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INFLUENCE OF DAILY SODIUM INTAKE ON MORTALITY IN HD PATIENTS

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Abstract

The aim of our study was to assess the influence of daily sodium intake (DSI) on the cardiovascular mortality in dialysis patients (pts).

In prospective, observational study, 156 pts on hemodialysis (HD) were followed for 36 months,until death or kidney transplantation.

Cardiovascular (CV) mortality was defined as death resulting from coronary heart disease, sudden death, stroke or complicated peripheral vascular disease and was notified from the patients' medical history at baseline.

Estimated DSI, as a major predictor for CV mortality, was calculated using formula European Best Practice Guidelines (EBPG) on Nutrition.

In respect of median DSI (11.7 ± 2.87 g/day) pts were stratified in two groups: Group 1 – pts with low DSI (<11.7 g/day) and Group 2 – patients with high DSI (> 11.7 g/day). The prevalence of CV comorbidities was not significantly different between two groups at baseline. At the end of the study, 41 pts (26.3%) died, among which 24 pts (60%) died from CV diseases.

Kaplan-Mayer survival log rank test demonstrated that there was no difference in the cardiovascular survival between HD pts with high DSI and HD pts with low DSI($p>0.05$).**S**erum levels of C-reactive protein (CRP) and mean age were significantly higher in pts diseased from CV disease compared to survived pts.

Our results showed that HD pts may be particularly susceptible to non-osmotic sodium accumulation in skin and muscles. This study have shown that there was no significant influence of baseline DSI on the CV mortality of the pts included in the study.

Keywords: Dietary; mortality; renal dialysis; sodium chloride.

Introduction

Treatment with hemodialysis (HD) in patients with chronic kidney disease (CKD) is complex and inevitably requires great patient's compliance which include an adequate intake of energy, protein, potassium, phosphorus, sodium and fluids [1]. Sodium is the major determinant of plasma osmolality with great influence on blood pressure and volume status of the extracellular compartment [2,3].

According to NerbassFB.*etal.*,in underdeveloped countries salt added to foods is the main source of sodium, contributing for 72% of daily sodium intake (DSI) [1]. Processed food and food additives can also contribute todietary sodium intake, especially in industrialized countries [1,2].

Dialysate with high sodium concentration is another potential source of exogenous sodium in patients performing HD [1].

Restriction of DSI is traditionally advised in patients on HD in order to control extracellular volume, hypertension and subsequent cardiovascular morbidity. In anuric patients, like those with long HD vintage, higher intake of sodium is associated with an increased fluid intake leading to higher interdialytic weight gain (IDWG) [4,5].

European Best Practice Guidelines (EBPG) on Nutrition recommends daily intake of no more than 80 - 100 mmol (2000 - 2300 mg) sodium or 5 - 6 g (75 mg/kg body weight) per day of sodium

chloride and Interdialytic weight gain (IDWG) should not exceed 4 - 4.5% of dry body weigh [6]. However, only a few studies have examined the association between DSI and mortality in HD patients.

Recently there have been doubts concerning the association between DSI and all-cause mortality. Ikenoue T. *et al.* failed to prove increased risk of death among HD patients with high salt intake [7].

Moreover, Dong J. *et al.* have demonstrated that low DSI increases the death risk in patients on peritoneal dialysis which raise doubts about restriction of the salt intake in HD patients to a low level [8].

Inspired by these new observations for long-term Na^+ balance and traditional recommendations for salt restriction in HD patients, the aim of our study was to assess the influence of DSI on the cardiovascular mortality in dialysis patients.

Material and methods

We conducted a prospective, observational study comprising156 outpatients who underwent hemodialysis treatment for more than 3months at a single dialysis center. All patients were followed for 36 months or until death, kidney transplantation or until the end of the observational period.

Cardiovascular (CV) mortality was defined as death resulting from coronary heart disease, sudden death, stroke or complicated peripheral vascular disease.

To eliminate the possible influence of sodium elimination with urine, we only included patients who were anuric with diuresis lower than 100 ml per day.

In-center hemodialysis treatment prescription consisted of a three times weekly regime and 4 to 4.5 hours per dialysis session, at blood flow rate of 250mL/min and a dialyzer solution flow rate of 500 mL/min.

Dialysis treatments were performed with low-flux biocompatible dialyzer membranes with surface areas of 1.3-1.8m2. In order to reduce intradialytic discomforts and intra-dialytic hypotension (IDH), the sodium concentration in the dialysis fluid was individualized. For patients with IDH the dialysate sodium concentration of 143 to 138 mmol/L was used, and for patients with hypertension sodium level was 138 mmol/L.

Biochemical analyses (serum sodium concentration, C-reactive protein (CRP), serum creatinine, blood urea nitrogen and serum albumin), accompanied with body weight and blood pressure data were examined at baseline and thereafter at regular monthly intervals. Inter-dialytic weight gain (IDWG), intra-dialytic hypotension (IDH) and use of 20% NaCl solution were also regularly recorded per dialysis sessions.

At baseline, the study group was evaluated for the following parameters: age, HD vintage, serum sodium levels, daily sodium intake (DSI), weekly use of 20% NaCl, inter-dialytic weight gain (IDWG), dialysis adequacy using DaurgidasspK*t/V ratio [6] and CRP. In addition, calculations oftotal body water (TBW) using a formula (TBW= 2.447 - 0.09516 X age + 0.1074 X height + 0.3362 X weight) [6] and body mass index were obtained. Daily salt intake was calculated using the formula (see below) recommended by the European Best Practice Guidelines (EBPG) on Nutrition, published in Nephrology Dialysis Transplantation in year 2007 [6].

$$\text{NaCl (g/day)} = \frac{8 \times \text{serum Na (mmol/l)}}{140(\text{mmol/L}) \times (\text{mean weekly interdialysis weight gain} - \text{kg} \times 3/6{,}5)}$$

The presence of previous cardiovascular comorbidities was notified from patients' medical history at baseline.

Statistical Analyses

Data were summarized as mean±SD. Student's t-test was used to analyze the differences between two mean values. Categorical data were compared between groups by the chi-square test. To compare the difference in respect of DSI, patients were stratified by median level of sodium intake.

The groups were compared using the variance method. Survival curves were assessed using Kaplan-Meier analysis (logrank test). After follow-up, patients were once again stratified into two groups as survived and diseased and compared for differences with the Student's t test. P values <0.05 were considered statistically significant. SPSS statistical software (version 14.0; SPSS Chicago, II, USA) was used for analysis.

Results

We followed 156 patients on maintenance hemodialysis (86 men and 70 women) with a mean age of 55.6 ± 13.5 years and a mean HD vintage of 8.9 ± 6.6 years for 36 months.

The main characteristics of all patients involved in the study are summarized in Table 1.

Table 1. Baseline clinical and laboratory parameters of the study population

Study group characteristics N=156	
Variable	**Mean/median ± standard deviation**
Age (years)	55.6 ± 13.5
HD vintage (years)	8.9 ± 6.6
Serum Na (mmo/L)	138.8 ± 1.1
DSI (g/day)	11.7 ± 2.87
Weekly 20% NaCl (mg)	15
IDWG (Kg)	3.2 ± 0.84
K*t/V	1.38 ± 0.2
CRP (mg/L)	7.24 ± 8.6
TBW (%)	29.9 ± 1.1
BMI (Kg/m2)	23.6 ± 4.56

The median sodium intake in our cohort was 11.7 g/day (11.7 ± 2.87 g/day). According to the median DSI, patients were divided in two groups:

Group 1 - patients with low DSI (below 11.7 g/day) **N= 79**

Group 2 - patients with high DSI (above 11.7 g/day). **N= 77**

Participants with higher intake of sodium were more likely to be younger, male, with higher body weight and higher serum creatinine (Table 2). They had a higher rate of intradialytic hypotension (IDH) and higher interdialytic weight gain (IDWG).

The prevalence of diabetes mellitus (DM) and cardiovascular comorbidities (CVC) were not significantly different between the two groups at baseline. No significant differences in average HD vintage, albumin and serum CRP levels were also observed between groups.

Table 2. Comparison of baseline demographic and clinical characteristics between two groups of patients

Variable	**Group 1: low DSI(N= 79)**	**Group 2: high DSI; (N= 77)**	**Sign. p < 0.05**
Age (years)	58.72	52.48	0.004
HD vintage (years)	8.5	9.1	ns.
K*t/V	1.4	1.3	0.005
Serum creatinine (mmol/L)	864	1003	0.0001
BMI (Kg/m2)	22.4	24.9	0.001
IDWG (Kg)	1.61	3.81	0.0001
Albumin (g/L)	38.6	39.0	ns.
CRP (mg/L)	7.4	6.7	ns.
Cardiovascular comorbidities (CVC) (% of pts. with CVC)	14.3 %	16.3%	0.72
Gender (% of male)	21.6 %	34.5 %	0.005
IDH (% of pts. with IDH)	8.1 %	17.6 %	0.039
Diabetes mellitus (% of pts. with DM)	10.1 %	10.1%	ns.

At the end of the study, 41 patients (26.3%) died, 1 patient (0.6%) was kidney transplanted and 114 patients (73.1%) survived, as shown in Figure 1.

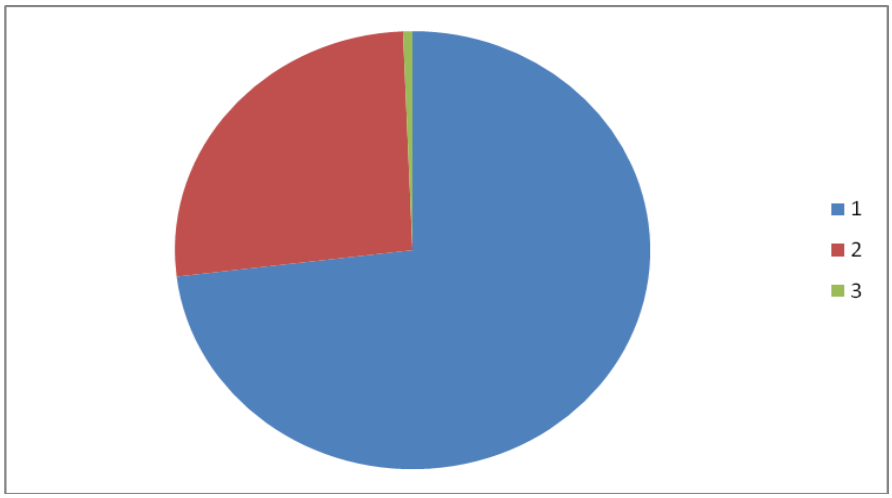

Figure 1. Outcome of the study patients at the end of observational period

Table 2. Cardiovascular mortality and survival in respect of baseline DSI			
Variable	**Group 1 (N= 79)**	**Group 2 (N= 77)**	**Sign. p**
CV mortality	11 (46%)	13 (54%)	0.09
CV survival (months)	33.7±2	32.9±5	Log Rank, P= 0.827

We investigated the survival of patients with regard to cardiovascular mortality in relation to low DSI (below 11.7 g/day) or high DSI (above 11.7 g/day). The Kaplan-Mayer survival log rank test demonstrated that there was no difference in the cardiovascular survival in respect of baseline daily sodium intake ($p>0.05$). (Figure 2).

Also, the cox regression analysis showed no higher risk of death in the group with higher salt intake.

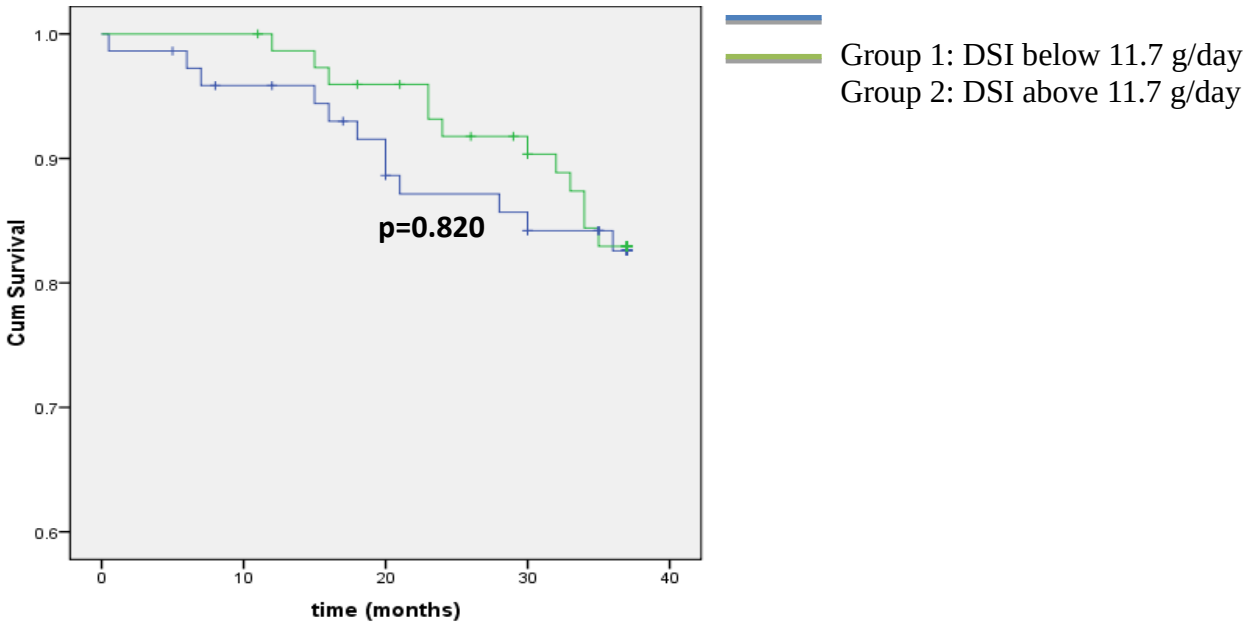

Figure 2. Cardiovascular survival in respect to DSI (below or above median level)

Furthermore, there was no significant difference for all other analysed parameters (HD vintage, K*t/V, serum creatinine, BMI, IDWG, serum albumin, diabetes mellitus, gender, IDH), except for serum levels of C-reactive protein (CRP) and mean age between survived and patientsdiseased from CV diseases.

Table 2. Comparison of survived (Group a) and diseased patients from CV diseases (Group b)

Variable	**Group a**	**Group b**	**p < 0.05**
Mean age (years)	54	60.5	**0.04**
Mean CRP (mg/L)	5.8	11.2	**0.015**
DSI (g/day)	11.8	11.5	0.976

Discussion

Cardiovascular diseases (CVD) are the most common cause of death in patients with end-stage renal disease (ESRD) and patients on maintenance hemodialysis, accounting for 39.4% of all deaths [9]. Hypertension with consecutive left ventricular hypertrophy, chronic volume overload, anemia, inflammation, oxidant stress, hyperhomocysteinemia and other components of uremic milieu are considered major contributors for this condition [9, 10].

It is thought that increased intake of salt leads to increased thirst and water intake resulting in expansion of ECV and higher IDWG. Elevated plasma volume may increase cardiac output and blood pressure, which leads to left ventricular hypertrophy and higher CV mortality [5, 10].

However, some recent analyses of the HEMO study performed by Mc Causland R.F.*et al.* showed that diet-Na (g/day) and sodium:calorie (mg/kcal/day) were only modestly associated with requirements for greater ultrafiltration (UF) in adjusted analyses (0.14 and 0.17l, respectively; $p<0.001$) and inconsistently associated with pre-dialysis systolic blood pressure (SBP) (1.58 mmHG; $p<0.001$ and 1.65 mmHg; $p>0.05$, respectively) or mortality.

They also pointed that they cannot identify a 'safe' upper limit for sodium intake in HD patients, particularly because restriction of sodium intake was connected with unintended concomitant intake of other macronutrients.

The authors admitted that in HD patients other sources of sodium (hypernatremic dialysate, non-osmotic mediated thirst, habitual drinking) might have greater role in determining of IDWG compared to DSI [2,3].

Moreover, Dong J. *et al.*showedthat low dietary sodium intake was independently associated with high overall and CV mortality in patients on peritoneal dialysis (PD) and this correlation could not be entirely explained by deficient protein and energy intake [8].

Ikenoue T. *et al.*,in an analysis of more than 88,000 dialysis patients in Japan showed that the group with low sodium intake (<6 g/day) had an increased risk for all-cause mortality and CV death, contrary to current clinical guidelines which recommend salt intake of less than 5-6 g/day.

They also noted that HD patients with different salt intake may have the same IDWG, suggesting that there was not a linear correlation between IDWG and DSI in HD patients. In their study, the lowest risk for all-cause and CV mortality was seen among HD patients with daily salt intake of 9 g/day [7].

Our analysis also showed that there was no difference in CV mortality in HD patients with high (above 11.7 g/day) and low (below 11.7 g/day) sodium intake.

These findings are in accordance with the results published by Ikenoue T. *et al.* [7] and Hecking M. *et al.* [11], but they do not support current clinical guidelines which recommend restricting salt intake of less than 5-6 g/day.

The results obtained in our study might be partly explained by the good individual sodium profiling in patients with high DSI and restriction in use of 20% NaCl during hemodialysis. But also, these results could be another proof of the theory of water-free storage of sodium under the skin, which abolishes the effect of volume overload –associated with cardiovascular morbidity and mortality.

Recent findings obtained from studies in patients using ^{23}Na-MRI non-invasive technique have showed that remarkable amounts of sodium are stored in muscle and skin without concomitant water retention [12, 13].

This storage of sodium has an important role in ultra-long Na^+ balance, which is independent of daily salt intake. The main participants in this process are glycosaminoglycans in the skin that have a strong negative charge because of their sulfate content [13-16].

Kopp Ch. *et al.*found that increasing Na^+ storage in the skin is followed by increasing in glycosaminoglycans content in skin. In addition, the authors noted that genetic markers of synthesis of these Na^+ binders in the skin (chondroitin synthase mRNA) coincided with dietary salt intake.

This means that prolonged high daily intake of sodium induces a greater production of glycosaminoglycans, whichcreate bigger pool for sodium storage that consecutively reduces the serum sodium's level and retention of water [13].

In year 2015, Dahlmann A. *et al.*assessed tissue sodium storage and its removal in 24 patients on hemodialysis (HD) and 27 age-matched healthy controls using ^{23}Na magnetic resonance imaging.

Their results showed that age was associated with an increased sodium storage in muscles and skin in HD patients and in control group. Tissue sodium content increases more progressively in HD patients compared toage-matched controls [12].

We assume that inability to lose sodium with urine in HD patients give much greater role of these alternative ways of storage of daily sodium intake which might be one possible explanation for our results. Namely, patients with higher DSI stored greater amount of sodium in their skin and muscle which abolishes the effect of hypernatremia in inducing thirst and volume overload

In our study, men had greater intake of sodium compared to women, but at the end of the observational period there was no difference in CV mortality between genders. Men usually have greater muscle mass and greater skin surface which give them much greater pool for water-free storage of sodium in skin and muscles.

Dahlmann A. *et al.*also noted that muscle Na^+ content in younger HD patients was not different from controls, so that ultrafiltration with HD will actually reduce muscle Na^+ content in those patients below the control level [12].

In our study, young HD patients had greater intake of sodium,but the mortality caused byCVD was the same in both groups.

According to the results mentioned above, HD in young patients might create an "empty pool" for additional sodium storage in skin and muscles which abolishes the effect of higher intake in those patients.

Another source of exogenous sodium in HD patients is in a form of dialysate with high sodium concentration. Higher dialysate sodium is associated with better hemodynamic stability, but it also has an important role in inducing thirst with higher intake of fluids that leads to greater IDWG and higher blood pressure in HD patients [2, 3].

These effects are particularly emphasizedin HD patients with high-normal or high pre-dialysis serum sodium levels [3].

Many review articles have emphasized the importance of reducing sodium overload caused by dialysate with high sodium concentration in order to avoid hypertension and CV mortality.

Akdag S. *et al.*in their study of 46 HD patients showed that twenty-four hour SBP, daytime SBP and nighttime diastolic blood pressure (DBP) were significantly reduced in low-sodium dialysate group ($P<0.05$), with less common use of antihypertensive drugs in this group.

Further analysis also showed that IDWG was significantly decreased in low-sodium dialysate group after 6 months ($P<0.001$) HeckingM. *et al.*[17].

The Dialysis Outcomes and Practice Patterns Study (DOPPS) demonstrated that HD patients with serum sodium levels < 137 mEq/l had a 45% higher risk of death compared to patients with serum sodium levels >= 140 mEq/l (hazard ratio 1.45; 95% confidence interval, 1.26-1.67).

They concluded that dialysate sodium concentration > 140 mEq/l had a potential benefit in the subgroup of patients with low serum sodium, related to improved intradialytic cardiovascular stability in those patients [11].

According to these findings, we preformed individually adjusted use of dialysate with different sodium concentration, based on intradialytic blood pressure and serum sodium concentration of HD patients.

For patients with IDH and low serum sodium we used dialysate fluid with sodium concentration from 143 to 138 mmol/L, and for patients with hypertension,dialysatesodium level was 138 mmol/L.

The use ofan individual dialysate prescription allowed us to avoid cardiovascular instability in patients with low serum sodium levels, and, on the other hand, to avoid unnecessary sodium overload and hypernatremia in patients with high DSI and to prevent CV mortality associated with volume overload.

Our study has some limitations.

First, the estimation of salt intake in our patients has been made with mathematical equation, using mean IDWG and serum sodium levels at baseline.

Over time patients might have different intake of fluids, food and salt (for example during holidays) which may lead to different gain of weight in interdialytic period.

In order to achieve the most accurate IDWG at baseline for a single patient, we used mean value of IDWG based on regular data recorded months before the study was initiated.

In addition, Ikenoue T. *et al.*showed that patients with the same DSI could have different IDWG [7].

Therefore, assessment of salt intake from a food frequency questionnaire over a long period could be more accurate. Secondly, our results are based on evaluation of a relatively small number of dialysis patients and further studies with more participants are essential for proper conclusion.

Thirdly, salt intake can be affected by sweat, feces, seasonal factors and physical activity. In order todisregardthe possible influence of sodium elimination with urine, we only included patients who were anuric (diuresis less than 100 ml per day).

Fourthly, in our study the observational period was 36 months, which might be short to assess the impact of high salt intake on CV mortality. Fifthly, the average DSI in our HD patients washigher than recommended amount which unable us to assess the effect of low salt intake (below 5-6 g/day) on CV mortality.

Conclusion

Our results showed that that there was no difference in the cardiovascular survival between HD patients with high and HD patients with low DSI.

HD patients may be susceptible to non-osmotic sodium accumulation in skin and muscles as one of the possible explanations for our results. The results of our study have also shown that recommendations for daily salt intake in HD patients of less than 5-6 g/day are too restrictive for Macedonian HD patients.

Namely, the medial DSI in our patients was 11.7 g/day, which is much higher than recommended amount and only a few of them adhered to thisamount. Many authors have also suggested that more than half of the HD patients in their studies cannot adhere to these recommended DSI, especially in countries that traditionally use food rich in salt (Japan) [7, 19].

The use of dialysate with different sodium levels is essential in order to avoid sodium overload or unnecessary cardiovascular instability.

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