http://www.kidney-international.org

Sodium restriction improves the gustatory threshold for salty taste in patients with chronic kidney disease

Tetsuro Kusaba[1], Yasukiyo Mori[1], Okagaki Masami[2], Neriya Hiroko[2], Takaomi Adachi[1], Chikako Sugishita[1], Kazuhiro Sonomura[1], Taikou Kimura[1], Noriko Kishimoto[1], Hisako Nakagawa[1], Mitsuhiko Okigaki[1], Tsuguru Hatta[3] and Hiroaki Matsubara[1]

[1]Division of Cardiology and Nephrology, Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan; [2]Department of Nutrition, Kyoto Prefectural University of Medicine, Kyoto, Japan and [3]Division of Nephrology, Omihachiman Community Medical Center, Shiga, Japan

Sodium restriction is important in the treatment of chronic kidney disease; however, it is sometimes difficult to achieve. Decreased taste sensitivity may be a factor influencing inadequate control of oral salt intake and subsequent high blood pressure. To measure this, the gustatory threshold (recognition and detection) for salty taste was determined in 29 patients with chronic kidney disease using a sodium-impregnated test strip and relevant factors determining taste sensitivity were analyzed. Compared with 11 healthy volunteers, recognition and detection thresholds were increased in the patients with chronic kidney disease. Oral sodium intake correlated positively but serum zinc correlated negatively with the recognition threshold. Patients with diabetic nephropathy had a higher detection threshold than non-diabetic patients. Both recognition and detection thresholds were increased in patients with diuretic administration. After 1 week of sodium restriction, the average recognition threshold decreased significantly. Our study verified that latent taste dysfunction and zinc deficiency are common in patients with chronic kidney disease. Further, the recognition threshold for salty taste improved even after a short period of salt restriction.

Kidney International (2009) **76,** 638–643; doi:10.1038/ki.2009.214; published online 10 June 2009

KEYWORDS: chronic kidney disease; salt taste acuity; sodium restriction

Correspondence: *Tetsuro Kusaba, Division of Cardiology and Nephrology, Department of Medicine, Kyoto Prefectural University of Medicine, 456 Kajii-cho, Kamigyo-ku, Kyoto 602-8566, Japan. E-mail: fwnk5760@mb.infoweb.ne.jp*

Received 27 August 2008; revised 17 April 2009; accepted 21 April 2009; published online 10 June 2009

It is well known that excessive oral salt intake may induce high blood pressure in salt-sensitive individuals.[1,2] In addition, high blood pressure is widely known to be an important predictor for progression to end-stage renal disease and several clinical trials have proved that appropriate blood pressure control was required to prevent the progression of chronic kidney disease (CKD).[3–8] High blood pressure due to CKD is generally salt-sensitive, non-dipper (less than 10% of nocturnal blood pressure decline) and sometimes intractable.[3] Thus, sodium restriction is quite a beneficial and reasonable treatment for high blood pressure in CKD patients; however, sodium restriction is sometimes difficult to achieve and excessive restriction affects a patient's quality of life.

One candidate factor relevant to the disturbance of salt restriction is impaired sensitivity to salty taste. If the patient cannot sense salty taste accurately, oral sodium intake may increase. To assess taste acuity, two different gustatory thresholds, the recognition and the detection threshold, are used. The detection threshold was defined as the concentration of solution at which the subjects clearly indicated it as different from deionized water, but not necessarily recognizing the type of stimulus. The recognition threshold was defined as the concentration of a solution at which the subjects clearly and accurately identified the type of stimulus, that is, the taste.[9] Sensitivity for salty taste differs among individuals and is influenced by various causes, such as aging, zinc status or both.[10–12] One clinical experience proved that excess sodium intake increases the taste threshold for salty taste.[13] In addition, concerning the effect of sodium restriction on the gustatory threshold for salty taste, only one clinical experiment in young human volunteers showed that 10-day sodium depletion decreased the sodium threshold.[14]

On the basis of these previous investigations, we hypothesized that taste acuity is impaired in CKD patients and is improved by appropriate sodium restriction. The purpose of this study was to analyze the gustatory threshold for salty taste in CKD patients using a sodium-impregnated test strip (SALSAVE; Advantec Toyo Co. Ltd, Tokyo, Japan)

and we also investigated the effect of short-term salt restriction on the gustatory threshold.

RESULTS

Patient characteristics

The patient characteristics shown in Table 1, showed that their renal function was moderately altered and a moderate amount of urinary protein was observed. The primary causes of CKD included 10 diabetic nephropathy, four hypertensive nephrosclerosis, 13 chronic glomerulonephritis and two others. In our patients, mean 24-h blood pressure was relatively well controlled (24-h average blood pressure: 130.3 ± 16.6/70.1 ± 11.7 mm Hg) by several antihypertensives (mean classes of administered antihypertensives: 2.38 ± 1.54), however, the circadian rhythm of blood pressure was severely disturbed (average nocturnal blood pressure decline: 3.1 ± 5.9%) and only three patients (10.7%) presented with the dipper type of blood pressure. Mainly, angiotensin-converting enzyme inhibitor (ACEI)/angiotensin-2 receptor blocker (72%) and calcium channel blocker (72%) were used and diuretics was administered for 12 patients (41%). Average serum zinc was relatively low and serum zinc was severely decreased (lower than 60 μg per 100 ml) in 10 patients. Estimated oral protein intake calculated according to Maroni's formula[15] did not correlate with the serum zinc value (data not shown).

Increased salty taste threshold in CKD patients

In our analysis, as a normal control, recognition and detection thresholds were measured in 11 healthy age-matched volunteers. Seventy-one percent of CKD patients presented with a recognition threshold above 0.8%, which was 27% in healthy volunteers (Figure 1a). In addition, 39% of CKD patients presented with a detection threshold above 0.8%, whereas it was 18% in healthy volunteers (Figure 1b). The recognition threshold was significantly higher in CKD patients than in healthy volunteers (0.86 ± 0.26 vs 0.68 ± 0.14%, $P<0.05$; Figure 1c). The detection threshold was also significantly higher in CKD patients than in healthy volunteers (0.74 ± 0.21 vs 0.64 ± 0.08%, $P<0.05$; Figure 1c). Although the detection threshold obviously never exceeded the recognition threshold, a discrepancy was observed in 10 patients (Figure 1d).

Table 1 | Patient characteristics

	CKD patients	Normal subjects
Number of subjects	29	11
Age	62.9 ± 15.9	37.7 ± 8.62
Gender (M/F)	19/10	8/3
Smoking (Yes/No)	0/29	0/11
False teeth (Yes/No)	12/17	0/11
Diabetic nephropathy (Yes/No)	10/19	0/11
Laboratory parameters		
Creatinine (mg per 100 ml)	3.36 ± 1.36	0.75 ± 0.18
eGFR (ml/min/1.73 m^2)	20.85 ± 12.2	89.8 ± 8.9
Urinary protein (g/day)	2.21 ± 2.67	Not available
Urinary sodium (mmol/day)	89.1 ± 37.9	Not available
Serum zinc (μg per 100 ml) 80–160	70.9 ± 18.3	Not available

Significant correlation between urinary sodium excretion and salt taste acuity

Multivariate analysis of the factors relevant to the increase in the recognition threshold for salty taste revealed that high urinary sodium excretion, low serum zinc, diabetic patients and diuretics administration significantly correlated with taste acuity in CKD patients. Twenty-four-hour sodium excretion, as an indicator for evaluating the amount of dietary sodium intake, correlated positively and significantly with the recognition threshold ($r=0.57$, $P<0.01$, Figure 2a), not with the detection threshold in CKD patients ($r=0.45$, not significant (NS), Figure 2b). In contrast, serum zinc was correlated negatively and significantly with the detection threshold ($r=-0.67$, $P<0.05$, Figure 2d), but not with the recognition threshold in CKD patients ($r=-0.40$, not significant, Figure 2c).

Taste acuity impairment in patients with diabetic nephropathy or diuretics administration

Concerning the genesis of CKD, the detection threshold (0.88 ± 0.28% in diabetic and 0.66 ± 0.12% in non-diabetic patients, $P<0.05$), but not the recognition threshold (0.97 ± 0.35% in diabetic and 0.82 ± 0.23% in non-diabetic patients, NS), was increased in patients with diabetic

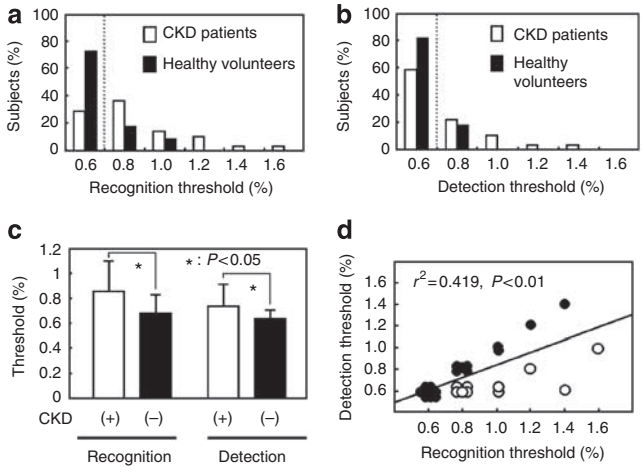

Figure 1 | Gustatory threshold for salty taste in chronic kidney disease (CKD) patients and healthy volunteers. (**a**) Distribution of recognition threshold on admission. In all, 71% of CKD patients presented with a recognition threshold above 0.8%, which was only 27% in healthy volunteers. (**b**) Distribution of detection threshold on admission. A total of 39% of CKD patients presented the recognition threshold above 0.8%, which was only 18% in healthy volunteers. (**c**) Both the recognition and detection threshold were significantly higher in CKD patients than in healthy volunteers. The detection threshold was also significantly higher in CKD patients than in healthy volunteers. (**d**) Single correlation between recognition and detection thresholds. Nineteen patients presented with no difference in concentration (closed circles); however, a discrepancy was observed among 10 patients (open circles).

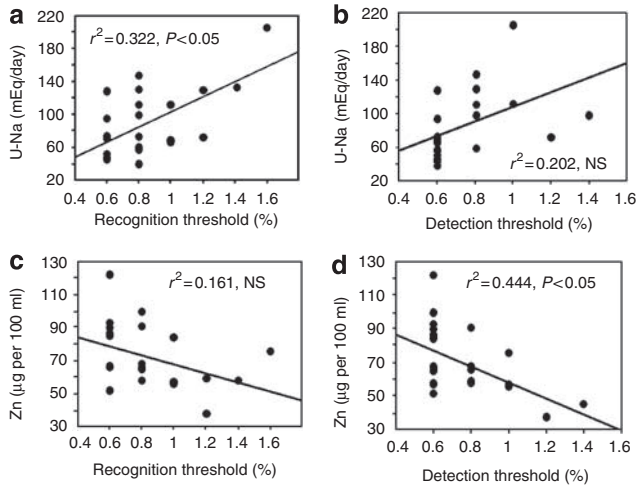

Figure 2 | Correlation of gustatory threshold, urinary sodium excretion, and serum zinc concentration. (**a**, **b**) There was a positive and significant correlation between urinary sodium excretion, indicating oral sodium intake, and the recognition threshold; however, there was no significant correlation with the detection threshold. (**c**, **d**) There was a negative and significant correlation between serum zinc concentration and the detection threshold; however, there was no significant correlation with the recognition threshold.

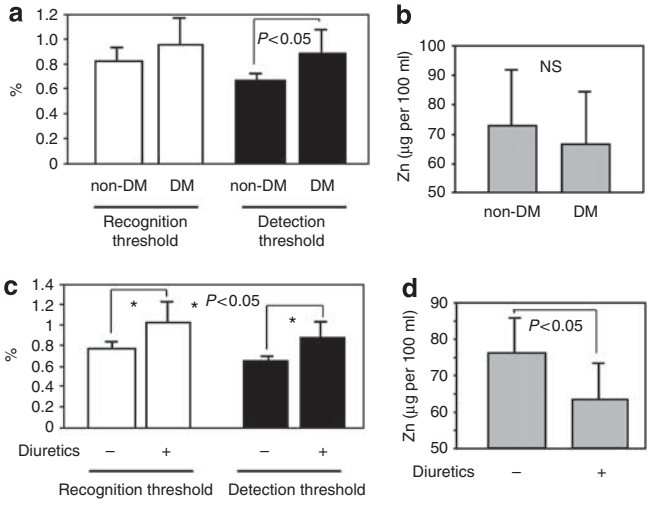

Figure 3 | Impact of diabetes mellitus (DM) or the use of diuretics on gustatory threshold. (**a**) Diabetic patients presented with a remarkable increase in the detection threshold but not the recognition threshold. (**b**) Serum zinc concentration was not different between diabetic and non-diabetic patients. (**c**) Patients with diuretics administration presented with both impaired recognition and detection thresholds. (**d**) Serum zinc concentration was remarkably decreased in patients with diuretic administration.

nephropathy (Figure 3a). Serum zinc was not different between diabetic and non-diabetic patients (66.7 ± 17.7 μg per 100 ml in diabetic and 73.1 ± 18.4 μg per 100 ml in non-diabetic patients, NS, Figure 3b). Concerning the administrated antihypertensives, both recognition and detection

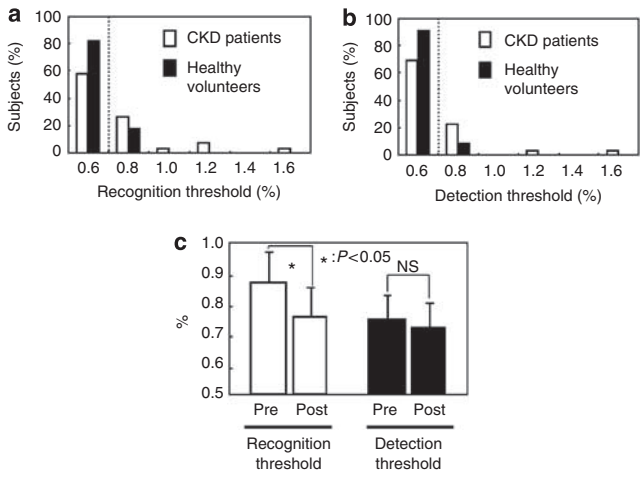

Figure 4 | One-week sodium restriction improves gustatory threshold for salty taste. Sodium restriction was performed only in chronic kidney disease (CKD) patients, not in healthy volunteers. (**a**) Distribution of recognition threshold 1 week after the examination. Approximately 42% of CKD patients presented with a recognition threshold above 0.8%, which was only 18% in healthy volunteers. (**b**) Distribution of detection threshold 1 week after the examination. About 31% of CKD patients presented with a recognition threshold above 0.8%, which was only 9% in healthy volunteers. (**c**) The average value of the recognition threshold decreased from 0.84 to 0.76% with statistical significance. In contrast, the average detection threshold decreased from 0.74 to 0.71% with no statistical significance.

thresholds were increased in CKD patients with only diuretics administration (recognition threshold; 1.03 ± 0.35% with diuretics and 0.76 ± 0.13% without diuretics administration ($P<0.01$), and detection threshold; 0.87 ± 0.27% with diuretics and 0.65 ± 0.09% without diuretics administration ($P<0.01$) Figure 3c). In addition, serum zinc was lower in CKD patients with diuretics administration (63.5 ± 16.0 vs 76.3 ± 18.5 μg per 100 ml, $P<0.05$, Figure 3d). The age, gender, use of false teeth, and degree of renal insufficiency did not correlate with the recognition and detection thresholds for salty taste in CKD patients. In addition, neither the recognition nor detection threshold correlated with several BP parameters, such as systolic, diastolic, mean, diurnal, nocturnal and during 24 h in CKD patients.

Sodium restriction improves gustatory threshold for salty taste

After 1 week of sodium restriction, the percentage of CKD patients with a recognition threshold above 0.8% remarkably decreased from 71 to 39% (Figures 1a and 4a). In addition, the percentage of CKD patients with a detection threshold above 0.8% decreased from 39 to 31% (Figures 1b and 4a). The average value of the recognition threshold in CKD patients decreased from 0.84 ± 0.27 to 0.76 ± 0.25% with statistical significance ($P<0.05$). The average value of the detection threshold in CKD patients also decreased from 0.74 ± 0.21 to 0.71 ± 0.23%; however, there was no statistical significance (Figure 4b). To eliminate the possibility that

repeated tests affect the taste threshold, we examined the same taste tests in healthy volunteers after a 1-week interval. The percentage of healthy volunteers with a detection and recognition threshold above 0.8% was decreased (27–18% in recognition threshold; Figure 4a, 18 to 9% in detection threshold; Figure 4b); however, the average value of both the recognition and detection thresholds in healthy volunteers was almost unchanged (recognition threshold: 0.68 ± 0.14 to 0.65 ± 0.09%, detection threshold: 0.64 ± 0.08 to 0.62 ± 0.06 NS).

DISCUSSION

In this study, daily urinary sodium excretion, indicating oral sodium intake, correlated with the recognition threshold for salty taste, not the detection threshold. In addition, we proved that sodium restriction improved the recognition threshold for salty taste, but not the detection threshold. Previous reports revealed that taste dysfunction was frequently observed in CKD patients.[16–20] Taste dysfunction in CKD patients had various causes, such as metabolic disorders, deficiencies of various micronutrients including zinc, degree of kidney dysfunction, alterations of peripheral nerve activity, and administered drugs. The fact that taste acuity improved after the initiation of hemodialysis[19] indicates that the accumulation of uremic toxins may be partly responsible for the impaired gustatory threshold in CKD patients.

Taken together, the amount of usual oral sodium intake is one of the candidate factors influencing on the recognition threshold for salty taste. In contrast, the detection threshold is affected by metabolic disorders, such as low serum zinc, or organic neural dysfunction, such as diabetic neuropathy. Previous investigations concerning the relationship between sodium intake and taste threshold are limited. Moreover, these results are still controversial and showed that sodium depletion by diuretics administration and/or sodium restriction did not affect the taste threshold.[14,21] In contrast, Huggins *et al.* showed that a 2-week oral sodium tablet administration increased the taste threshold. They also showed that the increment in urinary sodium excretion was linearly related to the taste threshold,[13] which may be congruent with our results.

Low serum zinc is a major cause of taste dysfunction and a previous report showed that serum zinc was reduced in CKD patients.[22,23] Zinc is bound to gustin, an essential protein involved in taste perception. Zinc deficiency induces gustin deficiency and subsequent impairment of taste acuity.[24] In our analysis, albeit with a weak correlation, serum zinc significantly correlated with the detection threshold, indicating that zinc deficiency might partly contribute to taste acuity impairment. One candidate's cause of zinc deficiency in CKD patients is that appetite loss and subsequent inappropriate food intake by uremia may induce deficiencies in multiple micronutrients.[18,19] As for other candidates, because zinc intake is closely related to protein intake, a low protein diet for CKD also accelerates zinc deficiency; however, our study did not verify the effect of a low protein diet on zinc deficiency. In addition, low serum zinc does not always reflect total body deficiency but abnormal redistribution, based on the fact that the zinc content of hair and erythrocytes is normal even if serum zinc is reduced.[22,23] The mechanism of abnormal zinc redistribution is unknown; however, as serum zinc increased after dialysis initiation, uremia might induce abnormal zinc metabolism.[23] On the basis of these considerations, serum zinc is easily depleted and should be evaluated in CKD patients.

Concerning the administered antihypertensives, our study demonstrated that only diuretics administration increased the gustatory threshold, which occurred partially through zinc deficiency. Generally, diuretics improve sodium sensitivity to blood pressure and also shift the blood pressure circadian rhythm from non-dipper to dipper, as does dietary sodium restriction,[25,26] which is preferable to prevent CKD and CVD. The mechanisms of zinc deficiency due to diuretics are unclear. Some reports have shown that diuretics, especially hydrochlorthiazide, increased the urinary excretion of zinc.[27–29] In contrast, other reports showed that diuretics reduced the zincuretic effect of captopril by binding to its sulphydryl group within the tubular lumen.[30] From these reports, the effects of diuretics on zinc metabolism are still undefined, but warrant further and larger examination to reach a clear conclusion.

The initial step in taste signal transduction occurs in taste receptor cells located in the taste buds, which are innerved by afferent neurons.[31] Once substances coat the mouth, changes in the taste receptor cell membrane occur and ion channels open, subsequently allowing stimulus ions to enter directly through the channels.[31] The perception of salt and sour tastes is thought to result from the interaction between ion channels at the cell membrane, whereas sweet and bitter tastes are dependent on protein-bound secondary messengers within the cells.[10,32] Curiously, a previous report showed taste dysfunction in CKD patients, especially bitter and salty taste sensitivity.[20] The preferable effect of sodium restriction on salt taste acuity may be induced by improved ion channel sensitivity and subsequent recognition threshold improvement. In contrast, based on the fact that both zinc deficiency and diabetic nephropathy patients showed an increased detection threshold, our results suggested that the increased detection threshold was caused by impaired subsequent signal transduction, such as gustin deficiency or peripheral nerve dysfunction. A previous report showed that the taste nerve transduction function is impaired during the diabetes course and that the strongest associations with taste dysfunction were found with peripheral neuropathy and microalbuminuria.[33]

Several methods, such as the whole-mouth method, the micropipette method and the electrogustometer are used to measure the gustatory threshold for salty taste in clinical practice;[34–36] however, these methods are complicated and not suitable for routine clinical screening. In contrast, SALSAVE examination is easy and inexpensive, and takes

only a few minutes. In addition, the mean magnitude of the response to SALSAVE significantly correlated with the results of other taste tests.[36] Thus, a taste test using SALSAVE is useful for screening for salty taste dysfunction.

Our study has several limitations, such as the small sample size, leading to inadequate assessment. For example, although advanced age and the use of false teeth induce taste dysfunction,[37] our analysis did not provide a significant correlation between these parameters and taste dysfunction. Concerning the taste threshold examination, although SALSAVE can easily evaluate the gustatory threshold for salty taste in screening, impregnated sodium concentrations of SALSAVE are limited on the market and we could not evaluate the patient's taste threshold accurately, especially lower than 0.6% and higher than 1.6%. In our analysis, although the threshold in most healthy volunteers was 0.6% at the first and second examinations, we could not eliminate the possibility that the threshold was overestimated. In addition, the inter-trial interval can significantly influence the taste threshold. Theoretically, a shorter inter-trial interval might enhance adaptation and thus elevate the threshold.[38] Furthermore, when determining each threshold, strips of higher salt concentration were applied once followed by strips with lower concentration, which might also enhance the taste threshold; however, during our experiments, we considered that oral rinsing with distilled water might be sufficient to eliminate residual salt stimulus.

Finally, we used 24-h urinary sodium excretion as an indicator of the amount of sodium intake. Although 24-h urinary sodium excretion, if complete, has been used broadly as the estimated daily sodium intake in many clinical investigations,[39–42] it is considered to be equal to sodium intake only at the equilibrium blood pressure calculated from the natriuresis–blood pressure curve proposed by Guyton.[43] In our experiment, to minimize the effect of sodium restriction under hospitalization and to assess the pre-hospitalized salt intake, urinary sodium excretion measured just after hospitalization was used for analysis; however, there is a possibility that sodium excretion was not assessed precisely and might have been lower than at home. In addition, because the urine sample was measured only once, the samples did not accurately reflect the daily variation of urinary sodium excretion. We cannot exclude the possibility that these limitations affected the results of our analysis.

In conclusion, we verified that taste dysfunction and zinc deficiency are common in CKD patients. In addition, even during a short period, sodium restriction improved the recognition threshold for salty taste. To restrict sodium easily and effectively to treat hypertension, physicians should be more concerned with taste disturbance in CKD patients and taste acuity should be assessed in the usual clinical practice.

MATERIALS AND METHODS

Subjects

In this study, we enrolled 29 CKD patients (mean age: 62.9 ± 15.9 years old, 19 men and 10 women), defined as having eGFR below 60 ml/min/1.73 m^2. All were consecutive patients who were admitted to the hospital of Kyoto Prefectural University of Medicine to attend a 1-week educational program on CKD. During hospitalization, a meal with low salt (5 g/day), low protein (0.8 g/kg/day × ideal body weight) and low potassium (1500 mg/day) was served to all patients. The calories were not altered for either diet, unless the patient had diabetes mellitus. We ascertained whether the subject was a current smoker and wore false teeth. In addition, 11 volunteers (mean age: 37.7 ± 8.62 years old, eight men and three women) without renal insufficiency (eGFR: 77–101 ml/min/1.73 m^2, average eGFR 89.8 ± 8.9 ml/min/1.73 m^2) or any serious systemic diseases were enrolled to measure taste acuity. The research protocol was approved by the institutional review board of the hospital of Kyoto Prefectural University of Medicine and all patients gave written consent to this study.

Blood and urinary examination and blood pressure measurement

We measured serum creatinine (Cr; mg per 100 ml) on admission and eGFR according to the MDRD formula as described previously.[44] Serum zinc, a major cause of taste dysfunction, was also measured using fasting blood in the morning. A urine sample was collected for 24 h from 1100 hours on the admission day to the same time the next day and urinary sodium excretion, urinary urea nitrogen excretion, and the amount of urinary protein were measured. Simultaneously, ambulatory blood pressure (ES-H531; TERUMO Corporation, Tokyo, Japan) was monitored for 24 h and blood pressure was measured every 15 min during the day and every 30 min at night. Mean blood pressure was defined as diastolic blood pressure plus one-third of the pulse pressure.

Gustatory threshold for salty taste measurements

In CKD patients, on the admission day and 1 week later, we measured two different gustatory thresholds; the recognition and detection thresholds, as described previously.[36] To assess the effect of repeated tests on the taste threshold, we also measured the gustatory thresholds in healthy volunteers after a 1-week interval. The detection threshold was defined as the lowest concentration at which a subject could distinguish a sodium-impregnated test strip from a no-sodium strip (no salty taste). The recognition threshold was defined as the lowest concentration at which a salty taste could be recognized.[9] The impregnated salt concentration was initially 0% and increased in 0.2% intervals from 0.6 to 1.6%. The patients held the test strips in their mouths for a few seconds to assess the salt concentration and were then asked, 'is there any taste? If yes, what kind of taste?' Before each application of a paper strip, the subjects gargled with distilled water. Strips with increasing salt concentration were applied until the subject correctly identified any taste. The same concentration was reapplied, and if the subject could not identify the taste, the next highest concentration was presented. When the same concentration had been correctly identified two times, strips with successively lower concentrations were applied until the subject made an incorrect identification in one of the two applications. The next highest concentration was considered to be the detection threshold. In addition, if the patients could taste something, but failed to identify the correct taste of 'salty', the examination was continued until they could identify the taste correctly. The recognition threshold was determined as the next highest concentration at which the subjects could correctly identify 'salty' two times.

Statistical analysis

A statistical analysis was performed using StatView – SAS institute Inc., version 5.0 software. All values are expressed as the mean ± s.e.m. when applicable. Spearman's correlation coefficient by rank was used to analyze the correlation between the gustatory threshold and measurements such as blood and urine examination, blood pressure and so on. Multivariate analysis was performed with the gustatory threshold as a dependent variable and age, gender, the degree of renal dysfunction, urinary sodium excretion and serum zinc as independent variables. Student's unpaired *t*-test and the Mann–Whitney test were used to evaluate differences in several variables. *P*-values less than 0.05 were considered significant.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 h urinary sodium and potassium excretion. *BMJ* 1988; **297**: 319–328.
2. Fujita T, Ando K, Ogata E. Systemic and regional hemodynamics in patients with salt-sensitive hypertension. *Hypertension* 1990; **16**: 235–244.
3. Bakris GL, Williams M, Dworkin L *et al.* Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* 2000; **36**: 646–661.
4. Yamagata K, Ishida K, Sairenchi T *et al.* Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int* 2007; **71**: 159–166.
5. Sarnak MJ, Levey AS, Schoolwerth AC *et al.* Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Circulation* 2003; **108**: 2154–2169.
6. Tozawa M, Iseki K, Iseki C *et al.* Blood pressure predicts risk of developing end-stage renal disease in men and women. *Hypertension* 2003; **41**: 1341–1345.
7. Klag MJ, Whelton PK, Randall BL *et al.* Blood pressure and end-stage renal disease in men. *N Engl J Med* 1996; **334**: 13–18.
8. Jafar TH, Stark PC, Schmid CH *et al.* Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med* 2003; **139**: 244–252.
9. Gomez FE, Cassis-Nosthas L, Morales-de-Leon JC *et al.* Detection and recognition thresholds to the 4 basic tastes in Mexican patients with primary Sjogren's syndrome. *Eur J Clin Nutr* 2004; **58**: 629–636.
10. Stewart-Knox BJ, Simpson EE, Parr H *et al.* Zinc status and taste acuity in older Europeans: the ZENITH study. *Eur J Clin Nutr* 2005; **59**(Suppl 2): S31–S36.
11. McDaid O, Stewart-Knox B, Parr H *et al.* Dietary zinc intake and sex differences in taste acuity in healthy young adults. *J Hum Nutr Diet* 2007; **20**: 103–110.
12. Mojet J, Christ-Hazelhof E, Heidema J. Taste perception with age: generic or specific losses in threshold sensitivity to the five basic tastes? *Chem Senses* 2001; **26**: 845–860.
13. Huggins RL, Di Nicolantonio R, Morgan TO. Preferred salt levels and salt taste acuity in human subjects after ingestion of untasted salt. *Appetite* 1992; **18**: 111–119.
14. Beauchamp GK, Bertino M, Burke D *et al.* Experimental sodium depletion and salt taste in normal human volunteers. *Am J Clin Nutr* 1990; **51**: 881–889.
15. Maroni BJ, Steinman TI, Mitch WE. A method for estimating nitrogen intake of patients with chronic renal failure. *Kidney Int* 1985; **27**: 58–65.
16. Middleton RA, Allman-Farinelli MA. Taste sensitivity is altered in patients with chronic renal failure receiving continuous ambulatory peritoneal dialysis. *J Nutr* 1999; **129**: 122–125.
17. Burge JC, Schemmel RA, Park HS *et al.* Taste acuity and zinc status in chronic renal disease. *J Am Diet Assoc* 1984; **84**: 1203–1206 1209.
18. Vreman HJ, Venter C, Leegwater J *et al.* Taste, smell and zinc metabolism in patients with chronic renal failure. *Nephron* 1980; **26**: 163–170.
19. Burge JC, Park HS, Whitlock CP *et al.* Taste acuity in patients undergoing long-term hemodialysis. *Kidney Int* 1979; **15**: 49–53.
20. Fernstrom A, Hylander B, Rossner S. Taste acuity in patients with chronic renal failure. *Clin Nephrol* 1996; **45**: 169–174.
21. Teow BH, Di Nicolantonio R, Morgan TO. Sodium chloride preference and recognition threshold in normotensive subjects on high and low salt diet. *Clin Exp Hypertens A* 1985; **7**: 1681–1695.
22. Mafra D, Cuppari L, Cozzolino SM. Iron and zinc status of patients with chronic renal failure who are not on dialysis. *J Ren Nutr* 2002; **12**: 38–41.
23. Condon CJ, Freeman RM. Zinc metabolism in renal failure. *Ann Intern Med* 1970; **73**: 531–536.
24. Shatzman AR, Henkin RI. Gustin concentration changes relative to salivary zinc and taste in humans. *Proc Natl Acad Sci USA* 1981; **78**: 3867–3871.
25. Uzu T, Kimura G. Diuretics shift circadian rhythm of blood pressure from nondipper to dipper in essential hypertension. *Circulation* 1999; **100**: 1635–1638.
26. Uzu T, Kazembe FS, Ishikawa K *et al.* High sodium sensitivity implicates nocturnal hypertension in essential hypertension. *Hypertension* 1996; **28**: 139–142.
27. Golik A, Modai D, Weissgarten J *et al.* Hydrochlorothiazide-amiloride causes excessive urinary zinc excretion. *Clin Pharmacol Ther* 1987; **42**: 42–44.
28. Wester PO. Urinary zinc excretion during treatment with different diuretics. *Acta Med Scand* 1980; **208**: 209–212.
29. Mountokalakis T, Dourakis S, Karatzas N *et al.* Zinc deficiency in mild hypertensive patients treated with diuretics. *J Hypertens Suppl* 1984; **2**: S571–S572.
30. Golik A, Averbukh Z, Cohn M *et al.* Effect of diuretics on captopril-induced urinary zinc excretion. *Eur J Clin Pharmacol* 1990; **38**: 359–361.
31. Kinammon SC. *Sensory Transduction in Olfactory Receptor Neurons and Gustatory Receptor Cells*. Raven Press: New York, 1991.
32. Drewnowski A. The science and complexity of bitter taste. *Nutr Rev* 2001; **59**: 163–169.
33. Le Floch JP, Le Lievre G, Labroue M *et al.* Early detection of diabetic patients at risk of developing degenerative complications using electric gustometry: a five-year follow-up study. *Eur J Med* 1992; **1**: 208–214.
34. Hinchcliffe R. Clinical quantitative gustometry. *Acta Otolaryngol* 1958; **49**: 453–466.
35. Bartoshuk L. Clinical evaluation of the sense of taste. *Ear Nose Throat J* 1989; **68**: 331–337.
36. Nishimoto K, Hirota R, Egawa M *et al.* Clinical evaluation of taste dysfunction using a salt-impregnated taste strip. *ORL J Otorhinolaryngol Relat Spec* 1996; **58**: 258–261.
37. Schiffman SS. Taste and smell losses in normal aging and disease. *JAMA* 1997; **278**: 1357–1362.
38. O'Mahony M. Salt taste adaptation: the psychophysical effects of adapting solutions and residual stimuli from prior tastings on the taste of sodium chloride. *Perception* 1979; **8**: 441–476.
39. Kihara M, Fujikawa J, Ohtaka M *et al.* Interrelationships between blood pressure, sodium, potassium, serum cholesterol, and protein intake in Japanese. *Hypertension* 1984; **6**: 736–742.
40. Whelton PK, He J, Cutler JA *et al.* Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA* 1997; **277**: 1624–1632.
41. Kawasaki T, Itoh K, Kawasaki M. Reduction in blood pressure with a sodium-reduced, potassium- and magnesium-enriched mineral salt in subjects with mild essential hypertension. *Hypertens Res* 1998; **21**: 235–243.
42. Iseki K, Iseki C, Itoh K *et al.* Urinary excretion of sodium and potassium in a screened cohort in Okinawa, Japan. *Hypertens Res* 2002; **25**: 731–736.
43. Guyton AC. Renal function curve – a key to understanding the pathogenesis of hypertension. *Hypertension* 1987; **10**: 1–6.
44. Imai E, Horio M, Nitta K *et al.* Modification of the modification of diet in renal disease (MDRD) study equation for Japan. *Am J Kidney Dis* 2007; **50**: 927–937.