Impact of salt intake on urinary albumin excretion in patients with type 2 diabetic nephropathy: a retrospective cohort study based on a generalized additive model

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Abstract. Diabetic kidney disease is an important and common cause of end-stage renal disease. Measurement of urinary albumin excretion (UAE) requires the diagnosis of the stage of diabetic nephropathy and the prognosis of renal function. We aimed to analyze the impact of lifestyle modification on UAE in patients with stage 2 and 3 type 2 diabetic nephropathy who received comprehensive medical care, using a generalized additive model (GAM), an explanatory machine learning model. In this retrospective observational study, we used changes in HbA1c, systolic blood pressure (SBP), and diastolic blood pressure (DBP) levels; body mass index (BMI); and daily salt intake as factors contributing to changes in UAE. In total, 269 patients with type 2 diabetic nephropathy were enrolled (stage 2, 217 patients; stage 3, 52 patients). The rankings that contributed to changes in UAE over 6 months by permutation importance were the changes in daily salt intake, HbA1c, SBP, DBP, and BMI. GAM, which predicts the change in UAE, showed that with increase in the changes in salt intake, SBP, and HbA1c, the delta UAE tended to increase. Salt intake was the most contributory factor for the changes in UAE, and daily salt intake was the best lifestyle factor to explain the changes in UAE. Strict control of salt intake may have beneficial effects on improving UAE in patients with stage 2 and 3 diabetic nephropathy.

Key words: Urinary albumin excretion, Generalized additive model, Type 2 diabetes, Salt intake, Explainable artificial intelligence

DIABETIC KIDNEY DISEASE (DKD), which occurs in more than 40% of patients with type 2 diabetes, is one of the most important and common causes of end-stage renal disease [1-3]. General measures for diabetic nephropathy vary depending on the disease stage, but they mainly include blood pressure control, blood glucose control, and lifestyle modification [4, 5]. Dialysis is necessary for the treatment of end-stage renal failure; however, it is expensive and imposes a heavy burden on the patient and the healthcare system [6]. Annually, there has been an increase in the number of new patients requiring dialysis due to diabetic nephropathy worldwide.
and efforts have been taken globally and nationally toward the prevention of diabetic nephropathy. Therefore, it is important to detect diabetic nephropathy at an early stage and provide timely treatment to prevent its progression to the severe stage. The measurement of urinary albumin excretion (UAE) is useful for the early diagnosis of diabetic nephropathy, prognosis of renal function, and prediction of cardiovascular diseases [4, 5, 7]. In clinical practice, comprehensive therapeutic interventions such as blood glucose control, obesity reduction, blood pressure control, and sodium restriction are necessary, and it is recommended that doctors, nurses, and nutritionists actively provide medical care guidance in this regard [8, 9].

Recently, with advances in technology, artificial intelligence (AI)-based learning models and computational power are expected to be applied in the medical field. Particularly, the development of new tools based on machine learning and deep learning for predictive diagnosis and prognosis aids in providing efficient and high-quality futuristic medicine [10, 11]. However, the application of AI technology is sometimes not possible for human studies owing to the complexity of the computational process (black box). Consequently, AI technologies may not be preferred or actively used in medical fields requiring explanations, such as for diagnosis and treatment decisions [12, 13]. The generalized additive model (GAM) is widely used as an effective learning model as an extension of the generalized linear model relative to a nonlinear model [14]. The main advantage of using GAM is its ability to improve accuracy while maintaining interpretable machine learning, making GAM an easily applicable analysis method in the medical field.

In this study, we aimed to analyze the impact of lifestyle modification, involving weight, blood glucose, blood pressure, and salt intake, on UAE in patients with type 2 diabetic nephropathy who received comprehensive medical care; for this purpose, we used GAM, an explanatory AI analysis technique. This study intended to identify which lifestyle factors contribute to the exacerbation or improvement of UAE.

Materials and Methods

Study design

This study had a retrospective observational design. The study was conducted among patients who met the following criteria: (1) had type 2 diabetes mellitus (DM) and underwent follow-up at the Center of Diabetes and Metabolism of the Japan Community Healthcare Organization (JCHO) Hospital for more than 6 months between January 2013 and December 2018; (2) had stage 2 and stage 3 diabetic nephropathy at enrollment; and (3) received outpatient treatment by a diabetologist, medical care guidance by a nurse, and nutritional guidance by a dietitian who had knowledge and skill in providing diabetes-specific medical nutrition therapy (MNT) at each outpatient visit. The exclusion criteria were as follows: (1) had stage 4 nephropathy and (2) were on lipid-improving and antihypertensive medications that were changed in terms of type and dose during the study period. The classification of diabetic nephropathy was performed depending on the staging system developed by the Joint Committee on Diabetic Nephropathy in 2014 [15].

Ethical approval

The study was approved by the ethics committees of the JCHO Kanazawa Hospital (No. 19-06-00), and a waiver for patient consent was obtained from the ethics committees. All procedures were performed in accordance with the 1964 Declaration of Helsinki and its later amendments. Patients were given the opportunity to refuse to participate in the study through an opt-out method.

Nutritional therapy

MNT was performed according to the lifestyle guidance standards for diabetic nephropathy [15]. Dietary guidance was provided according to the classification of nephropathy progression. The nutritional guidance was as follows: nephropathy stage 2; total energy, 25–30 kcal/kg ideal body weight/day; protein, less than 20% energy; salt intake, <6 g/day, if hypertension; nephropathy stage 3; total energy, 25–30 kcal/kg ideal body weight/day; protein, 0.8–1.0 g/kg ideal body weight/day; salt intake, <6 g/day. Patients in all stages of the disease were instructed to maintain proper weight (body mass index [BMI] <25 kg/m²). The nurses provided medical treatment guidance by understanding and assessing different conditions and the living environment of each patient and by setting individual goals such as quitting smoking, avoiding excessive alcohol intake, and adhering to exercise therapy.

Data collection and measurement

Data on systolic blood pressure (SBP), diastolic blood pressure (DBP), BMI, hemoglobin A1c (HbA1c), estimated glomerular filtration rate (eGFR), daily salt intake, and UAE were collected every 6 months for up to 36 months. Data were also collected from patients’ medical records, especially information on medications such as antihypertensive agents, lipid-lowering agents, oral hypoglycemic agents, insulin, and GLP-1 agonists used at the time of study enrollment. BP was measured in an
examination room according to an established procedure and using a sphygmomanometer with an appropriately sized cuff positioned at the level of the heart. HbA1c, eGFR, and UAE were determined using standard laboratory procedures. Daily salt intake was evaluated by calculating the sodium and creatinine levels in urine samples [16]. The change in each variable over the 6-month period represents the before–after difference and is expressed as a Δ variable.

**Statistical analysis**

Data are expressed as the mean ± SD. Statistical significance was set at \( p < 0.05 \). Comparisons between the two groups were made using the Student’s \( t \)-test for data with normal distribution and the Mann–Whitney \( U \)-test for data with non-normal distribution. The change in UAE over the 36 months was analyzed using repeated-measures analysis of variance. Missing values were complemented by the last observation carried forward.

The difference of each variable from 6 months ago was expressed as Δ value. We created a total of 16 variables as follows: age; sex; UAE; BMI; SBP; DBP; HbA1c; daily salt intake; eGFR; angiotensin receptor blocker (ARB) or angiotensin-converting enzyme-inhibitor (ACE-i) treatment at baseline; and changes in BMI, SBP, DBP, HbA1c, daily salt intake, and eGFR. The 16 variables were assessed for multicollinearity with ΔUAE using the Variance Inflation Factor (VIF) and were excluded during the construction of the explanatory variable for GAM if the VIF was greater than 10. The accuracy of the GAM was shown by the coefficient of determination. The evaluation of the features that contributed to the improvement of the prediction accuracy of the model was analyzed using permutation importance [17]. Data analyses and artwork were carried out using Python 3.8.3 (Python Software Foundation, Delaware, USA) and SciPy 1.4.1.

**Results**

A total of 269 patients with type 2 diabetic nephropathy who met the inclusion criteria were enrolled. Table 1 shows the clinical characteristics of the 217 patients with stage 2 diabetic nephropathy and 52 patients with stage 3 diabetic nephropathy. Of these patients, 168 patients with stage 2 diabetic nephropathy and 52 patients with stage 3 nephropathy required salt restriction (<6.0 g/day).

The achievement rates for 6 g/day salt-intake restriction among stage 2 patients were 5.1%, 7.7%, 3.7%, 9.0%, 3.4%, and 5.3% at 6, 12, 18, 24, 30, and 36 months, respectively. The corresponding achievement rates in stage 3 patients were 1.9%, 8.2%, 9.5%, 7.7%, 3.3%, and 7.4%.

Table 1 Clinical background characteristics in patients with type 2 diabetic nephropathy stages 2 and 3

|                  | Stage 2 | Stage 3 |
|------------------|---------|---------|
| N                | 217     | 52      |
| Female (%)       | 23.5    | 21.2    |
| Age (yrs)        | 63 ± 12 | 65 ± 12 |
| BMI (kg/m²)      | 26.2 ± 4.5 | 25.1 ± 3.4 |
| SBP (mmHg)       | 132 ± 15† | 140 ± 16 |
| DBP (mmHg)       | 77 ± 12  | 80 ± 12 |
| HbA1c (%)        | 7.3 ± 0.9† | 6.9 ± 0.8 |
| s-Cr (mg/dL)     | 0.85 ± 0.25† | 0.97 ± 0.31 |
| eGFR (mL/min/1.73 m²) | 73.3 ± 24.5† | 63.5 ± 21.2 |
| UAE (mg/gCr)     | 85.8 ± 65.9† | 780.3 ± 696.9 |
| Salt intake (g/day) | 9.8 ± 2.2 | 10.3 ± 2.6 |

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; s-Cr, serum creatinine; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion. † \( p < 0.01 \); ‡ \( p < 0.001 \) vs. stage 3.

Then, 206 (94.9%) and 50 (96.2%) patients with stage 2 and stage 3 diabetic nephropathy, respectively, were taking oral hypoglycemic agents, insulin, or glucagon-like peptide-1 agents at the time of enrollment. Overall, 160 patients (stage 2, \( n = 118 \); stage 3, \( n = 42 \)) were taking ARBs or ACE-i, and 136 (stage 2, \( n = 108 \); stage 3, \( n = 28 \)) were taking lipid-lowering medications (Supplemental Table 1).

Fig. 1 shows the changes in the UAE over the 36-month period according to the nephropathy classification. After 36 months, the UAE of stage 2 patients became significantly higher (\( p < 0.0001 \)). Multiple comparisons showed that there were significant differences between baseline and the 30-month period (\( p = 0.012 \)) and the 36-month period (\( p = 0.017 \)) in UAE in those with stage 2 diabetic nephropathy. The UAE in those with stage 3 diabetic nephropathy showed an upward trend, but there was no significant change (\( p = 0.081 \)).

Among the 16 variables, 7 explanatory variables that showed strong multicollinearity with ΔUAE with VIF > 10 were excluded from the analysis of GAM and permutation importance. The seven excluded variables were age, preBMI, preSBP, preDBP, preHbA1c, preGFR, and pre salt intake. The permutation importance of the factors contributing to the change in UAE over 6 months is shown in Fig. 2. Delta salt intake, delta SBP, delta DBP, delta HbA1c, and delta BMI contributed to the change in UAE at 6 months in the rank order. The GAM that predicted ΔUAE are shown in Fig. 3 for ΔBMI, ΔSBP, ΔDBP, ΔHbA1c, and Δsalt intake. The same for the other four variables is shown in Supplemental Fig. 1.
mean coefficient of determination was $-0.616 \pm 1.492$.
We also noted that with increase in the changes in delta SBP, delta HbA1c, and delta salt intake, the delta UAE tended to increase.

**Discussion**

The GAM and permutation importance revealed that salt intake contributed the most to the change in UAE. In

**Fig. 1** Changes in the excreted levels of urinary albumin after adhering to continuous nutritional and therapeutic guidance for 3 years.

**Fig. 2** Permutation importance ranking of lifestyle related factors contributing to urinary albumin excretion.

**Fig. 3** Results of a generalized additive model predicting changes in urinary albumin excretion.
this cohort study, we actively provide nutritional guidance in a specialized diabetic hospital. In the early stages of diabetic nephropathy, the estimated daily salt intake has rarely been assessed in daily clinical practice. Moreover, there are only few reports on the continuous measurement of daily salt intake and medical care guidance as being effective in preventing the severity of nephropathy; therefore, this study is considered to present useful and notable findings.

BP in insulin-independent diabetes patients was thought to be due to high salt sensitivity, sodium retention, and increased vascular reactivity to angiotensin II [18, 19]. Underwood et al. reported that NonModulation (NMOD), wherein adrenal aldosterone secretion is suppressed in response to exogenous angiotensin II (ANGII) stimulation, contributes to the pathogenesis of salt-sensitive hypertension in patients with type 2 diabetes despite a normal renin response at low sodium concentrations. They reported that NMOD contributes to the pathogenesis of salt-sensitive hypertension in patients with type 2 diabetes.

In addition, the nephroprotective effects of SGLT-2 inhibitors have recently attracted attention. The Empagliflozin Removal Excess Glucose Outcome study (EMPA-REG OUTCOME), Canagliflozin Cardiovascular Assessment Study (CANVAS), and Dapagliflozin: The Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLEAR-TIMI 58) study results showed that SGLT2 inhibitors were effective in preventing the severity of diabetic nephropathy [20]. However, since only about 3% of the patients in this study received SGLT2 inhibitors, we cannot demonstrate the efficacy of SGLT2 inhibitors for UAE. The effect of SGLT2 inhibitors on UAE should be explored using a different study design.

In diabetic nephropathy, maintenance of proper weight [21, 22], strict blood glucose levels [23, 24], and blood pressure control [25, 26] are important, and remission can be expected with early intervention. In the Steno-2 Study, patients with type 2 diabetes and those with microalbuminuria received comprehensive treatment by a diabetic care team consisting of physicians, nurses, and dieticians, including strict blood glucose and blood pressure control, ACE-i or ARBs, and diet and exercise therapy. During an observation period of 7.8 years, the progression rate from early nephropathy to overt nephropathy was 61% less than that in the usual care group, and 30% of patients had normalized microalbuminuria [27]. A follow-up study reported that comprehensive treatment contributed to an approximately 50% reduction in total mortality, cardiovascular death, and worsening nephropathy [28]. In the J-DOIT3 study of Japanese patients with type 2 diabetes, the risk of developing or progressing to nephropathy, a secondary endpoint, was reduced by 32% in the multifactorial enhancement group compared to that in the conventional treatment group [29]. However, in patients with more advanced diabetic nephropathy, there are studies reporting that an enhanced multifactorial intervention did not show significant improvement [30, 31]. Perhaps this enhanced multifactorial intervention should be used at an earlier stage.

It has been reported that it is difficult to promote lifestyle modification and behavioral change in diabetes patients, even with the actual intervention of the diabetes care team [32, 33]. According to a report published by the Japan Diabetes Clinical Data Management Study Group that examined the achievement rate of BP and lipid control goals, 21.7% of patients in the group who achieved all three goals had nephropathy-related complications. The rate was 43.2% in the group of patients who did not meet any of the criteria [32]. It is also difficult to avoid salt intake [34] and maintain proper weight [35-39]. There remains one question: Which of the lifestyle habits, such as blood glucose control, blood pressure, weight control, and lipid management, should be prioritized for efficient renal protection and prevention of severe disease among patients with diabetic nephropathy? At present, there is no strong research evidence to answer this question. Even if the results are available, comprehensive lifestyle modifications will remain the most desirable approach for patients with diabetic nephropathy.

Our study has several limitations, as it was a retrospective observational study. (1) We did not evaluate whether dietary treatments other than salt restriction, such as protein restriction, were strictly adhered to. (2) ARBs, ACE-i, and lipid-lowering drugs were not administered to all patients with hypertension or dyslipidemia. However, in actual clinical practice, there are cases in which treatment cannot be intensified for the patient owing to side effects or other personal reasons. (3) The urinary Na/Cr ratio in spot urine is used to assess salt intake, which is different from the method based on 24-hour urine sample, dietary sodium intake by 24-hour diet recalls, and data in dietary records. These factors may have influenced the results.

In conclusion, in patients with diabetic nephropathy, we analyzed the amount of change in UAE using an explanatory machine learning model. Compared with weight loss, HbA1c, and blood pressure control, daily salt intake was the best lifestyle factor to explain the change in UAE. Strict control of salt intake may be a more efficient approach for improving UAE among patients with diabetic nephropathy patients stages 2 and 3 disease. Future prospective studies and further analyses using big data are desirable.
Authorship

K.F. and S.K. contributed to the study design and conducted the study. Y.K. and Shige. K. wrote the manuscript. Y.K., S.K., M.K., and H.N. analyzed the data. K.F. and M.K. prepared the application to the ethics committee. T.Y., Y.T., D.A., H.M., and Seigo. K. edited the manuscript. K.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read the manuscript and approve this submission.

Acknowledgments

We would like to thank the nutritionists Sumiko Hashimoto, Tomoko Kitagawa, Atsuko Ikeda, Megumi Koshiyama, and Maika Tani and the nurses Ai Sato, Kae Arai, Yukie Hoshima, Yoko Miyashita, Dr. Naoto Yamaaki of JCHO Kanazawa Hospital, who provided guidance to the patients. We also thank the medical office staff who provided the data registry. English language editing was performed by Editage (www.editage.jp).

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