

Original Article

Simple method to estimate daily sodium intake during measurement of dialysis adequacy in chronic peritoneal dialysis patients

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Background and Objectives: Restriction of dietary sodium intake for peritoneal dialysis (PD) patients is recommended, but there is limited information on the measurement and monitoring of sodium intake. We have developed a simple method to estimate daily sodium intake during the measurement of dialysis adequacy in PD patients. **Methods and Study Design:** A total of 83 PD patients were enrolled in the study. The patients were divided into two groups based on residual renal function (RRF). We measured total sodium removal and estimated daily sodium intake using dietary recall for one day, during the assessment of dialysis adequacy. **Results:** There were 39 patients in the RRF(-) group and 44 in the RRF(+) group. In both groups, and all patients, there were significant positive correlations between sodium intake and total sodium removal: RRF(-) group, $r=0.598$; RRF(+) group, $r=0.577$; total patients, $r=0.595$. There were linear relationships between dietary sodium intake and total sodium removal in both groups: RRF(-) group, sodium intake (mg/d) = $19.3 \times$ peritoneal sodium removal (mEq/d) + 211; RRF(+) group, sodium intake (mg/d) = $15.4 \times$ total sodium removal (mEq/d) + 609. All PD patients, sodium intake (mg/d) = $15.6 \times$ total sodium removal (mEq/d) + 646. **Conclusions:** The measurement of total sodium removal during the assessment of dialysis adequacy could be an effective and simple method to estimate dietary sodium intake in PD patients. A dietary intake of 2,000 mg of sodium corresponds to a total sodium removal of approximately 87 mEq/d.

Key Words: dietary sodium intake, peritoneal dialysis, peritoneal sodium removal, urinary sodium removal, dialysis adequacy

INTRODUCTION

A high sodium diet is known to be the main cause of fluid overload in dialysis patients, and is associated with increased cardiovascular mortality.^{1,2} Recent studies have reported that dietary sodium intake can influence the permeability of the peritoneal membranes in chronic peritoneal dialysis (PD) patients, by epithelial to mesenchymal transition and fibrosis-mediated up-regulation of TGF- β and IL-6 mRNA.^{3,4} Although some treatment guidelines have recommended dietary salt restriction, detailed information about the measurement and monitoring of dietary sodium intake is limited for chronic PD patients.^{5,6} The most widely used method for evaluating sodium intake in these patients is the dietary recall method. However, this method has limitations because it is prone to errors in self-reporting, often uses inaccurate or incomplete food tables, often has missing data, and is inconvenient for routine use.⁷ Therefore, we developed a

simple method to estimate daily sodium intake during the measurement of dialysis adequacy in chronic PD patients.

METHODS

Study subjects

All adult patients visiting the Asan Medical Center PD clinic between July 2010 and August 2011 were included in this cross-sectional study. The exclusion criteria were

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(1) a PD duration of less than 3 months; (2) an acute systemic illness defined by C-reactive protein >0.5 mg/dL; (3) the presence of a systemic disease that influences the sodium regulation mechanisms, such as advanced liver disease, or congestive heart failure defined by ejection fraction <40%; (4) malignancy; and (5) an inability to record a dietary diary. Using these criteria, 83 chronic PD patients were eligible and participated in this study. All patients visited the clinic at least once every three months. Demographic and clinical baseline data were collected, including age, sex, body height, body weight, blood pressure, underlying renal disease, and the presence of comorbid disease. All patients used glucose-based PD solutions as follows: 68 patients used Physioneal (Baxter, Deerfield, IL), nine used Stay-safe (Fresenius, Homberg, Germany), and six used Gambrosol-trio (Gambro, Lund, Sweden). Thirty-two patients used a PD cyclor.

The initial dialysis regime was maintained throughout the study period, unless a significant fluid imbalance occurred. Residual renal function was defined as having a daily urine output greater than 100 mL, and the patients were divided into residual renal function negative (RRF(-)) and positive (RRF(+)) groups. A comprehensive informed consent was obtained from each participating patient. All study procedures were approved by the Institutional Review Board of Asan Medical Center (IRB No. 2011-0491).

Measurement of sodium intake

All patients received a dietary education from the practice dietitian. Patients were asked to retain their usual meals and before returning to the PD clinic, were asked to record a one day diet diary, in which the times, places, recipes and main food names of the day were recorded. To increase the accuracy of the food diary, the patients were asked to record how many spoonfuls of salt were added to red pepper and soy bean paste, and to check the amount of salt in processed food, using the information on the labels. A dietitian reviewed the diet diaries and evaluated the sodium levels for each patient, using a food model. Foods were coded using the Computer Aided Nutritional Analysis software version 3.0 (Korean Nutrition Society, Korea, 2006). The food composition data for calculating nutrients were based on the following tables: Food Values

include nutrient database 3495 - common Korean foods (Korean Nutrition Society, Seoul, Korea, 1998). An example of sodium assessment from dietary recall was described in Table 1. Total sodium intake was defined using the amount of elemental sodium, rather than the amount of sodium chloride.

Dialysate specimens

All patients were asked to record the details of their dialysis regimes (times, frequencies and glucose concentrations). Using cyclers, the patients were asked to measure the amounts of drained dialysate once, on the morning of the clinic visit (for nightly intermittent PD patients), or twice, from the second dialysis the day before clinic and from the first dialysis on the day of the visit (for chronic, cycler-assisted PD patients). The patients were also asked to collect 1/100th of each drained dialysate, after shaking the dialysis bag two or three times. Sodium, blood urea nitrogen, protein, and creatinine from the dialysates were measured using a COBAS Integra Chemistry Analyzer (Roche Diagnostics, Basel, Switzerland).

Urine sampling

For patients with residual renal function, 24 h urine samples were collected from the second urine on the day before the clinic visit, to the first urine on the day of the clinic visit. Sodium, blood urea nitrogen, and creatinine from these 24 h urine samples were measured.

Dialysis adequacy and total sodium removal

Dialysis adequacy was calculated by collecting dialysates and urine samples. Weekly total peritoneal and renal Kt/V urea and residual renal function were calculated using standard methods. Nutritional status was assessed using the normalized protein equivalent of nitrogen appearance (nPNA), estimated according to the Bergström formula, i.e., normalized protein equivalent of nitrogen (g/kg/day) = (13 + 0.204 urea appearance (mmol/day) + protein loss (g/day)) / (VWatson/0.58), where the Watson formula is, for men, (L) = 2.447 + 0.3362 × body weight (kg) + 0.1074 × height (cm) - 0.09516 × age, and for women, (L) = -2.097 + 0.2466 × body weight (kg) + 0.1069 × height (cm). Peritoneal sodium was defined as the difference between the amount of sodium in the effluent dialysate

Table 1. An example of sodium assessment from Dietary recall

Diet	Time	Place	Food	Ingredient	Amount	Sodium (mg)
Breakfast	8:10	Home	Cooked rice	Well polished rice	1 bowl (210 g)	6.3
				Bean paste stew	Potato	1/4 piece (70 g)
			Young pumpkin		1/2 piece (80 g)	0.8
			Onion		1/3 piece (50 g)	1.0
			Soybean curd		1/5 piece (80 g)	4.0
			Soybean paste		2 tea spoon (10 g)	402
			Grilled Spanish mackerel		Spanish mackerel	1/3 EA (70 g)
				Soy sauce	1 teaspoon (5 g)	293
			Seasoned pan-fried eggplant	Eggplant	1/3 cup (70 g)	2.1
				Olive oil	1 teaspoon (5 g)	1.3
				Fermented red pepper paste	1 teaspoon (10 g)	251
			Kimchi (fermented salted vegetable)	Kimchi, Chinese cabbage	1/2 dish (50 g)	573

and the influent dialysate: peritoneal sodium removal (mEq/L) = [in effluent dialysate Na level (mEq/L) × total effluent dialysate volume (L)] – [influent dialysate Na level (mEq/L) × influent dialysate volume (L)], and total sodium removal was defined as the sum of peritoneal sodium added to the amount of sodium in the 24h urine sample.

Statistical analysis

Parametric values are expressed as the means and standard deviations. The correlations between variables were assessed using Pearson's correlation coefficient (*r*). The differences between categorical values were assessed using the Chi square test. Linear regression equations were used to analyze the relationship between daily sodium intake and total sodium removal, while *p*-values less than 0.05 were considered as statistically significant. All statistical analyses were performed using SPSS version 18.0 (Chicago, IL).

RESULTS

Baseline clinical characteristics

There were 39 patients in the RRF(–) group and 44 patients in the RRF(+) group. The baseline clinical characteristics of these patients are summarized in Table 2. There were no significant differences between the two groups in terms of age, gender, height, weight, presence of diabetes mellitus, blood pressure, numbers of anti-hypertension medication, the use of icodextrin dialysate, mode of PD, or peritoneal membrane transporter types. The only difference between these two groups was that the mean PD duration in the RRF(–) group was longer than in the RRF(+) group (5.9 vs 2.5 years, *p*<0.01).

Dietary sodium intake and sodium removal

Dietary sodium intake, sodium removal through the peritoneum and urine, and PD adequacy parameters are summarized in Table 3. The mean daily sodium intake appears slightly higher in the RRF(+) group compared with the RRF(–) group, but this difference was not statistically

significant. The mean peritoneal sodium removal was not significantly different between the two groups, but the total sodium removal, calculated as the sum of peritoneal and urinary sodium, was significantly higher in the RRF(+) group compared with the RRF(–) group (181±45 vs 144±33, *p*<0.01). The mean dialysate glucose concentration was slightly higher in the RRF(–) group compared to the RRF(+) group, but this difference was not statistically significant.

The mean peritoneal ultrafiltration volume was significantly higher in the RRF(–) group, however the mean total fluid removal volume, including urine, was significantly higher in the RRF(+) group. The mean total weekly Kt/V was slightly higher in the RRF(+) group than the RRF(–) group, but this difference was not statistically significant (Table 3).

Correlations between dietary sodium and total sodium removal

In this patient group, there was a positive linear correlation between dietary sodium intake and total sodium removal. The correlation coefficients between dietary sodium intake and total sodium removal were 0.598 in the RRF(–) group and 0.577 in the RRF(+) group (both *p*<0.01), and the correlation coefficient between dietary sodium intake and total sodium removal in the total group of 83 patients was 0.595 (*p*<0.01, Figure 1). The linear equations for the RRF(–) and RRF(+) groups are: RRF(–), dietary sodium intake (mg/d) = 19.3 × total sodium removal (mEq/d) + 211, and RRF(+), dietary sodium intake (mg/d) = 15.4 × total sodium removal (mEq/d) + 609. For the total patient group, the equation is dietary sodium intake (mg/d) = 15.6 × total sodium removal (mEq/d) + 646.

Correlations between dietary sodium intake and peritoneal or urinary sodium removal

Dietary sodium intake showed a positive correlation with peritoneal sodium removal in both groups: RRF(–)group, *r*=0.603, *p*<0.01; RRF(+) group, *r*=0.442, *p*<0.01. Dietary

Table 2. Baseline characteristics of PD patients

	RRF(–) group (n=39)	RRF(+) group (n=44)	<i>p</i> -value
Age, years	48±15	55±15	0.05
Male gender, n (%)	22 (56)	27 (61)	0.66
Height, cm	162±7	162±10	0.91
Weight, kg	60.8±11.2	64.8±11.3	0.10
Systolic blood pressure, mmHg	126±27	132±22	0.26
Diastolic blood pressure, mmHg	76.0±13.5	77.8±11.8	0.52
Anti-hypertension drug, n	2.5±1.9	2.4±1.8	0.67
Presence of diabetes mellitus, n (%)			0.66
Diabetes mellitus	21 (54)	26 (59)	
Non-Diabetes mellitus	18 (46)	18 (41)	
Mode of peritoneal dialysis, n (%)			
CPD/APD	25/14 (64/36)	26/18 (59/41)	0.65
Peritoneal membrane transporter type, n (%)			0.98
High	5 (13)	6 (14)	
High average	27 (69)	29 (66)	
Low average	6 (15)	8 (18)	
Low	1 (3)	1 (2)	
Duration of peritoneal dialysis, years	5.9±3.7	2.5±2.0	<0.01

PD: peritoneal dialysis; RRF: residual renal function; CPD: conventional peritoneal dialysis; APD: automatic peritoneal dialysis.

Table 3. The measurements of sodium and dialysis adequacy in PD patients

	RRF(-) group (n=39)	RRF(+) group (n=44)	p-value
Total energy intake, kcal	1460±445	1490±445	0.82
Dietary sodium intake, mg/day	2990±1060	3400±1120	0.10
Total sodium removal, mEq/day	145±33	181±45	<0.01
Peritoneal sodium removal, mEq/day	144±33	145±42	0.88
Urinary sodium removal, mEq/day	4.3±0.6	36.4±19.2	<0.001
Total fluid removal, L/day	1.47±0.26	1.78±0.29	<0.01
Peritoneal ultrafiltration volume, L/day	1.46±0.27	1.22±0.22	<0.01
Urine volume, L/day	0.008±0.02	0.56±0.23	<0.001
Residual renal function, mL/min	0.48±0.66	2.82±3.02	<0.001
Glucose concentration of dialysate (%)	1.92±0.40	1.74±0.43	0.06
Use of icodextrin, n (%)	19/20 (49/51)	14/30 (32/68)	0.17
nPNA	1.78±0.77	1.80±0.91	0.90
Weekly peritoneal Kt/V	2.08±0.75	1.85±1.01	0.28
Weekly renal Kt/V	0.03±0.01	0.56±0.65	<0.001
Weekly total Kt/V	2.08±0.75	2.41±1.23	0.18

nPNA: normalized protein nitrogen appearance.

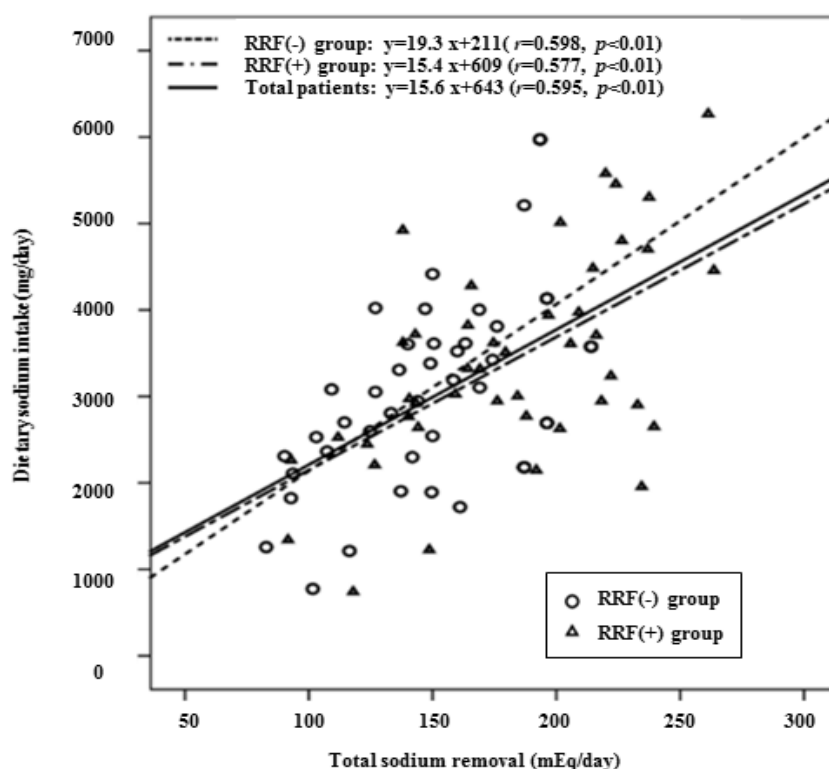


Figure 1. Correlation between dietary sodium intake and total sodium removal. The figure shows the significant positive correlation and linear relationships between dietary sodium intake and total sodium removal in PD patients with and without residual renal function, and in all PD patients.

sodium intake also showed a positive correlation with urinary sodium removal in the RRF(+) group ($r=0.381$, $p<0.01$), but not in the RRF(-) group. The total amount of ultrafiltration was correlated with the peritoneal sodium removal in the RRF(+) group ($r=0.637$, $p<0.01$), but not in the RRF(-) group.

DISCUSSION

This report examines the estimation of daily sodium intake during the assessment of dialysis adequacy in chronic PD patients, and shows significant correlations between dietary sodium intake and total sodium removal.

Although sodium intake and removal are both factors that affect adequate fluid balance in PD patients, most studies in chronic PD patients have focused on other factors associated with fluid balance, or the clinical outcomes of peritoneal sodium removal,⁸⁻¹⁰ and there is little detailed information on sodium removal as a tool to measure dietary sodium intake.

Wang et al showed that changes in total sodium intake do not lead to proportionate changes in total sodium removal in continuous ambulatory PD patients, and suggested that the total sodium removal could not be a surrogate marker of sodium intake.¹¹ However, that study ex-

aminated total sodium intake and total sodium removal over a three month period. In this study, we have shown a positive correlation between dietary sodium intake and total sodium removal measurements that were taken on the same day. For the total population of chronic PD patients, a linear equation was drawn to describe the relationship between dietary sodium intake and sodium removal: dietary sodium intake (mg/d) = 15.6 × total sodium removal (mEq/d) + 646. According to this equation, a dietary sodium intake of 2,000 mg corresponds to a sodium removal of approximately 87 mEq/d. These results suggest that the measurement of peritoneal and urinary sodium removal during the assessment of dialysis adequacy is a simple and effective method to monitor sodium intake in chronic PD patients.

Although residual renal function is small in chronic PD patients, its preservation is important to achieve adequate small solute clearance and volume control. Konings et al, reported that chronic PD patients with a residual glomerular filtration rate <2 mL/min showed poor volume status compared to those with a glomerular filtration rate >2 mL/min, despite similar amounts of total fluid removal.¹² We also divided our patients into two groups based on residual renal function and analyzed the data in both groups. We found positive correlations between dietary sodium intake and total sodium removal in both groups, irrespective of the presence or absence of residual renal function. According to the linear equations described in the Results, a dietary sodium intake of 2,000 mg corresponds to a sodium removal of approximately 90mEq/d in the RRF(-) group and 92 mEq/d in the RRF(+) group.

It is uncertain whether the measurement of urinary sodium can represent dietary sodium intake in end-stage renal disease patients. Shemin et al showed that the exogenous administration of natriuretic peptides in dogs with chronic and acute renal disease does not consistently increase renal sodium excretion,¹³ whereas several studies have reported that sodium homeostasis is well maintained in advanced renal failure due to increased fractions of sodium in urinary excretions that reflect sodium intake, even if there is a decrease in functional renal mass.^{14,15} We have previously demonstrated significant correlations between sodium intake, estimated by dietary recall, and 24h urinary sodium measurements both in chronic kidney disease patients and in stage V chronic kidney disease patients.¹⁶ In the present study, urinary sodium removal was correlated with dietary sodium intake in the RRF(+) group ($r=0.381$, $p<0.01$). These results support the hypothesis that, in chronic PD patients with residual renal function, urinary sodium reflects dietary sodium intake.

General treatment guidelines recommend a sodium restriction of approximately 2,000 mg/day,¹⁷ however from the results of a double-blind crossover study in chronic PD patients, Adrian et al. reported that this recommended sodium intake is too restrictive.¹⁸ In the present study, although there was no significant difference in the sodium intake between the two groups, both groups had a higher sodium intake than is recommended (RRF(+) 3,400 mg and RRF(-) 2,990 mg). It should be noted that, traditionally, Koreans tend to eat salted food. A 2009 government report on the nutritional status of South Korea highlighted that 4.6 mg of sodium per capita per day is consumed,

and that South Korea is a country with a high average sodium intake.¹⁹ It is therefore possible that traditional dietary habits affected the sodium intake of the patients in the present study, despite the provision of a continuous dietary education.

The present study has several limitations. First, it is a single center and cross-sectional case-control study. Second, dietary recall for only one day was analyzed. However, according to Caggiula's study, to compare the single vs multiple-day nutrition records to estimate sodium intake, one day dietary records were as accurate as the six day average, or estimates made using multiple-day records. And the author concluded that one day dietary recall could represent the six day dietary recall.²⁰ In the present study, the experienced dietitian carefully collected and analyzed one day dietary records, considering dietary habits of the patients. Therefore, we hold our data reasonable to support the correlation of the dietary sodium intake and total sodium removal in PD patients.

Conclusion

The present study demonstrated a positive correlation between dietary sodium intake and total sodium removal. The measurement of total sodium removal during the assessment of dialysis adequacy could be a simple and effective method to estimate dietary sodium intake in chronic PD patients. A dietary sodium intake of 2,000 mg corresponds to an approximate total sodium removal of 87 mEq/d.

AUTHOR DISCLOSURES

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REFERENCES

1. Forman JP, Scheven L, de Jong PE, Bakker SJ, Curhan GC, Gansevoort RT. Association between sodium intake and change in uric acid, urine albumin excretion, and the risk of developing hypertension. *Circulation*. 2012;125:3108-16. doi: 10.1161/CIRCULATIONAHA.112.096115.
2. KDOQI. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis*. 2005;45(4 Suppl 3):S1-153.
3. Pletinck A, Consoli C, Van Landschoot M, Steppan S, Topley N, Passlick-Deetjen J, Vanholder R, Van Biesen W. Salt intake induces epithelial-to-mesenchymal transition of the peritoneal membrane in rats. *Nephrol Dial Transplant*. 2010;25:1688-96. doi: 10.1093/ndt/gfq036.
4. Sanders PW. Salt intake, endothelial cell signaling, and progression of kidney disease. *Hypertension*. 2004;43:142-6. doi: 10.1161/01.HYP.0000114022.20424.22
5. Tennankore KK, Bargman JM. Nutrition and the kidney: recommendations for peritoneal dialysis. *Adv Chronic Kidney Dis*. 2013;20:190-201. doi: 10.1053/j.ackd.2012.10.010.
6. McCann LM, Foulks CI. Nutritional recommendations for patients undergoing continuous ambulatory peritoneal dialysis. *Semin Dial*. 1992;5:136-41. doi: 10.1111/j.1525-139X.1992.tb00131.x
7. Espeland MA, Kumanyika S, Wilson AC, Reboussin DM, Easter L, Self M, Robertson J, Brown WM, McFarlane M; TONE Cooperative Research Group. Statistical issues in

- analyzing 24-hour dietary recall and 24-hour urine collection data for sodium and potassium intakes. *Am J Epidemiol.* 2001;153:996-1006. doi: 10.1093/aje/153.10.996.
8. Shan YS, Ding XQ, Ji J, Lv WL, Cao XS, Zhong YH. Clinical factors associated with sodium removal in peritoneal dialysis patients. *J Int Med Res.* 2011;39:1883-9. doi: 10.1177/147323001103900532.
 9. Rodríguez-Carmona A, Fontán MP. Sodium removal in patients undergoing CAPD and automated peritoneal dialysis. *Perit Dial Int.* 2002;22:705-13.
 10. Dong J, Li Y, Yang Z, Luo J, Zuo L. Time-dependent associations between total sodium removal and mortality in patients on peritoneal dialysis. *Perit Dial Int.* 2011;31:412-21. doi: 10.3747/pdi.2010.00103.
 11. Cheng LT, Wang T. Changes in total sodium intake do not lead to proportionate changes in total sodium removal in CAPD patients. *Perit Dial Int.* 2006;26:218-23.
 12. Konings CJ, Kooman JP, Schonck M, Struijk DG, Gladziwa U, Hoorntje SJ, van der Wall Bake AW, van der Sande FM, Leunissen KM. Fluid status in CAPD patients is related to peritoneal transport and residual renal function: evidence from a longitudinal study. *Nephrol Dial Transplant.* 2003;18:797-803. doi: 10.1093/ndt/gfg147.
 13. Shemin D, Dworkin LD. Sodium balance in renal failure. *Curr Opin Nephrol Hypertens.* 1997;6:128-32.
 14. Bricker NS, Klahr S, Lubowitz H, Rieselbach RE. Renal function in chronic renal disease. *Medicine (Baltimore).* 1965;44:263.
 15. Bricker NS. On the meaning of the intact nephron hypothesis. *Am J Med.* 1969;46:1-11.
 16. Kang SS, Kang EH, Kim SO, Lee MS, Hong CD, Kim SB. Use of mean spot urine sodium concentrations to estimate daily sodium intake in patients with chronic kidney disease. *Nutrition.* 2012;28:256-61. doi: 10.1016/j.nut.2011.06.006.
 17. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr et al. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension.* 2003;42:1206-52. doi : 10.1161/01.HYP.0000107251.49515.c2.
 18. Fine A, Fontaine B, Ma M. Commonly prescribed salt intake in continuous ambulatory peritoneal dialysis patients is too restrictive: results of a double-blind crossover study. *J Am Soc Nephrol.* 1997;8:1311-4.
 19. Korea Centers for Disease Control and Prevention. Korea Health Statistics 2009: Korea National Health and Nutrition Examination Survey (KNHANESIV-3). Seoul: Statistics Korea; 2010. (In Korean)
 20. Caggiula AW, Wing RR. The measurement of sodium and potassium intake. *Am J Clin Nutr.* 1985;43:391-8.