low in multiple regression analysis even if we added non-fasting predialysis blood glucose level as a possible factor. Therefore, hyponatremia reflects on a mixture of underlying causes. Pérez-García et al. reported that HD patients with hyponatremia have a poor prognosis and present malnutrition or fluid overload [23]. Poulikakos et al. reported that low serum sodium is associated with protein energy wasting and increased interdialytic weight gain in HD patients [24]. Dekker et al. found that hyponatremia is associated with malnutrition, inflammation, and fluid overload [25]. Our study supports their findings because the low sodium group had significantly lower CGR, higher WBC count, and larger interdialytic weight gain (Table 4). Interdialytic weight gain was inversely correlated with serum sodium concentration especially in older patients (Fig. 2). It might be due to the body water compartments with human aging. Intracellular water was reported lower in elderly HD patients than in young HD patients [26]. Thus, fluid overload may be also related to poor prognosis in our low serum sodium group.

Consequently, low sodium concentration is a prognostic marker related to current blood glucose level, as well as interdialytic weight gain, malnutrition, and inflammation. It means that the intervention to resolve the causes described above should be done to correct hyponatremia. Control of serum sodium concentration by dialysate sodium prescription will not have a direct effect on mortality.

The strength of this study is a long observation period. The limitation is a lack of a representative inflammation marker such as C-reactive protein. High WBC count was chosen as a risk factor for all-cause mortality in age-stratified analysis (Additional file 3: Table S3 and Additional file 5: Table S5). It suggested that inflammation is also related to mortality in our cohort. Another limitation of this study is that the finding of this study might not be applied to all patients with HD because the characteristics of enrolled patients were different from national data concerning age and the rate of the patients with diabetic nephropathy [3, 12].

Conclusions

In summary, low serum sodium concentration is an easily detectable and routinely examined prognostic factor in stable HD patients common to a wide range of ages. Causes of hyponatremia are complicated. Causes consist of not only malnutrition, inflammation, and fluid overload but also the predialysis blood glucose level. Our study suggested that current diabetic status should be checked when we see the stable HD patients with low serum sodium concentration.

Additional files

Additional file 1: Table S1. Demographic and clinical characteristics of stable hemodialysis patients analyzed in age-stratified analysis (PDF 142 kb)

Additional file 2: Table S2. Causes of death in stable middle-aged and older patients. (PDF 94 kb)

Additional file 3: Table S3. Significant independent factors associated with all-cause mortality in stable middle-aged patients. (PDF 134 kb)

Additional file 4: Table S4. Significant independent factors associated with cardiovascular mortality in stable middle-aged patients. (PDF 124 kb)

Additional file 5: Table S5. Significant independent factors associated with all-cause mortality in stable older patients. (PDF 137 kb)

Additional file 6: Table S6. Significant independent factors associated with cardiovascular mortality in stable older patients. (PDF 121 kb)

Additional file 7: Table S7. Demographic and clinical characteristics of low sodium or high sodium stable middle-aged patients. (PDF 130 kb)

Additional file 8: Table S8. Demographic and clinical characteristics of low sodium or high sodium stable older patients. (PDF 131 kb)

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Availability of data and materials
Please contact the corresponding author for data requests.

Authors' contributions
KT designed and promoted the study. SU acquired and summarized data. KN statistically analyzed the results and wrote the manuscript. TD gave critical revision of article. JM conceived and reviewed the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate
All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki, and all patients gave their informed consent. This study was approved by the Research Ethics Committee of Kawashima Hospital.

Consent for publication
We have also obtained consent to publish from the participants to report individual patient data.

Competing interests
The authors declare that they have no competing interests.

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