

Relations Between Urinary Albumin Excretion and a Dietary Intake of Fruits in Patients With Type 2 Diabetes

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Abstract

Background: It was reported that microalbuminuria and a decline in renal function were associated with cardiovascular disease (CVD) mortality and renal events and prognostic serious complications. Dietary factors and nutrients affecting microalbuminuria in type 2 diabetes remain unclear, and accordingly we conducted a cross-sectional study on the possible relevance of dietary factors to urinary albumin excretion in patients with type 2 diabetes.

Methods: Forty-two patients with type 2 diabetes participated in this study, and these subjects were categorized into patients without microalbuminuria group with urine albumin-to-creatinine ratio (ACR) of less than 30 mg/g Cr (n = 29) and a microalbuminuria group with ACR of 30 - 299 mg/g Cr (n = 13). ACR levels were measured using spot urine samples. At the time of examination, body mass index (BMI) and systolic and diastolic blood pressures were measured and recorded. We performed sampling fasting-blood and spot urine and conducted a food frequency questionnaire based on food groups to examine dietary habits for the past 1 - 2 months.

Results: There were no significant differences in sex, age, duration, BMI, blood pressures, biochemical data, and the median of daily intakes of energy and macronutrients between patients without microalbuminuria and microalbuminuria groups. In the intake of 17 food groups per day, fruits were significantly lower in the microalbuminuria group than in patients without microalbuminuria group (the median was 38 g vs. 120 g/day, $P < 0.05$), but intakes of other food groups were not significantly different between the two groups.

Moreover, we examined a model of partial correlation between ACR to the intake of fruits, adjusted by age, sex, glycated hemoglobin and BMI. This partial correlation was insignificantly seen but close to a significant level (partial correlation coefficient: -0.270 , $P = 0.102$).

Conclusions: These results suggest that the intake of fruits may be inversely associated with microalbuminuria in Japanese type 2 diabetic patients. It would be necessary to investigate the exact types and amounts of fruits to be consumed to address microalbuminuria.

Keywords: Type 2 diabetes; Urinary albumin excretion; Microalbuminuria; Food frequency questionnaire survey; Fruits

Introduction

Diabetic nephropathy is one of the major complications of diabetes as well as retinopathy and neuropathy, and it is representative of diabetic microangiopathy. Recently, the concept of diabetic kidney disease (DKD) is advocated. DKD is a clinical diagnosis according to levels of albuminuria and/or estimated glomerular filtration rate (eGFR). Diabetic nephropathy is a renal disease characteristic of diabetic glomerulosclerosis with albuminuria, but DKD has a variety of the pathological changes because DKD includes chronic kidney disease (CKD) with diabetes in addition to diabetic nephropathy [1]. Thus, the previous diagnosis in diabetic nephropathy can be interpreted DKD [2]. In Japan, diabetic nephropathy has become the leading cause of chronic dialysis therapy since 1998, and it accounted for 43.2% of total cases of dialysis therapy in 2016 [3]. In diabetic patients, a serious complication for prognosis is cardiovascular disease (CVD), and diabetes patients are more at risk of developing CVD than non-diabetic patients [4]. Furthermore, the decline in renal function is associated with CVD mortality [5]. As a result, DKD is considered to provide a poor prognosis for life.

When microalbuminuria (30 - 299 mg albumin/g creatinine (mg/g Cr)) and a renal dysfunction with eGFR under 60 mL/min/1.73 m² are detected, the diagnosis of diabetic nephropathy (stage II; early kidney disease) is given [6]. The presence of microalbuminuria is a risk factor for CVD independent of renal dysfunction, and it has been reported that the onset of CVD is suppressed when urinary albumin excretion is decreasing [7]. In diabetic patients, correlations of urinary albumin to renal events, CVD or total mortality were reported,

Manuscript submitted February 4, 2021, accepted February 16, 2021
Published online March 19, 2021

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doi: <https://doi.org/10.14740/jocmr4440>

and accordingly the measurement of urinary albumin is recommended for clinical evaluation of DKD [8].

Nowadays, a dietary therapy, which includes restrictions in dietary protein and sodium intake, is used widely as a treatment for diabetic nephropathy and DKD. In diabetic patients, a dietary protein restriction is an effective treatment for suppressing the progression of renal dysfunction, leading to the reduction of urinary protein [9, 10]. In addition, since the excess intake of sodium potentially leads to hypertension and subsequent renal vascular injuries, the dietary sodium restriction is also recommended to diabetic patients with hypertension [11]. Thus, there are many papers on relations between specific nutrients and renal function, but dietary factors relevant to the development of microalbuminuria in type 2 diabetes with kidney disease are not well defined. Therefore, we investigated dietary factors affecting the urinary albumin excretion in patients with type 2 diabetes.

Materials and Methods

Forty-two patients with type 2 diabetes (29 men and 13 women) who visited Someya Outpatient Clinic of Diabetes in Tokyo participated in the present study. Diabetic patients with a history of liver disease, kidney disease except for microalbuminuria and macroalbuminuria (300 mg/g Cr or more) were excluded. Urine albumin-to-creatinine ratio (ACR) levels were measured using spot urine samples. When the ACR levels ranging from 30 to 299 mg/g Cr appeared more than once, microalbuminuria was diagnosed, based on Diabetes Nephropathy Diagnostic Criteria defined by the Japan Diabetes Association [12]. The study subjects were categorized into patients without microalbuminuria group (n = 29) with ACR of less than 30 mg/g Cr and a microalbuminuria group (n = 13) with ACR of 30 - 299 mg/g Cr.

At the time of examination, body mass index (BMI), and systolic and diastolic blood pressures in sitting position measured by automatic sphygmomanometer (Terumo, Inc.) were recorded. When blood pressures were higher than usual, they were measured again, and we used the lower values for the study data. Fasting samples were used for laboratory tests. Serum total protein (TP) was measured by biuret method. Aspartate amino transaminase (AST), alanine amino transaminase (ALT) and γ -glutamyl transpeptidase (γ -GT) were measured by JSCC transferable methods. Creatinine (Cr) and uric acid (UA) were measured by enzymatic methods. Urea nitrogen (UN) was measured by the urease-GLDH-ultraviolet method. Glycated hemoglobin (HbA1c) was measured by the latex agglutination method. These measurements of clinical samples were performed in the laboratory at BML INC (Tokyo, Japan). In addition, eGFR was calculated using the following formula (male: $194 \times \text{Cr} - 1.094 \times \text{age (years)} - 0.287$; female: male eGFR formula $\times 0.739$).

The daily food intake, including dietary energy and nutrients, was investigated by a food frequency questionnaire, which is standardized for population-based surveys and nutrition counseling in Japan (a food frequency questionnaire based on food group: FFQg version 3.5, created at the site of the

Shikoku University Nutrition Database). There were 17 food groups in the FFQg including cereals, potatoes, green and yellow vegetables, other vegetables/fungi, seaweeds, soybean/soy products, fishes and shellfishes, meats, eggs, milk and milk products, fruits, confectionery, alcohol and beverages, sugar, nuts and sesame, oil and fats, seasoning and spices. The survey form was filled out by the dietician to record dietary habits for the past 1 - 2 months, amounts of foods per day or per meal, and the number of times eaten in a week. The amount per day or per meal was expressed by comparing with the "normal" amount of each food. We chose a category from "not eaten", "somewhat", "normal" and "plenty". In the case of half the normal amount and 1.5 times the normal amount, "somewhat" and "plenty" were chosen, respectively. In addition, 0.5 times and 0 times were recorded when a food was eaten at a frequency of intake once every 2 weeks and less than once a month, respectively. When they were eaten at a frequency of 1 - 2 times, we recorded it as 1.5 times.

The intake of energy, protein, lipid, carbohydrate, potassium, fiber and salt per day was calculated from the results of FFQg. The ratio of animal protein to total protein intake was calculated from animal food groups (fish and shellfish, meat, egg, milk and milk products) in 17 food groups. The intake of 17 food groups was calculated in grams/day (g/day). A self-recorded survey on daily life, occupation, diet, smoking, sleeping and exercise was also conducted.

The protocol was approved by the Ethics Committee of the Japan Women's University (No. 188), and we explained the purpose and details of this study to the study subjects, and all patients gave written informed consent. This study was conducted in accordance with the Declaration of Helsinki.

We estimated that we would need a sample size of at least 12 patients to detect 100 kcal or 100 g differences in the intake of energy and major food groups in the FFQg, respectively at 5% type I error and 80% power for a two-tailed log-rank test. The results were expressed as median and interquartile range. Between patients without microalbuminuria group and the microalbuminuria group, we analyzed sex difference, the status of smoking, drinking and medication by Chi-square tests. Dietary energy, nutrients, food groups (the FFQg data), BMI, duration, blood pressure data and biochemical data between the two groups were compared by Mann-Whitney test. The correlation between ACR and the intake of fruits was evaluated by Spearman's rank correlation coefficient, and further analyzed by a model of partial correlation adjusted by age, sex, HbA1c and BMI. All the statistical analyses were performed in SPSS Statistics version 17.0 (IBM, Inc.). A significant difference was defined as $P < 0.05$.

Results

Table 1 shows the characteristics and biochemical data of patients without microalbuminuria group and the microalbuminuria group. There were no significant differences in sex, age, duration, BMI and other physiological and biochemical data between the two groups. HbA1c levels also were comparable between the two groups (median value of 7.3% vs. 7.4%).

Table 1. Characteristics of Subject and Biochemical Data

	Patients without microalbuminuria (n = 29)	Microalbuminuria (n = 13)
Subjects (male/female)	29 (19/10)	13 (10/3)
Age (years)	68 (63 - 78)	65 (59 - 71)
Duration of diabetes (years)	9 (6 - 15.5)	6 (1.5 - 9)
Smoking, n (%)		
Current	5 (17.2)	4 (30.8)
Ex-smoker	8 (27.6)	1 (7.7)
Never	16 (55.2)	8 (61.5)
Drinking alcohol, n (%)		
Moderate ^a	6 (20.7)	3 (23.1)
Heavy ^b	4 (13.8)	2 (15.4)
Non-drinker	19 (65.5)	8 (61.5)
Medication, n (%)		
ARB	5 (17.2)	3 (23.1)
Statin	8 (27.6)	1 (7.7)
Biguanide	9 (31.0)	5 (38.5)
DPP-4 inhibitor	14 (48.3)	6 (46.2)
Sulfonylurea	8 (27.6)	2 (15.4)
α -GI	0 (0.0)	1 (7.7)
Systolic blood pressure (mm Hg)	130 (121 - 137)	137 (125 - 150)
Diastolic blood pressure (mm Hg)	70 (63 - 80)	82 (71 - 88)
Body mass index (kg/m ²)	21.9 (20.2 - 23.7)	23.0 (20.9 - 25.0)
Total protein (g/dL)	7.2 (6.9 - 7.5)	7.4 (7.2 - 7.7)
Urinary albumin/creatinine (mg/g Cr)	9.3 (5.0 - 19.7)	75.6 (45.8 - 111.1)***
Albumin (g/dL)	4.4 (4.2 - 4.5)	4.3 (4.2 - 4.5)
Aspartate amino transaminase (U/L)	19 (18 - 24)	22 (15 - 27)
Alanine amino transaminase (U/L)	16 (14 - 24)	20 (16 - 26)
γ -Glutamyl transpeptidase (U/L)	20 (17 - 35)	25 (18 - 60)
Urea nitrogen (mg/dL)	16.7 (13.0 - 19.6)	16.1 (14.4 - 19.0)
Creatinine (mg/dL)	0.74 (0.62 - 0.83)	0.65 (0.58 - 0.91)
Uric acid (mg/dL)	5.0 (4.1 - 6.3)	5.2 (4.7 - 6.4)
eGFR (mL/min/1.73 m ²)	75.7 (63.2 - 82.1)	76.0 (70.0 - 97.5)
HbA1c (%)	7.3 (6.9 - 7.8)	7.4 (6.8 - 9.3)

The data were expressed as median (first quartiles to third quartiles). ***P < 0.0001 vs. patients without microalbuminuria. ^aModerate drinking alcohol are less than 20 g/day in purely alcohol. ^bHeavy drinking alcohol are above 20 g/day in purely alcohol. n: number; ARB: angiotensin II receptor blocker; DPP-4: dipeptidyl peptidase-4; α -GI: α -glucosidase inhibitor; eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin.

However, blood pressures tended to be insignificantly higher in the microalbuminuria group than patients without microalbuminuria group (the median of systolic blood pressure was 137 mm Hg vs. 130 mm Hg, P = 0.084, and the median of diastolic blood pressure was 82 mm Hg vs. 70 mm Hg, P = 0.072).

The daily energy and nutrient intake status in the two groups are shown in Table 2. The medians of energy intake levels were 1705 kcal in patients without microalbuminuria group and 1,713 kcal in the microalbuminuria group, and there was no significant difference between the two groups. The me-

dians of protein intake levels in the two groups were not different (59.2 g/day in patients without microalbuminuria group and 70.5 g/day in the microalbuminuria group), and the animal protein intakes also were not different between the two groups. The intake data of 17 food groups per day showed that fruits were significantly lower in the microalbuminuria group than in patients without microalbuminuria group (the median was 38 g vs. 120 g/day, P < 0.05) (Table 2). However, intake data of any food groups except for fruits were not significantly different between the two groups. Next, to describe the relationship

Table 2. The Daily Nutrient Intake Status and Intake Volume of Food Group by Food Frequency Questionnaire Based on Food Group (FFQg)

	Patients without microalbuminuria (n = 29)	Microalbuminuria (n = 13)
Nutrition intake		
Energy (kcal/day)	1,713 (1,416 - 1,981)	1,692 (1,482 - 1,921)
Protein (g/day)	59.2 (50.1 - 72.7)	70.5 (54.4 - 84.3)
Animal protein (%)	48.7 (40.2 - 57.4)	51.4 (44.3 - 56.8)
Fat (g/day)	50.3 (39.3 - 64.2)	51.8 (43.4 - 63.5)
Carbohydrate (g/day)	218.1 (197.7 - 259.0)	224.1 (179.2 - 262.5)
Potassium (mg/day)	2,237 (1,908 - 2,723)	2,635 (1,718 - 3,226)
Salt (g/day)	7.8 (6.5 - 9.7)	7.3 (6.2 - 9.1)
Food group (/day)		
Grain (g)	330 (264 - 378)	302 (200 - 329)
Potatoes (g)	29 (14 - 50)	24 (1 - 57)
Green and yellow vegetables (g)	75 (50 - 134)	75 (25 - 166)
Other vegetables/fungi (g)	143 (83 - 240)	78 (32 - 240)
Sea weeds (g)	5 (3 - 8)	6 (4 - 12)
Soybeans and soy products (g)	70 (31 - 140)	121 (61 - 138)
Fishes and shellfishes (g)	53 (41 - 91)	76 (35 - 108)
Meats (g)	43 (17 - 66)	42 (29 - 60)
Eggs (g)	18 (9 - 32)	21 (16 - 46)
Milk and milk products (g)	188 (49 - 276)	134 (78 - 237)
Fruits (g)	120 (55 - 150)	38 (8 - 77)*
Confectionaries (g)	34 (9 - 73)	31 (16 - 114)
Alcohol and beverages (g)	0 (0 - 183)	30 (0 - 390)
Sugar (g)	6 (3 - 10)	5 (3 - 9)
Nuts and sesame (g)	1 (0 - 4)	0 (0 - 2)
Oil and fats (g)	8 (3 - 21)	8 (3 - 10)
Seasoning and spices (g)	20 (13 - 28)	16 (15 - 22)

The data were expressed as median (first quartiles to third quartiles). *P < 0.05 vs. patients without microalbuminuria.

between ACR and the intake of fruits in the whole patients, we examined correlation analyses as follows. A single correlation coefficient between them was -0.225 (P = 0.153), although the intake of fruits was significantly lower in the microalbuminuria group. Furthermore, we examined a model of partial correlation adjusted by age, sex, HbA1c and BMI between ACR and the intake of fruits, and this partial correlation was close to a significant level (partial correlation coefficient: -0.270, P = 0.102).

Discussion

The relationships between microalbuminuria and meals/nutrients were reported in non-diabetic subjects [13], in patients with type 1 diabetes and in patients with type 2 diabetes [14, 15], but few studies on relations of urinary albumin to dietary patterns or food intake status in Japanese patients with type

2 diabetes have been reported so far. Therefore, in this study, we examined the daily dietary intake status of foods in Japanese patients with type 2 diabetes. The intake status was compared between the two groups to identify nutrients and foods affecting albuminuria. As a result, in the physiological and biochemical data, we found no significant differences between the two groups and most of the study subjects had eGFR levels more than 60 mL/min/1.73 m², and consequently, not only patients without microalbuminuria but also the microalbuminuria group subjects did not fall into CKD. Therefore, we thought that the microalbuminuria group subjects were in a mild stage of diabetic nephropathy. Previous studies [16, 17] reported that controlling plasma glucose and blood pressures reduces urinary albumin excretion, and the strict management of plasma glucose and blood pressures is considered important for preventing the development of urinary albumin excretion. In patients with DKD, sustaining hyperglycemia and insufficient concentrations of antioxidants in the blood could progress in-

flammation and arteriosclerosis, possibly leading to a decrease in glomerular function because such an inflammatory process may be involved in DKD progression [18].

The FFQg based on food groups as used in our study is more convenient than the FFQ based on a food list, because there are fewer questions in the FFQg. Moreover, the FFQg has been verified by using weighted dietary records in Japanese healthy volunteers and is a useful instrument for estimating individual intakes of dietary energy and nutrients [19]. Among the dietary energy and nutrient intakes acquired by the FFQg, the intake of fruits was significantly lower in the microalbuminuria group than in patients without microalbuminuria group ($P < 0.05$). Previous studies have suggested that the intake of fruits was associated with microalbuminuria. The estimated ACR levels were so lower that greater fruit amounts were consumed in subjects without clinical cardiovascular disease, diabetes and macroalbuminuria in the Multi-Ethnic Study of Atherosclerosis [13]. Although our findings about a partial correlation adjusted by age, sex, HbA1c and BMI between ACR and the intake of fruits, significantly lower than in the microalbuminuria group, was insignificant probably because of a small-sized study, a dietary pattern rich in fruits was associated with lower ACR, indicating that fiber or antioxidant components of fruits may partly contribute to the association as reported previously [13]. Furthermore, women with type 2 diabetes who ate more than three servings of fruit per week had a lower risk of developing CKD as compared with less frequent servings [20], and serum C-reactive protein (CRP) levels were lower in people with highly frequent intake of fruits and vegetables [21]. Likewise, subjects with higher levels of serum CRP had lower serum concentrations of dietary antioxidant lycopene, β -carotene, cryptoxanthin and retinol [22]. Antioxidant components such as carotenoids, vitamin C, vitamin E, and flavonoids contained in fruits and vegetables are considered to have anti-inflammatory effects [21].

Carotenoids exert strong neutralizing activities against singlet oxygen and lipid peroxidation. In the body singlet oxygen is generated in the functional process of neutrophils and macrophages which phagocytose and endocytose oxidative denaturation products of bacteria and low-density lipoprotein (LDL), leading to inflammation and arteriosclerosis [23]. Guessous et al [24] suggested that high-sensitive CRP, a marker of inflammation, could be an independent predictor of renal dysfunction. Wang et al [25] reported that elevated carotenoid levels in diet and serum were associated with lower carotid intima-media thickness (IMT) values. β -cryptoxanthin, a carotenoid contained in many citrus fruits such as mandarin, oyster, loquat and red pepper, is distributed and stored in kidney tissue in addition to liver and lung after being absorbed [26]. β -cryptoxanthin from orange juice inhibits the accumulation of macrophages in the kidney and acts on the pathological upstream of nephropathy and acute kidney injury, alleviating morphological abnormalities of basement membrane thickening and podocytes [27].

However, our study did not detect significant differences in the intake of green and yellow vegetables and other vegetables between the two groups. Green and yellow vegetables are rich in carotenoid-like phytochemicals and are a source of vitamins. The whole protein and animal protein intake were

also not significantly different between the two groups but was slightly higher in the microalbuminuria group. A previous study reported that a high intake of protein and animal protein was related to the presence of microalbuminuria [13, 15]. In an intervention study on early-stage nephropathy in Japanese patients with type 2 diabetes, a protein-restricted diet (0.8 g/kg) significantly decreased microalbuminuria [28]. It was suggested that the intake of protein may affect urinary albumin excretion. However, no difference in the intake of these food groups was found between the two groups because the sample size was relatively small, and consequently the variance in protein, the intake of green and yellow vegetables ranged widely in our study. In addition, whether the type of protein or vegetable consumed would be associated with urinary albumin excretion in diabetic patients remains unknown.

Nettleton et al [13] reported a dietary pattern rich in whole grains, fruits and low-fat dairy foods were associated with lower ACR in subjects without clinical cardiovascular disease, diabetes and macroalbuminuria. However, the present study did not address investigating these detailed contents of foods and the exact amounts of intake. In addition, according to a previous paper reported by Alissa et al, it may be more important to focus on whole foods and dietary patterns rather than individual nutrients, because a complicated set of several nutrients may interact with genetic factors to influence CVD risk [29]. Consequently, it would be necessary to investigate the exact types and amounts of foods to be consumed.

Several limitations should be noted in the present study. First, the plasma carotenoid concentrations were not measured. Previous study indicated that the sum of the plasma carotenoids other than lycopene was highly correlated with the total intake of vegetables and fruits, and multiple regression analyses showed that the total intake of vegetables and fruits was the most significant determinant of each plasma carotenoid except lycopene [30]. Thus, plasma carotenoid concentrations in the microalbuminuria group would be lower than in patients without microalbuminuria group, because fruits consumption in the microalbuminuria group was lower in our study. Furthermore, several investigators have reported that plasma carotenoids [31] and plasma concentrations of lycopene, β -carotene, α -carotene and cryptoxanthin [32] were significantly lower in patients with microalbuminuria. Second, the sample size is small as described above, resulting in a lack of power in part of the nutrients or food groups. The possibility of random error on the present results cannot be denied. Third, in the present cross-sectional survey study on the nutrients and dietary factors influencing urinary albumin excretion, the causal relationships between these factors and urinary albumin excretion remain unknown. In the future, it will be necessary to conduct intervention studies to reveal whether the intake of foods containing a variety of antioxidant components can reduce urinary albumin excretion in patients with type 2 diabetes.

Conclusions

The present study indicates the low dietary intake of fruits in type 2 diabetic patients with microalbuminuria. Whether the

intake of fruits and other foods can prevent the progression of diabetic nephropathy in Japanese patients with type 2 diabetes needs to be verified in further prospective studies.

Acknowledgments

This study was supported by Hana Onodera, Mizuho Komiya, Erika Shou and Mio Goto.

Financial Disclosure

Research funds were provided in part by the Jikei University Research Fund from the Jikei University School of Medicine and Grant-in-Aid for Scientific Research (number 17K09560) from Japan Ministry of Education, Culture, Sports, Science, and Technology (Hiroshi Yoshida).

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

All patients gave written informed consent.

Author Contributions

SM decided the conceptualization and protocol. YS provided the patient data. SM investigated on FFQ and analyzed and interpreted all data. SM was a major contributor in writing the manuscript. HY was supervision and gave opinion the manuscript. All authors read and approved the final manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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