High Salt Intake is Associated with Renal Involvement in Japanese Patients with Type 2 Diabetes Mellitus

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Abstract

Objective The aim of our study was to investigate clinical and nutritional factors associated with renal involvement in patients with type 2 diabetes.

Patients We performed a cross-sectional study of 71 patients with type 2 diabetes who were being educated at our hospital from September 2006 to February 2008. The patients were divided into two groups; Group I consisted of 40 patients with both an estimated glomerular filtration rate (eGFR) of ≥60 mL/min/1.73 m² and normoalbuminuria, and Group II consisted of 31 patients with either microalbuminuria/overt proteinuria or an eGFR of <60 mL/min/1.73 m². We compared the age, body mass index (BMI), blood pressure, duration from onset of diabetes, use of hypoglycemic agents and insulin, biochemistry data, including HbA1c, pulse wave velocity corrected by blood pressure (PWVc) and the daily intake of several nutrients between the two groups. A multivariate logistic regression analysis was performed to identify factors independently associated with renal involvement.

Results Group II had significantly higher values for BMI, the duration of diabetes, triglycerides, uric acid and PWVc than Group I. Group II tended to have a high salt intake compared to Group I. The multivariate logistic analysis revealed that the daily salt intake, PWVc and uric acid were independent factors associated with renal involvement (odds ratio, 1.15, 1.84 and 2.00; 95% confidence interval, 1.02-1.31, 1.04-3.27 and 1.04-3.85, respectively).

Conclusion Our data suggest that a high salt intake, in addition to arteriosclerosis, is associated with renal involvement in our cohort with type 2 diabetes.

Key words: diabetic nephropathy, microalbuminuria, macroalbuminuria, salt intake, arteriosclerosis

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Introduction

Diabetic nephropathy (DN), one of the major complications of diabetes mellitus, is the leading cause of end-stage renal disease (ESRD), and 45% of patients newly introduced to renal replacement therapy in 2009 in Japan had DN (1). Microalbuminuria in patients with type 2 diabetes is an important predictor of the development of DN, and the progression to overt proteinuria has been reported to be associated with a rapid decline in the renal function (2-4).

The cross-sectional study by Parving et al. demonstrated the overall global prevalence of micro- and macroalbuminuria to be 39% and 10%, respectively; the rates of these conditions were found to be highest in Asian patients, at 43% and 12%, respectively (5). On the other hand, Araki et al. reported that reductions in the urinary albumin excretion rate (UAER) to the normal range, i.e., remission of microalbuminuria, are common, with a six-year cumulative remission rate of 51% (6). Moreover, during a follow-up study over the subsequent eight years, the authors showed that the annual rate of decline in the estimated glomerular filtration rate (eGFR) among patients with a shift to normoalbuminuria and a reduction of more than 50% from the initial level

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of microalbuminuria was significantly lower than that observed in the subjects without such reductions. Therefore, microalbuminuria is considered to be an important therapeutic target for protecting against the progression of DN (7). Based on these previous findings, it is important to identify risk factors for the development of microalbuminuria and overt proteinuria in diabetic patients. In this regard, Parving et al. demonstrated that HbA1c, systolic blood pressure, ethnicity, retinopathy, the duration of diabetes, the kidney function, body height and smoking are independent risk factors for microalbuminuria (5). In addition, an observational cohort study by O’Seaghdha et al. demonstrated age, baseline diabetes, smoking, baseline urinary albumin creatinine ratio (UACR), female sex and high density lipoprotein cholesterol (HDL) cholesterol to be associated with incident albuminuria in an unsedated, middle-aged population (8).

Concerning the role of nutritional factors in the development of microalbuminuria, an increased intake of dietary protein and/or saturated fat is considered to be a risk factor for microalbuminuria, whereas a high intake of fish protein and/or polyunsaturated fatty acids, especially those of vegetal origin, has been reported to be associated with a lower risk of microalbuminuria. However, most of these studies included patients with type 1 DM (9-12), and there have been few reports regarding subjects with type 2 DM (13, 14). Therefore, the aim of this cross-sectional study was to investigate clinical and nutritional factors associated with renal involvement in Japanese patients with type 2 DM.

**Materials and Methods**

**Patients**

This study was a post-hoc analysis of data obtained from the “Relationship between Feeding Deflection and Food Intake in Japanese Subjects with Type 2 Diabetes” study published in the Journal of the Japan Diabetes Society (15). We performed a cross-sectional study of 71 patients (median age: 59 years, body mass index (BMI): 25.5 kg/m², HbA1c: 8.7%) with type 2 diabetes who were admitted to Jikei University Hospital for education between September 2006 and February 2008. The reason for hospitalization was either poor control of blood sugar or the need to receive nutritional education from a dietitian.

**Methods**

The patients were divided into two groups; Group I consisted of 40 patients with both an eGFR of ≥60 mL/min/1.73 m² and normoalbuminuria, and Group II consisted of 31 patients with either microalbuminuria/overt proteinuria or an eGFR of <60 mL/min/1.73 m². Group II included 19 patients with microalbuminuria, eight patients with overt proteinuria and four patients with both normoalbuminuria and an eGFR of <60 mL/min/1.73 m². We compared the clinical background characteristics at admission, i.e., age, BMI, blood pressure, duration from the onset of diabetes, use of hypoglycemic agents and insulin, biochemistry data, including the HbA1c (NGSP) (16), pulse wave velocity corrected by blood pressure (PWVc) and the daily intake of several nutrients, between groups I and II.

Microalbuminuria was defined as a rate of urinary albumin excretion ranging between 30-300 mg/day over 24 hours of urine collection or a urinary albumin/creatinine ratio of 30-300 μg/mg creatinine in a spot sample. Overt proteinuria was diagnosed as an albumin level above 300 mg/day or an albumin/creatinine ratio above 300 μg/mg creatinine. The eGFR was calculated according to the following equation for the Japanese population (17): eGFR (mL/min/1.73 m²) = 194 × serum creatinine^{1.094} × age^{-0.287} (if female, × 0.739). High blood pressure was defined as a systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg and/or the use of antihypertensive drugs. Dyslipidemia was diagnosed based on an abnormal amount of lipids, i.e., a total cholesterol (TC) level of ≥220 mg/dL, triglyceride (TG) level of ≥150 mg/dL, HDL-C level of <40 mg/dL or low density lipoprotein cholesterol (LDL-C) level of ≥140 mg/dL and/or the use of lipid-lowering agents. The daily nutrient intake of each subject was calculated using a food frequency questionnaire based on food groups (FFQ). The FFQ used in this study contained questions regarding the consumption of food items in 29 food groups for the past one or two months. The daily nutrient intake was calculated by multiplying the frequency of each food item consumed by the nutrient content of the portion size and adding the products for all food items. The FFQ was administered by a dietitian. The total energy, several nutrients and consumption of foods in 18 categories (cereals, nuts and seeds, potatoes, sugars and sweeteners, confections, fats and oils, beans, fruits, dark green and yellow vegetables, light vegetables, algae, seasonings, alcoholic beverages, sweetened beverages, fish and shellfish, meat, eggs, milk) and fatty acids (saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids) were calculated based on the FFQ.

Aortic PWV measurements were obtained using the right carotid and right femoral arteries with the patient in the supine position after resting for at least five minutes. The Vasera VS-1500A System (Fukuda Denshi, Tokyo, Japan) device was used at each site. All personnel were trained and certified to obtain blood pressure measurements from the right arm with a Tyco aneroid sphygmomanometer according to American Heart Association standards and carry out the aortic PWV measurement. The blood pressure values were obtained from the patient’s right arm while in a seated position using a standard sphygmomanometer (ADVANCE BP-203RVIII/C/D, OMRON colin, Tokyo, Japan) (Korotkoff I and V) with an appropriately sized cuff. Furthermore, the same investigator measured the patient’s blood pressure at each visit, always in the morning and after the patient had rested for at least 10 minutes in a quiet room. Three successive blood pressure readings were obtained at one-minute intervals, and the mean of the three readings was calculated. All subjects provided their written informed consent be-
**Table 1. Comparison of the Clinical Characteristics between Groups I and II**

|                         | Group I (n=40) | Group II (n=31) | p value |
|-------------------------|---------------|----------------|---------|
| Male (n)                | 26 (65)       | 22 (71)        | 0.594   |
| Age (years)             | 58.5 [53.5-64.0] | 63 [54.25-69.75] | 0.115   |
| Duration from onset of diabetes (years) | 5 [3.0-10.0] | 7 [4.0-20.0] | 0.061   |
| BMI (kg/m²)             | 24.1 [21.9-26.9] | 26.4 [25.1-28.4] | 0.003   |
| High blood pressure (n) | 13 (33)       | 23 (74)        | <0.001  |
| Systolic blood pressure (mmHg) | 129 ± 14 | 138 ± 17        | 0.028   |
| Diastolic blood pressure (mmHg) | 79 ± 9 | 81 ± 14        | 0.431   |
| eGFR (mL/min/1.73m²)    | 83.1 [76.3-94.0] | 66.0 [53.9-85.2] | 0.004   |
| TC (mg/dL)              | 209 [165-227] | 193 [180-230] | 0.921   |
| TG (mg/dL)              | 103 [80-150]  | 179 [151-282] | <0.001  |
| LDL-C (mg/dL)           | 126 ± 28      | 126 ± 41      | 0.968   |
| Uric acid (mg/mL)       | 4.9 ± 1.4     | 5.7 ± 1.5     | 0.026   |
| HbA1C (NGSP)(%)         | 9.0 [7.8-10.7] | 8.6 [8.1-10.2] | 0.785   |
| pulse wave velocity corrected by blood pressure (PWVc) (mm) | 8.9 ± 1.5 | 10.0 ± 1.8 | 0.005   |

PWVc: pulse wave velocity corrected by the blood pressure, eGFR: estimated glomerular filtration rate, TC: total cholesterol, TG: triglycerides, LDL-C: LDL cholesterol

Values are expressed as the median [interquartile range]: mean±standard deviation: or the number of patients (percentage)

**Table 2. Comparison of the Medical Treatment(s) Received between Groups I and II**

|                         | Group I (n=40) | Group II (n=31) | p value |
|-------------------------|---------------|----------------|---------|
| Oral hypoglycemic agent |               |                |         |
| Sulfonylurea            | 17 (43)       | 12 (39)        | 0.747   |
| Glimeide                | 1 (3)         | 0 (0)          | 0.898   |
| α-glucosidase inhibitor | 9 (23)        | 5 (16)         | 0.546   |
| Biguanide               | 7 (18)        | 7 (23)         | 0.594   |
| Thiazolidine            | 4 (10)        | 2 (6)          | 0.918   |
| Insulin                 | 5 (13)        | 8 (26)         | 0.151   |
| Antihypertensive agent  |               |                |         |
| CCB                     | 3 (8)         | 9 (29)         | 0.016   |
| ACEi                    | 1 (3)         | 2 (6)          | 0.821   |
| ARB                     | 5 (13)        | 12 (39)        | 0.010   |
| β-blocker               | 2 (5)         | 3 (10)         | 0.767   |
| α-blocker               | 0 (0)         | 1 (3)          | 0.898   |
| Loop diuretics          | 0 (0)         | 3 (10)         | 0.157   |
| Antiplatelet agents     | 2 (5)         | 5 (16)         | 0.247   |
| Statin                  | 8 (20)        | 5 (16)         | 0.676   |

CCB: calcium channel blocker, ACEi: Angiotensin Converting Enzyme Inhibitors, ARB: Angiotensin II Receptor Blockers

Individual variables were compared using the chi-squared test.

fore participating in the study, and the study protocol was approved by the ethics committee of the Jikei University School of Medicine.

**Statistical analysis**

The Ekuseru-Toukei 2006 for Windows software program (Social Survey Research Information, Tokyo, Japan) was used for the statistical analysis. We examined the normality of individual variables among the clinical data using the Shapiro-Wilk test. Normally distributed items were then analyzed using Student’s t-test, and the values were expressed as the mean ± standard deviation. Non-parametric items were analyzed according to Mann-Whitney’s U-test, with the values expressed as the median and interquartile ranges. Categorical variables were compared using the chi-squared test, with the values expressed as percentages. A multivariate logistic regression analysis in which the variables with a p value of <0.1 in the univariate analysis were selected as predictors was performed to identify factors independently associated with renal involvement. A p value of <0.05 was considered to be statistically significant.

**Results**

**Characteristics of the patients**

The clinical data for the patients in Groups I and II at admission are shown in Table 1. BMI, eGFR, triglycerides, uric acid, PWVc and the percentage of patients with hypertension were significantly higher in Group II than in Group I (p<0.05). Moreover, the patients in Group II exhibited a longer duration from the onset of diabetes compared to those in Group I (p=0.061). Sex, age, dyslipidemia, total cholesterol, LDL-C and HbA1c were not significantly different between the two groups.

The treatments received at admission in Groups I and II are shown in Table 2. Regarding antihypertensive agents, calcium channel blockers (CCBs) and angiotensin II receptor blockers (ARBs) were more frequently used in Group II than in Group I (p<0.05), whereas the rates of use of oral hypoglycemic agents, insulin and statins were comparable between Groups I and II.

**Dietary intake**

Table 3 shows the data regarding the intake of total energy and several nutrients. The total energy intake, carbohydrate intake, protein intake and fat intake were not significantly different between Groups I and II. On the other hand, the salt intake tended to be high in Group II compared to Group I (p=0.099), although the difference did not reach statistical significance. Table 4 shows the data for the intake
Table 3. Comparison of the Intake of Total Energy and Several Nutrients between Groups I and II

| Nutrient                      | Group I (n=40) | Group II (n=31) | p value |
|-------------------------------|---------------|-----------------|---------|
| Total energy intake (kcal/kg/day) | 31.5 (29.3-40.3) | 31.9 (26.1-43.0) | 0.908   |
| Carbohydrate intake (g/kg/day)  | 4.1 (3.4-5.0)  | 4.3 (3.5-5.8)   | 0.339   |
| Protein intake (g/kg/day)      | 1.2 ± 0.3      | 1.2 ± 0.3       | 0.663   |
| Fat intake (g/kg/day)          | 1.0 (0.8-1.2)  | 1.0 (0.7-1.4)   | 0.876   |
| Salt intake (mg/kg/day)        | 15.5 (12.8-20.0) | 17.4 (14.2-20.2) | 0.099   |

Values are expressed as the median (interquartile range), or mean ± standard deviation.

Table 4. Comparison of the Food Categories and Fatty Acids between Groups I and II

| Food Categories                      | Group I (n=40) | Group II (n=31) | p value |
|--------------------------------------|---------------|-----------------|---------|
| Cereals (kcal/kg/day)                | 11.20 (9.97-13.73) | 12.10 (10.57-13.46) | 0.465   |
| Nuts and Seeds (kcal/kg/day)         | 0.11 (0.03-0.24) | 0.09 (0.02-0.25) | 0.545   |
| Potatoes (kcal/kg/day)               | 0.20 (0.10-0.45) | 0.20 (0.10-0.50) | 0.781   |
| Sugars and Sweeteners (kcal/kg/day)  | 0.39 (0.13-0.71) | 0.41 (0.26-0.69) | 0.578   |
| Confectioneries (kcal/kg/day)        | 2.12 (0.37-4.51) | 2.60 (0.74-6.13) | 0.281   |
| Fats and Oils (kcal/kg/day)          | 1.38 (0.37-1.03) | 1.37 (0.31-0.68) | 0.179   |
| Beans (kcal/kg/day)                  | 1.05 (0.58-1.86) | 1.12 (0.55-1.72) | 0.595   |
| Fruits (kcal/kg/day)                 | 0.58 (0.20-1.20) | 0.30 (0.22-1.69) | 0.407   |
| Dark green and yellow vegetables (kcal/kg/day) | 0.34 (0.23-0.61) | 0.25 (0.18-0.49) | 0.154   |
| Light vegetables (kcal/kg/day)       | 0.51 (0.37-0.76) | 0.39 (0.31-0.68) | 0.179   |
| Algae (kcal/kg/day)                  | 0.03 (0.01-0.04) | 0.03 (0.02-0.05) | 0.776   |
| Seasonings (kcal/kg/day)             | 0.78 (0.46-1.03) | 0.93 (0.71-1.14) | 0.095   |
| Alcoholic Beverages (kcal/kg/day)    | 0.33 (0.2-2.23)  | 0.0 (0-9.20)     | 0.714   |
| Sweetened Beverages (kcal/kg/day)    | 0 (0-0.44)       | 0 (0-1.04)       | 0.454   |
| Fish and Shellfish (kcal/kg/day)     | 1.96 (1.05-2.84) | 1.65 (1.23-2.44) | 0.741   |
| Meat (kcal/kg/day)                   | 3.39 (2.02-5.23) | 3.51 (2.10-4.94) | 0.853   |
| Eggs (kcal/kg/day)                   | 0.54 (0.37-1.01) | 0.79 (0.36-1.11) | 0.348   |
| Milk (kcal/kg/day)                   | 2.34 (1.46-3.51) | 2.15 (1.02-3.45) | 0.487   |
| Fatty acids                          |                |                 |         |
| Saturated (g/kg/day)                 | 0.32 (0.26-0.39) | 0.33 (0.21-0.43) | 1.000   |
| Monounsaturated (g/kg/day)           | 0.34 (0.27-0.44) | 0.35 (0.24-0.46) | 0.917   |
| Polyunsaturated (g/kg/day)           | 0.21 (0.16-0.25) | 0.20 (0.15-0.25) | 0.790   |

Values are expressed as the medians (interquartile range).

Table 5. Results of a Logistic Regression Analysis for Independent Factors Associated with the Renal Involvement

| Factor                              | Odds ratio (95% CI) | p value |
|-------------------------------------|---------------------|---------|
| Duration from onset of diabetes (years) | 1.11 (0.99, 1.25)   | 0.071   |
| BMI (kg/m²)                         | 1.23 (1.00, 1.53)   | 0.054   |
| Systolic blood pressure (mmHg)      | 1.03 (0.98, 1.08)   | 0.211   |
| Triglycerides (mg/dL)               | 1.01 (1.00, 1.02)   | 0.086   |
| Uric acid (mg/dL)                   | 2.00 (1.04, 3.85)   | 0.039   |
| PWVc (m/s)                          | 1.84 (1.04, 3.27)   | 0.036   |
| Salt intake (mg/kg/day)             | 1.15 (1.02, 1.31)   | 0.028   |

CI: confidence interval, PWVc: pulse wave velocity corrected by the blood pressure

Multivariate analysis of risk factors

The associations between renal involvement and the clinical background characteristics and dietary intake data in the multivariate logistic regression model are shown in Table 5. The analysis revealed that the level of daily salt intake, PWVc and uric acid were independent factors associated with renal involvement (odds ratio, 1.15, 1.84 and 2.00; 95% confidence interval, 1.02-1.31, 1.04-3.27 and 1.04-3.85, respectively) when adjusted for the duration of diabetes, BMI, systolic blood pressure and triglycerides.

Discussion

The present study was performed to elucidate the clinical and nutritional factors associated with early and overt nephropathy in patients with type 2 DM. The results indicated that the BMI, systolic blood pressure, eGFR, triglycerides, uric acid and PWVc values and the frequency of hypertension were significantly higher in the diabetic patients with
renal involvement than in those without renal involvement. Furthermore, the duration from the onset of diabetes and the intake of salt and seasonings were marginally higher in the patients with renal involvement. Therefore, a multivariate logistic regression model was designed including these factors as independent variables, with the exception of the intake of seasonings due to the close association of this variable with salt intake (18). The logistic regression analysis revealed that the level of salt intake, PWVc and uric acid were independent factors significantly associated with renal involvement.

There have been few studies examining nutritional factors associated with the incidence of microalbuminuria in patients with type 2 DM (13, 14); however, these studies did not investigate the role of salt intake. Although a prospective study by Hu et al. demonstrated that a high sodium intake is significantly associated with the development of type 2 diabetes, independent of other risk factors, including physical inactivity, obesity and hypertension, the authors did not elucidate whether this parameter also predicted the development of DN (19).

In the present study, a multivariate logistic regression analysis revealed a higher intake of dietary salt to be an independent factor associated with microalbuminuria and/or renal dysfunction. Concerning the association between salt intake and microalbuminuria, a cross-sectional study by Konta et al. demonstrated that the 24-hour urinary sodium excretion is independently associated with microalbuminuria in women in the Japanese general population (20). Furthermore, a randomized crossover trial reported by He et al. demonstrated that a modest reduction in salt intake induces a significant reduction in urinary albumin excretion (21).

In a previous study of 3,348 women with a normal renal function that examined the relationship between the cumulative average intake of various nutrients over 14 years and a decline in the eGFR of 30% or more from baseline, a high salt intake was shown to be a significant predictor of such a decline in eGFR, independent of other nutrients (22). Moreover, a retrospective study by Cianciaruso et al. demonstrated that patients with chronic kidney disease (CKD) who consumed a low-sodium diet at baseline achieved better renal outcomes during a 3-year follow-up period compared to those who consumed a high-sodium diet at baseline (23).

Interestingly, the mean blood pressure during the study period was comparable between the two groups, suggesting that efficacious salt restriction in CKD patients improves the outcomes of renal disease, independent of any antihypertensive effects (23). These previous studies suggest that a high salt intake is associated with microalbuminuria and/or deterioration of the renal function.

In the present study, the PWVc was shown to be an independent factor associated with microalbuminuria or renal dysfunction. Similarly, Ishikawa et al. reported in a cross-sectional study of 328 subjects from the general population of Ohasama town in Japan that microalbuminuria was associated with the brachial-ankle pulse wave velocity (baPWV), independent of other cardiovascular risk factors (24). More recently, an observational cohort study by Bouchi et al. demonstrated that aortic stiffness, as evaluated according to the carotid-femoral pulse wave velocity, is associated with incidental albuminuria and a decreased GFR in type 2 diabetes patients (25). Although the mechanisms linking increased albuminuria and/or a decreased GFR with a higher degree of arterial stiffness have not been thoroughly clarified, several previous studies have indicated that albuminuria reflects the presence of systemic vascular abnormalities, particularly endothelial dysfunction. For example, studies examining the association between albuminuria and endothelial dysfunction in the brachial or coronary arteries have demonstrated impaired endothelium-dependent vasodilation in association with increased systemic urinary albumin excretion (26, 27). Therefore, microalbuminuria is recognized to be a risk factor for the development of arteriosclerosis.

The FFQ used in this study was developed to calculate the average meal and nutrient intake over the past one or two months. The propriety and plasticity were ascertained according to a previously reported examination of the relationship between the FFQ and seven-day weighed-diet records (28). The level of sodium intake determined using the FFQ method has been shown to exhibit a good correlation with the level of urinary sodium in men (correlation coefficient=0.66) (29). Based on these previous observations, the FFQ can be considered an objective investigation method with both propriety and plasticity (15, 30, 31).

In the present study, the serum uric acid level was identified to be associated with renal involvement in the patients with type 2 diabetes mellitus. As several previous studies have demonstrated an elevated serum uric acid level to be a strong predictor of the development of micro- or macroalbuminuria in patients with type I diabetes (32, 33), our results may support these findings.

There are several limitations associated with the present study that should be kept in mind. First, this study was a cross-sectional study of a small population. In order to confirm the importance of the factors found to be associated with renal involvement in our patients, it is necessary to follow a larger population of diabetic patients prospectively to obtain the final renal outcome. Second, in the present study, the level of salt intake was estimated according to the FFQ, not data obtained from the 24-hour urine collection. In small studies in particular, the level of sodium intake should also be assessed using data for the 24-hour urine collection due to the potential for underestimation of the salt intake based on dietary surveys, as indicated in a previous study (34). Moreover, we placed the patients with normoalbuminuria and an eGFR of <60 mL/min/1.73 m² and those with microalbuminuria or overt proteinuria together in the same group (Group II), since the number of patients meeting the former criteria was very small. However, these two subgroups should be analyzed separately because the pathogenetic factors underlying renal involvement may differ between patients with urinary abnormalities and those with deteriora-
tion of the renal function.

In summary, the present findings suggest that a high salt intake, as well as arteriosclerosis and an elevated serum uric acid level, play important roles in renal involvement in our cohort with type 2 diabetes. However, it remains unclear whether efficacious salt restriction in diabetic patients prevents the onset of DN, although it has been reported that salt restriction improves glomerular hyperfiltration, kidney enlargement and microalbuminuria in an experimental rat model of diabetes (35). A prospective study is therefore needed to clarify whether a low-salt diet helps to protect the renal function over the long term.

The authors state that they have no Conflict of Interest (COI).

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