

Salt Intake and All-Cause Mortality in Hemodialysis Patients

Tatsuyoshi Ikenoue^{a, b, f} Kiyomi Koike^c Shingo Fukuma^{a, f} Satoshi Ogata^d
Kunitoshi Iseki^e Shunichi Fukuhara^a

^aDepartment of Healthcare Epidemiology, Kyoto University Graduate School of Medicine and Public Health, Yoshida Konoe-cho, Kyoto, Japan; ^bFujiidera Keijinkai Clinic, Fujiidera, Japan; ^cDivision of Nephrology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan; ^dCommittee of the Renal Data Registry, The Japanese Society for Dialysis Therapy, Tokyo, Japan; ^eClinical Research Support Center, Tomishiro Central Hospital, Tomigusuku, Japan; ^fHuman Health Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan

Keywords

Sodium chloride · Dietary · Renal dialysis · Mortality

Abstract

Background: Although some clinical practice guidelines regarding hemodialysis recommend salt restriction, few studies have examined the association between salt intake and clinical outcomes in hemodialysis patients. This study aimed to clarify the association between salt intake and mortality in hemodialysis patients. **Methods:** This retrospective cohort study was based on the Japanese Society for Dialysis Therapy renal data registry database (2008) and included 88,115 adult patients who had received hemodialysis for at least 2 years. Estimated salt intake was the main predictor and was calculated from intra-dialytic weight loss and pre- and post-dialysis serum sodium levels. Nonlinear logistic regression was used to determine the association between salt intake and mortality, adjusting for potential confounders. The outcomes considered were all-cause mortality and cardiovascular death at 1 year. **Results:** The median (25–75th percentile) salt intake at baseline was 6.4 (4.6–8.3) g/day. At 1 year, all-cause mortality occurred in 1,845 (2.1%) patients, including 807 cardiovascular deaths. The low salt intake group (<6 g/

day) demonstrated the highest all-cause mortality and cardiovascular deaths. No association was observed between high salt intake, all-cause mortality and cardiovascular deaths. The lowest risk for all-cause mortality and cardiovascular death occurred among patients with an estimated salt intake of 9 g/day. **Conclusion:** Low salt intake, but not high salt intake, was associated with all-cause and cardiovascular mortality in Japanese hemodialysis patients. Further studies to justify including a lower limit of salt intake for hemodialysis patients are suggested.

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Introduction

It is often recommended that patients on hemodialysis lower their salt intake to assist with weight control and because they are at increased risk for cardiovascular disease. European guidelines recommend a salt intake of 5–6 g/day [1], US guidelines recommend 5 g/day [2], and Japanese guidelines recommend 6 g/day [3]. The Dialysis Outcomes and Practice Patterns Study reported that the Japanese participants in that study had a salt intake of 9 g/day, as estimated from a food frequency questionnaire

[4]. Patients on hemodialysis in Western countries consume 6–7 g/day of salt, as estimated using a simple equation. It is suggested that half the number of hemodialysis patients cannot adhere to the recommended salt intake. Many hemodialysis patients are required to restrict dietary intake, including restricting sodium intake [5]. This can be of particular discomfort to some hemodialysis patients in terms of a perceived burden, and perceived burdens among hemodialysis patients are strongly associated with an elevated risk for death [6].

Inter-dialytic salt intake for hemodialysis patients can be approximately determined from their inter-dialytic weight gain (IDWG) [7–12]. An anuric hemodialysis patient responding to salt-induced osmometric thirst will show about 1 kg of IDWG for every 8 g of salt consumed [8]. Some observational studies have reported an association between high mortality and high IDWG [11–14]. In a small selected sample, higher salt intake was independently associated with greater all-cause mortality [15]. Findings such as these have led to expressions such as, “The lower the sodium intake, the better,” [8, 16] and have resulted in medical staff imposing severe salt restrictions on hemodialysis patients.

Recently, there have been doubts concerning the association between salt intake and mortality. In non-end-stage renal disease patients, compared with a baseline sodium excretion of 4–5.9 g/day (10.2–15.2 g/day of salt), a sodium excretion of <3 g/day (7.6 g/day of salt) was associated with an increased risk for cardiovascular death [17]. In the general population, an estimated sodium intake of 3–6 g/day (7.6–15.2 g/day of salt) was associated with a lower risk for death and cardiovascular events than was either a higher or lower estimated level of salt intake [18]. The volume of salt intake associated with the lowest risk was higher than that recommended in the guidelines. Additionally, it is reported that a low dietary salt intake independently predicts high all-cause and cardiovascular mortality in peritoneal dialysis patients [19]. In this study, we conducted a thorough analysis of the Japanese Society for Dialysis Therapy (JSDT) renal data registry database to directly examine the association between salt intake and all-cause mortality in a population of hemodialysis patients.

Methods

Study Design

This was a retrospective cohort study. Data were collected from the JSDT renal data registry database. The design and detailed methods of the questionnaire survey used to collect information on hemodialysis patients have been previously described [20]. The

JSDT renal data registry database is a Japanese annual survey of dialysis facilities and patients, and has been prospectively collecting information on dialysis patients. The response rate to the questionnaire has exceeded 98% every year, meaning that the database accounts for nearly all Japanese hemodialysis patients. Data collection is conducted every December. Details on the inception, limitations, validity, variables, and questionnaires used are available online at the JSDT website (www.jsdt.or.jp). This study followed the Declaration of Helsinki principles. The Ethical Committee of JSDT approved this study.

Study Participants

We obtained baseline and 1-year follow-up data from the JSDT renal data registry database in 2008 and 2009 respectively. We only included patients who had undergone hemodialysis for at least 2 years at baseline. Further, to prevent any improper estimation of salt intake, we excluded patients whose IDWG was below 0 kg, whose estimated salt intake was <0.5th or >99.5th percentile, who were not receiving hemodialysis 3 times weekly, and who received peritoneal dialysis.

Exposure/Comparison and Outcomes

The main predictor of outcomes was estimated salt intake at baseline, which was calculated from intra-dialytic weight loss (IDWL) and serum sodium levels before and after dialysis. This method has been previously validated [21, 22]. In the original approach, IDWG was used to calculate salt intake. Given that IDWL is strongly correlated with preceding IDWG, this study used IDWL instead of IDWG [23].

The main outcome in this study was all-cause mortality over a period of 1 year. The secondary outcome was cardiovascular death and all-cause mortality without cancer death over a period of 1 year. Cardiovascular death included sudden death; death from heart failure, myocardial infarction, or stroke; and death from other vascular diseases. We considered that poor nutrition among cancer patients would strengthen the association between low salt intake and mortality; therefore, we conducted a secondary analysis excluding cancer-related death to avoid overestimating this association.

Statistical Analysis

Nonlinear logistic regression was used to determine the association between salt intake and mortality, adjusting for age, gender, body mass index (BMI), hemodialysis vintage, dialysis time per one-dialysis session, Kt/V (used to quantify dialysis), protein catabolic rate normalized to body weight (nPCR), comorbidity conditions, cause of end-stage renal disease, type of vascular access, serum potassium, phosphate, calcium, C-reactive protein levels, and endotoxin level in the dialysate. Systolic blood pressure was not adjusted for because it is affected by salt intake and is an intermediate factor in the causal pathway between salt intake and cardiovascular death [24–27]. Cubic splines were plotted with the reference being median salt intake and 4 knots. Salt intake was categorized into 2 g/day increments (daily salt intake: <2, 2–3.99, 4–5.99, 6–7.99, 8–9.99, 10–11.99, and ≥12 g) and associations between the categories and mortality were examined. Kt/V and nPCR have been defined in a previous study [23]. Confounders were only measured at baseline. These covariates were reported as potential confounders between all-cause mortality and salt intake.

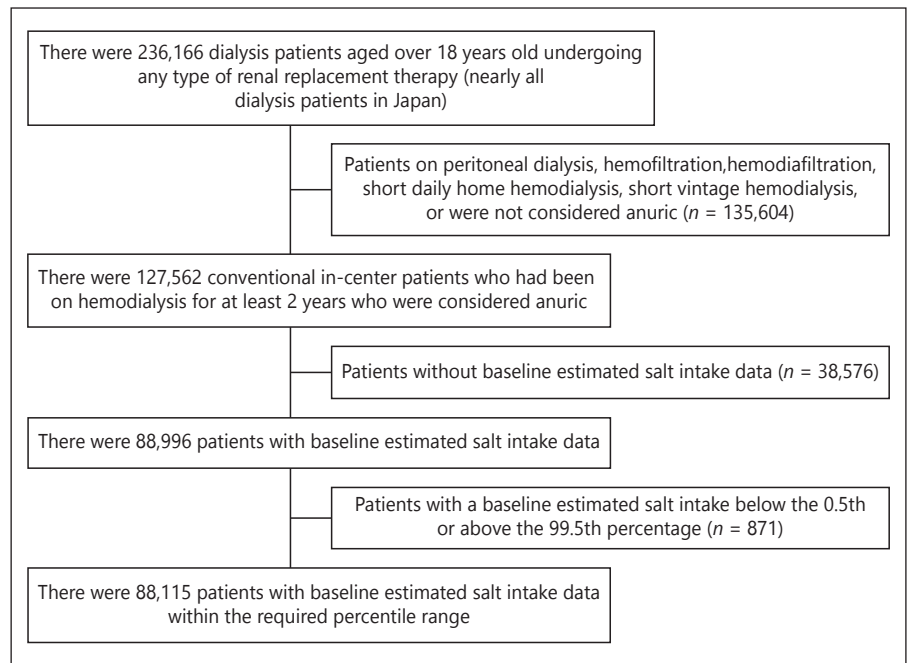


Fig. 1. Flowchart of the study enrolment process.

Multivariate imputation using chained equations was used to impute for missing variables [28]. Ten copies of data were used, each with missing values suitably imputed. We estimated mean ORs and adjusted 95% CIs using Rubin's rules [29]. *p* values are reported as 2-sided and a *p* value <0.05 was considered statistically significant. Stata/IC 13.1 (Stata Corp., College Station, TX, USA) and R 3.50 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org/) with the 'rms' package were used for analyses.

Stratified and Subgroup Analyses

To avoid any influence of nutritional status on findings, stratified analysis was performed. After dividing patients on the basis of nPCR, serum albumin, and BMI, we examined the association between salt intake and mortality. The examination was restricted to patients with serum albumin >3.8 g/dL and BMI >23 kg/m², in accordance with the concept of protein-energy wasting. To avoid any influence of IDWG on findings, stratified analysis by 4 groups divided on the basis of quantile points of IDWG was performed.

Sensitivity Analysis

Four sensitivity analyses were conducted. First, to estimate the influence of unmeasured confounding on the association between salt intake and mortality, array analysis was performed. The association between salt intake and mortality was determined in patients with a daily salt intake <6 g and 6–9.99 g. Sensitivity analysis was then performed to determine how strong and imbalanced the confounder would need to be in order to render any association non-significant [30, 31]. Second, to eliminate the influence of sodium excretion into the urine, we also conducted analysis on restricted patients who received hemodialysis for at least 5 years, who would be anuric. Third, to eliminate the influence of the vulnerable population, we conducted the analysis after excluding patients who died within 6 months.

Results

Study Participants

A total of 88,115 adult patients were enrolled in the study. The process by which patients were enrolled from the database is shown in Figure 1. Baseline characteristics (overall and based on the category of salt intake) are listed in Table 1. From the overall population, the mean age was 65.09 years, 60.2% were men, and 31.4% were on hemodialysis because of diabetic nephropathy. At baseline, the median (25–75th percentile) daily salt intake was 6.4 (4.6–8.3) g. There were 49,073 patients (55.7%) with a salt intake of >6 g/day. Generally, patients with a high salt intake were younger, had higher nPCR, BMI, and serum albumin, had lower serum C-reactive protein, and received dialysis for a longer period of time.

Distribution of All-Cause Mortality and Cardiovascular Death

After 1 year, all-cause mortality occurred in 1,845 (2.1%) patients and included 821 cardiovascular deaths. The all-cause mortality rate at 1-year post-examination was greatest in patients with a salt intake <2 g/day (52.5 deaths/1,000 persons) and lowest in those with a salt intake ≥12 g/day (8.5 deaths/1,000 persons; Table 2).

In the nonlinear model, there was a significant association between low salt intake and all-cause mortality over the

Table 1. Characteristics of the study participants at baseline according to estimated salt intake

	Overall (n = 88,115)	Estimated salt intake, g/day						
		<2 (n = 4,170)	2–3.99 (n = 12,031)	4–5.99 (n = 22,833)	6–7.99 (n = 24,349)	8–9.99 (n = 15,305)	10–11.99 (n = 6,479)	≥12 (n = 2,948)
Salt intake, g/day	6.50 (3.13)	1.09 (0.77)	3.16 (0.55)	5.06 (0.57)	6.97 (0.57)	8.88 (0.57)	10.83 (0.56)	12.94 (0.67)
nPCR, g/kg/day	1.16 (0.13)	1.08 (0.13)	1.12 (0.18)	1.15 (0.20)	1.17 (0.15)	1.18 (0.14)	1.19 (0.13)	1.20 (0.12)
Age, years	65.09 (13.76)	68.96 (13.79)	68.74 (12.13)	67.24 (12.02)	65.09 (11.62)	62.30 (11.55)	59.24 (11.38)	56.01 (11.51)
Vintage hemodialysis, years	9.07 (6.89)	8.02 (6.33)	8.88 (6.81)	9.27 (6.79)	9.23 (6.67)	9.10 (6.45)	8.92 (6.22)	8.74 (6.11)
Gender, male*	53,662 (60.9)	2,250 (54.0)	6,205 (51.6)	12,121 (53.1)	14,465 (59.4)	10,775 (70.4)	5,211 (80.4)	2,635 (89.4)
Cause of haemodialysis								
Chronic glomerulonephritis*	39,177 (44.5)	1,605 (38.5)	4,939 (41.1)	10,271 (45.0)	11,161 (45.8)	6,935 (45.3)	2,957 (45.6)	1,113 (44.5)
Diabetic nephropathy*	27,642 (31.4)	1,460 (35.0)	3,794 (31.5)	6,847 (30.0)	7,448 (30.6)	4,949 (32.3)	2,140 (33.0)	856 (34.2)
Nephrosclerosis*	5,215 (5.9)	289 (6.9)	845 (7.0)	1,465 (6.4)	1,367 (5.6)	806 (5.3)	304 (4.7)	112 (4.5)
Other*	16,081 (18.2)	816 (19.6)	2,453 (20.4)	4,250 (18.6)	4,373 (18.0)	2,615 (17.1)	1,078 (16.6)	421 (16.8)
Previous medical history								
Myocardial infarction*	5,235 (6.8)	268 (7.4)	722 (6.9)	1,360 (6.9)	1,488 (7.0)	901 (6.8)	350 (6.2)	121 (5.5)
Cerebral infarction*	10,944 (14.2)	707 (19.2)	1,933 (18.4)	3,189 (16.0)	2,777 (13.1)	1,525 (11.4)	556 (9.8)	165 (7.5)
Cerebral bleeding*	3,674 (4.8)	268 (7.4)	696 (6.7)	1,029 (5.2)	927 (4.4)	482 (3.6)	189 (3.3)	70 (3.2)
Leg amputation*	2,031 (2.6)	126 (3.4)	319 (3.0)	517 (2.6)	534 (2.5)	306 (2.3)	167 (2.9)	42 (1.9)
Femoral neck fracture*	1,844 (2.4)	175 (4.8)	389 (3.7)	588 (3.0)	412 (2.0)	204 (1.5)	57 (1.0)	14 (0.6)
BMI, kg/m ²	21.18 (3.77)	19.95 (3.66)	20.11 (3.14)	20.56 (3.20)	21.18 (3.65)	21.99 (3.88)	22.88 (4.13)	23.97 (4.29)
Serum potassium, mEq/L	5.04 (0.88)	4.64 (0.96)	4.83 (0.8)	4.98 (0.78)	5.10 (0.76)	5.19 (0.75)	5.26 (0.74)	5.25 (0.74)
Serum calcium-phosphorus product, mg ² /dL ²	48.33 (15.30)	42.56 (15.30)	44.79 (13.31)	46.91 (13.07)	48.90 (13.32)	50.62 (13.78)	52.96 (14.38)	54.58 (15.07)
CRP, mg/dL	0.48 (0.73)	1.00 (1.54)	0.64 (1.76)	0.48 (1.32)	0.41 (1.17)	0.38 (1.20)	0.39 (1.11)	0.37 (0.98)
Kt/V	1.19 (0.26)	1.21 (0.29)	1.23 (0.26)	1.22 (0.25)	1.20 (0.24)	1.16 (0.22)	1.11 (0.21)	1.08 (0.20)
Dialysis time, hours	3.99 (0.48)	3.80 (0.54)	3.86 (0.51)	3.94 (0.47)	4.01 (0.44)	4.08 (0.43)	4.14 (0.47)	4.21 (0.47)
Purification of dialysis	21,961 (28.8)	1,046 (29.0)	2,884 (27.7)	5,682 (28.8)	5,977 (28.3)	3,964 (29.9)	1,620 (28.8)	669 (30.3)
Vascular access								
Arteriovenous fistula*	63,506 (90.0)	2,877 (85.6)	8,338 (87.6)	16,131 (89.2)	17,683 (90.5)	11,384 (92.0)	4,850 (92.5)	1,907 (93.9)
Arteriovenous graft*	5,409 (7.7)	347 (10.3)	884 (9.3)	1,510 (8.4)	1,453 (7.4)	788 (6.4)	297 (5.7)	99 (4.9)
Other*	1,628 (2.3)	137 (4.1)	301 (3.2)	450 (2.5)	406 (2.1)	209 (1.7)	97 (1.9)	25 (1.2)

Continuous variables are expressed as mean (SD) and count data as number (percentage).

* Count data are summed.

nPCR, protein catabolic rate normalized to body weight; BMI, body mass index; CPR, C-reactive protein; Kt/V, used to quantify hemodialysis and peritoneal dialysis treatment adequacy.

1-year period (Fig. 2; online suppl. Fig. 2; for all online suppl. material, see www.karger.com/doi/10.1159/000492034). Mortality was highest in the low salt intake group. No marked association between high salt intake and all-cause mortality was observed. The association between low salt intake and mortality was stronger in the crude model than in the multivariate model. The lowest risk for all-cause mortality was 9.1 g/day in the multivariate model. The association between salt intake and cardiovascular death and between salt intake and all-cause mortality without cancer death was similar, with mortality being highest in the low salt intake group (online suppl. Fig. 1).

In the categorical model, when compared with an estimated salt intake of 8–9.99 g/day (the reference category), an estimated salt intake of 10 g/day or more was not associated with an increased risk for all-cause mortality (OR

1.06; 95% CI 0.83–1.36) or cardiovascular death (OR 0.95; 95% CI 0.68–1.34) in the multivariable analysis (Table 2). When compared with an estimated sodium excretion of 6–9.99 g/day, an estimated sodium excretion <6 g/day was associated with an increased risk for death from any cause (OR 1.59; 95% CI 1.40–1.80) and with death from cardiovascular causes (OR 1.61; 95% CI 1.35–1.91; Table 2).

Stratified and Subgroup Analyses

Regardless of nPCR, serum albumin level, or BMI, associations between salt intake and all-cause mortality remained relatively unchanged compared to initial findings (Table 3). Subgroup analysis of the non-malnutrition group failed to show any marked change in the association between salt intake and all-cause mortality, suggesting that this association was relatively strong.

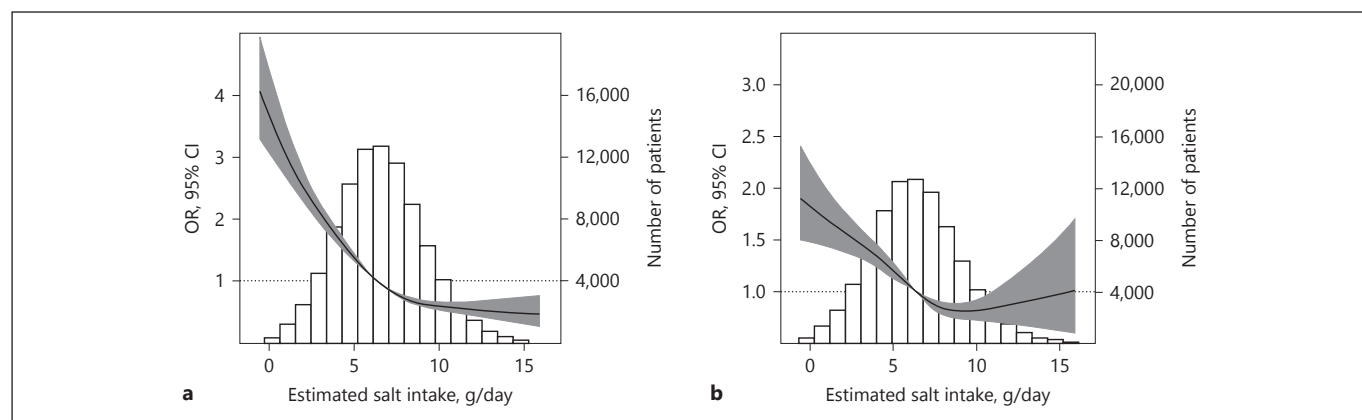


Fig. 2. Association between estimated salt intake and all-cause mortality. **a** Cubic splines between estimated salt intake and all-cause mortality using a crude analysis model. **b** Cubic splines between estimated salt intake and all-cause mortality using multivariate analysis. The multivariate model was adjusted for age, gender, body mass index, hemodialysis vintage, dialysis time per one dialysis session, Kt/V, protein catabolic rate normalized to body

weight, comorbidity conditions, type of vascular access, serum potassium, phosphate, calcium, and CRP levels, and endotoxin level in dialysate. Solid blue lines indicate point estimation. Grey zones indicate the 95% CI. The reference was median estimated salt intake (6.4 g/day) indicated by the dashed line. To convert the values for estimated salt intake to sodium excretion in g per day, divide by 2.5. Histogram indicates distribution of patients at risk.

Table 2. Associations between salt intake and mortality

	OR (95% CI) by salt intake, g/day						
	<2 (n = 4,170)	2–3.99 (n = 12,031)	4–5.99 (n = 22,833)	6–7.99 (n = 24,349)	8–9.99 (n = 15,305)	10–11.99 (n = 6,479)	≥12 (n = 2,948)
All-cause mortality, n (%)	219 (5.2)	411 (3.4)	580 (2.5)	361 (1.5)	178 (1.2)	71 (1.1)	25 (0.9)
Crude model	3.43 (2.86–4.10)	2.35 (2.04–2.71)	1.73 (1.52–1.98)	Reference	0.78 (0.65–0.94)	0.74 (0.57–0.95)	0.57 (0.38–0.85)
Multivariable model	2.05 (1.56–2.70)	1.65 (1.33–2.04)	1.39 (1.15–1.69)	Reference	1.03 (0.80–1.32)	1.13 (0.78–1.64)	1.18 (0.66–2.11)
All-cause mortality without cancer, n (%)	200 (4.8)	374 (3.1)	520 (2.3)	332 (1.4)	160 (1.1)	68 (1.1)	24 (0.8)
Crude model	3.41 (2.83–4.12)	2.32 (2.00–2.70)	1.69 (1.47–1.94)	Reference	0.76 (0.63–0.92)	0.77 (0.59–1.00)	0.59 (0.39–0.90)
Multivariable model	2.09 (1.57–2.77)	1.59 (1.27–2.00)	1.38 (1.13–1.69)	Reference	1.06 (0.81–1.38)	1.15 (0.78–1.70)	1.22 (0.67–2.24)
Cardiovascular death, n (%)	104 (2.5)	183 (1.5)	248 (1.1)	155 (0.6)	89 (0.6)	34 (0.5)	8 (0.3)
Crude model	3.79 (2.92–4.93)	2.41 (1.94–2.99)	1.71 (1.40–2.10)	Reference	0.91 (0.70–1.19)	0.82 (0.57–1.19)	0.42 (0.21–0.87)
Multivariable model	2.38 (1.62–3.50)	1.7 (1.25–2.33)	1.4 (1.05–1.86)	Reference	1.03 (0.72–1.48)	0.97 (0.56–1.68)	0.78 (0.31–1.97)

All-cause mortality without cancer was all causes of death excluding death from any cancer. Cardiovascular death included sudden death; death from heart failure, myocardial infarction, or stroke; and death from other vascular diseases. The multivariate model included age, gender, body mass index, vintage of hemodialysis, dialysis time per one dialysis session, Kt/V, protein catabolic rate normalized to body weight, comorbidity conditions, type of vascular access, serum potassium, phosphate, calcium, and C-reactive protein levels, and endotoxin level in dialysate.

Quantile points of IDWG were 25%, 1.90 kg; 50%, 2.50 kg; and 75%, 3.10 kg. In all groups divided into 4 strata on the basis of these quantile points, the lower levels of estimated salt intake were associated with an increased risk for death (online suppl. Fig. 3).

Sensitivity Analysis

Patients with a daily salt intake of <6 g showed a significantly higher mortality than patients with a daily salt intake of 6–9.99 g (adjusted OR 1.59; 95% CI 1.40–

1.80). Array-approach sensitivity analysis showed that an unmeasured confounder would have to be strongly associated with mortality or markedly imbalanced between patients with a daily salt intake of <6 g/day and those with a daily intake of 6–9.99 g/day to render the inverse association between salt intake and all-cause mortality non-significant. For example, if an unmeasured confounder was distributed in a 5:1 ratio between the low salt intake and high salt intake groups and the risk ratio for all-cause mortality was >3, then that con-

Table 3. Stratified analysis of the association between salt intake and all-cause mortality

	OR (95% CI) by salt intake, g/day						
	<2	2–3.99	4–5.99	6–7.99	8–9.99	10–11.99	≥12
<i>nPCR, g/kg/day</i>							
>1.2	1.51 (0.87–2.61) <i>n</i> = 531	1.43 (1.04–1.96) <i>n</i> = 2,803	1.57 (1.22–2.01) <i>n</i> = 7,376	Reference <i>n</i> = 9,557	0.99 (0.73–1.36) <i>n</i> = 6,537	1.01 (0.64–1.58) <i>n</i> = 2,918	1.21 (0.65–2.25) <i>n</i> = 1,448
1.2–1.0	2.14 (1.68–2.73) <i>n</i> = 2,710	1.56 (1.28–1.90) <i>n</i> = 7,633	1.32 (1.10–1.58) <i>n</i> = 13,553	Reference <i>n</i> = 13,442	1.01 (0.80–1.29) <i>n</i> = 8,106	1.27 (0.90–1.79) <i>n</i> = 3,299	1.04 (0.55–1.95) <i>n</i> = 1,379
<1.0	1.86 (1.19–2.91) <i>n</i> = 914	1.63 (1.08–2.46) <i>n</i> = 1,551	1.47 (0.98–2.20) <i>n</i> = 1,809	Reference <i>n</i> = 1,282	0.50 (0.22–1.13) <i>n</i> = 629	1.30 (0.49–3.44) <i>n</i> = 249	1.33 (0.27–6.44) <i>n</i> = 117
<i>CRP, mg/dL</i>							
<0.3	1.62 (1.14–2.30) <i>n</i> = 2,026	1.35 (1.04–1.74) <i>n</i> = 6,365	1.25 (1.00–1.56) <i>n</i> = 13,051	Reference <i>n</i> = 14,348	1.01 (0.77–1.33) <i>n</i> = 9,122	1.31 (0.90–1.90) <i>n</i> = 3,824	1.13 (0.59–2.13) <i>n</i> = 1,685
0.3–1.0	1.73 (1.12–2.67) <i>n</i> = 709	1.63 (1.16–2.29) <i>n</i> = 1,946	1.59 (1.18–2.14) <i>n</i> = 3,446	Reference <i>n</i> = 3,541	0.99 (0.66–1.48) <i>n</i> = 2,198	0.82 (0.42–1.58) <i>n</i> = 896	1.24 (0.55–2.79) <i>n</i> = 485
>1.0	2.28 (1.52–3.41) <i>n</i> = 636	1.76 (1.24–2.51) <i>n</i> = 1,325	1.70 (1.22–2.37) <i>n</i> = 1,863	Reference <i>n</i> = 1,590	1.27 (0.80–2.00) <i>n</i> = 889	0.72 (0.31–1.65) <i>n</i> = 388	1.26 (0.44–3.66) <i>n</i> = 172
<i>Albumin, mg/dL</i>							
>3.8	1.58 (0.88–2.86) <i>n</i> = 1,257	1.33 (0.89–2.01) <i>n</i> = 3,875	1.29 (0.93–1.79) <i>n</i> = 8,196	Reference <i>n</i> = 9,439	0.99 (0.66–1.47) <i>n</i> = 6,318	1.10 (0.62–1.94) <i>n</i> = 2,825	1.11 (0.49–2.53) <i>n</i> = 1,427
<3.8	2.40 (1.91–3.03) <i>n</i> = 2,790	1.79 (1.48–2.16) <i>n</i> = 7,752	1.54 (1.30–1.82) <i>n</i> = 13,899	Reference <i>n</i> = 14,145	0.92 (0.73–1.17) <i>n</i> = 8,504	1.08 (0.77–1.51) <i>n</i> = 3,433	0.91 (0.51–1.63) <i>n</i> = 1,423
<i>BMI, kg/m²</i>							
>23	1.81 (0.98–3.33) <i>n</i> = 675	1.52 (0.95–2.43) <i>n</i> = 1,962	1.67 (1.15–2.43) <i>n</i> = 4,436	Reference <i>n</i> = 6,007	0.96 (0.62–1.50) <i>n</i> = 5,043	1.58 (0.96–2.62) <i>n</i> = 2,743	1.34 (0.67–2.68) <i>n</i> = 1,593
<23	2.27 (1.80–2.85) <i>n</i> = 3,495	1.79 (1.49–2.15) <i>n</i> = 10,069	1.49 (1.26–1.76) <i>n</i> = 18,397	Reference <i>n</i> = 18,342	0.90 (0.72–1.13) <i>n</i> = 10,262	0.78 (0.54–1.12) <i>n</i> = 3,736	0.59 (0.30–1.17) <i>n</i> = 1,355
Albumin >3.8 mg/dL and BMI >23 kg/m ²	0 (0.00) <i>n</i> = 237	2.04 (0.78–5.34) <i>n</i> = 699	1.72 (0.79–3.72) <i>n</i> = 1,652	Reference <i>n</i> = 2,418	0.88 (0.37–2.12) <i>n</i> = 2,144	1.31 (0.49–3.47) <i>n</i> = 1,235	1.67 (0.54–5.19) <i>n</i> = 807

All were adjusted for age, gender, body mass index, vintage of hemodialysis, dialysis time per one dialysis session, Kt/V, protein catabolic rate normalized to body weight, comorbidity conditions, type of vascular access, serum potassium, phosphate, calcium, and CRP levels, and endotoxin level in dialysate. nPCR, protein catabolic rate normalized to body weight; BMI, body mass index; CPR, C-reactive protein.

founder can render the inverse association between salt intake and all-cause mortality nonsignificant (online suppl. Table 1).

When we limited patients to those with a history of hemodialysis of over 5 years, 58,804 were analyzed. Comparing the exclusion criteria between a history of hemodialysis over 2 years and a history of hemodialysis over 5 years, the association between mortality and estimated salt intake did not change (online suppl. Fig. 4).

When we limited outcomes that occurred after 6 months, the risk for all-cause mortality, all-cause mortality without cancer, and cardiovascular death were higher in the low estimated salt intake group; the risk for cardiovascular death was especially high in this group (online suppl. Fig. 5).

Discussion

A low salt intake (<6 g/day) was associated with an increased risk for all-cause mortality and cardiovascular death, resulting in an L-shaped association curve. The lowest risk for all-cause mortality and cardiovascular death was seen among patients with an estimated salt intake of 9 g/day. Regardless of nutritional indicators, associations between estimated salt intake and all-cause mortality and cardiovascular death remained relatively unchanged compared to initial findings. These findings do not support current clinical guidelines, which recommend restricting salt intake to <5–6 g per day.

Guidelines have recommended the restriction of the salt intake of a patient on hemodialysis to a low level [1–3]. We found that there is an unsafe lower limit for salt intake and, therefore, do not affirm these recommendations. We did not observe an increased risk for death among high salt intake patients. Among non-end-stage renal disease patients, a high salt intake was found to be associated with an increased risk for cardiovascular events and death in hypertensive populations, while the association between a low salt intake and an increased risk for cardiovascular events and death was observed in those with or without hypertension [32]. Possibly, the increase of cardiovascular death might be observed among hemodialysis patients with a higher salt intake range such as over 15 g/day, which we could not observe in this study and which is in accordance with the recent advisory in the United States to limit the UF rate to <13 mL/kg/h [33]. These findings suggest that a range of salt intake with targeted upper and lower limits should be discussed in clinical guidelines.

This study has some strengths. First, we assessed a direct association between salt intake and mortality. Some previous studies have discussed the association between IDWG and mortality as though IDWG could simply be substituted with salt intake [8]. The equation for estimating salt intake mainly comprises IDWG and pre- and post-dialysis serum sodium. Because IDWG is greatly affected by fluid intake, we could not assess the effect of salt intake directly from the association between IDWG and mortality [9]. In this study, we found variations in estimated salt intake even in the same IDWG strata, and low salt intake showed a high mortality ratio in all IDWG strata. These results suggest the significance of assessing estimated salt intake rather than IDWG. Second, we analyzed a large nationwide hemodialysis registry in Japan, including more than 88,000 dialysis patients. Third, we conducted several sensitivity analyses and confirmed the robustness of the associations between salt intake and mortality in this population.

Assessment of the association between salt intake and mortality using observational data may have methodological issues [34]. In particular, confounding by malnutrition may overestimate the association between low salt intake and mortality. Previous studies reported that low IDWG [7, 35–37] and low pre-dialysis serum sodium [38, 39] are associated with malnutrition parameters [34, 40]. To eliminate the influence of malnutrition on the association between salt intake and mortality, we performed a subgroup analysis based on nutrition parameters (nPCR, serum albumin level, or BMI) and found similar associations to the results in the total population. We also conducted an array-

approach sensitivity analysis and found a low probability that residual confounding would render the association between salt intake and mortality nonsignificant.

This study has some limitations. First, we were unable to assess smoking and socioeconomic status. In dialysis patients, smoking is reported to be associated with all-cause mortality [41]. However, an array-approach sensitivity analysis showed a low possibility that those unmeasured factors (such as smoking and socioeconomic status) alter the association between salt intake and mortality [30, 31]. Second, the follow-up period was only 1 year, which might be too short to assess the effect of high salt intake on mortality. Analysis of data with a longer observation period (for example, 10 years or more) should be performed in future study. Third, the estimation of salt intake was based on a single series of hemodialysis at baseline. Estimations based on a single series of hemodialysis can lead to random errors because salt intake varies daily [34, 42]. A random error usually reduces the statistical power to detect the association, but a large sample size, such as in this study, would compensate for it. Although salt intake may change over time, we only used baseline salt intake data because the association between time-varying salt intake and mortality would be overestimated due to reverse causality (i.e., patients in the process of dying take less salt). Fourth, estimation of salt intake may be affected by sweat, feces, residual renal function, seasonal factors, and physical activity [21, 22]. Regarding the residual renal function of patients who underwent hemodialysis for more than 2 years, we assumed that such patients developed anuria. However, some patients such as those with polycystic kidney may have residual renal function even after 2 years from the initiation of hemodialysis. In our sensitivity analysis, we confirmed that patients who underwent hemodialysis for more than 5 years developed almost complete anuria. Although hemodialysis patients with residual renal function showed lower mortality compared with patients without this function, there were similar results between the main analysis and the sensitivity analysis. Baseline information for the estimation of salt intake was collected in December of each year (winter in Japan); therefore, any possible sweat bias would be reduced during this time. Patients that undertake regular physical activity have lower mortality [43, 44], and tend to sweat more. Therefore, it is possible that salt intake was underestimated and the risk for death between the low salt intake and high salt intake groups might be larger. It is suggested that an underestimation of salt intake would not affect the association between low salt intake and all-cause mortality. Fifth, we also found

that 30,020 (34.1%) of 88,115 patients had missing values, which may have affected the association between salt intake and all-cause death. We used a multiple imputation approach to adjust for missing covariates and found similar associations compared to the results from the full analysis set ($n = 58,095$; online suppl. Fig. 6). Sixth, we did not have data regarding dietary contents including specific Japanese foods (miso and seaweed) in this study. However, the effect of these specific Japanese foods on health outcomes has not been verified. In addition, salt intake is said to be independently associated with health outcomes [45]. In future studies, it will be necessary to examine the effect of dietary content on health outcomes in this population. Seventh, we only analyzed the Japanese dialysis population, which is less likely to have diabetes and a longer survival prognosis, compared to the U.S. dialysis population [46]. We also found similar associations even after stratification by the presence of diabetes and nephrosclerosis (online suppl. Fig. 7).

Low salt intake was found to be associated with high all-cause mortality and cardiovascular death in Japanese hemodialysis patients in the current study. These findings do not support current clinical guidelines, which recommend

restricting salt intake to $<5\text{--}6$ g per day. Including a lower limit of salt intake in the clinical guidelines for hemodialysis patients is suggested based on the results of this study. In the future, a quasi-experimental study assessing the effect of intervention (such as the introduction of clinical guidelines that set the lower limit of salt intake) on mortality and cardiovascular events is required to confirm these results.

Acknowledgments

The authors thank the JSDT, the principal investigators of all the prefectures, and all personnel at the participating institutions involved in the JSDT renal data registry. In particular, Yoshiharu Tsubakihara, Ikuto Masakane, and the Committee of the Renal Data Registry of the JSDT contributed to the data management.

Disclosure Statement

The authors have no conflicts of interest to disclose.

Funding Source

None.

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