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NEPHROLOGY - ORIGINAL PAPER

Association of urinary liver-type fatty acid-binding protein with renal functions and antihyperglycemic drug use in type 2 diabetic nephropathy patients

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Abstract

Purpose In diabetic nephropathy exacerbation, a reduction in the estimated glomerular filtration rate (eGFR) without raised albuminuria or proteinuria has been frequently observed. This study aimed to clarify the clinical usefulness of urinary liver-type fatty acid-binding protein (L-FABP) in the exacerbation of diabetic nephropathy in type 2 diabetes.

Methods A cross-sectional study and a retrospective observational study of 227 patients with type 2 diabetes were conducted to investigate the relationship between urinary L-FABP and renal dysfunction. Changes in urinary L-FABP with or without additional administration of antihyperglycemic drugs were examined in 63 patients.

Results Baseline urinary L-FABP was significantly associated with baseline eGFR ($\rho = -0.34$, $p < 0.001$) and baseline albuminuria ($\rho = 0.64$, $p < 0.001$). In multivariate regression analysis, baseline urinary L-FABP was a significant independent factor for eGFR reduction [$\beta = -0.348$, 95% confidence interval (CI) = −0.482 to −0.214, $p < 0.001$]. Cox regression analysis showed that patients with a baseline urinary L-FABP above 6.5 μg/g creatinine exhibited a higher hazard ratio (HR) for the renal dysfunction surrogate end point (HR = 15.00, 95% CI 3.640–61.40, $p < 0.001$). In logistic regression analysis, administration of sodium glucose cotransporter-2 inhibitors was associated with a statistically significant reduction in urinary L-FABP levels, independent of changes in systolic blood pressure, glycosylated hemoglobin, and eGFR (odds ratio = 0.75, 95% CI 0.56–0.99, $p = 0.04$).

Conclusion Urinary L-FABP may be associated with the future decrease in renal functions in type 2 diabetic nephropathy patients. Additionally, urinary L-FABP could be used as a marker of the effectiveness of diabetic nephropathy treatment.

Keywords Urinary L-FABP · eGFR · Diabetic nephropathy · Type 2 diabetes · SGLT-2 inhibitors

Introduction

Diabetic nephropathy is classified based on albuminuria, proteinuria, and estimated glomerular filtration rate (eGFR). Recently, due to the effects of aging and atherosclerosis, clinical courses characterized by eGFR decline without an increase in albuminuria or proteinuria have been observed in diabetic nephropathy exacerbation. Therefore, it is necessary to identify novel biomarkers for renal dysfunction, other than albuminuria or proteinuria.

Urinary liver-type fatty acid-binding protein (L-FABP) is a low-molecular-weight (15 kDa) intracellular carrier protein that is excreted into the urine due to oxidative stress or ischemic changes in the proximal tubules [1]. Since urinary L-FABP reflects the degree of peritubular capillary blood flow, it is an important factor for renal dysfunction with aging [2]. According to a cross-sectional study in patients with diabetic nephropathy of type 2 diabetes, a significant increase in urinary L-FABP levels together with raised albuminuria and proteinuria were observed. Furthermore, high levels of urinary L-FABP were associated with the development of microalbuminuria, macroalbuminuria, end-stage renal failure, or induction of hemodialysis in a prospective observational follow-up study [3].

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The US Food and Drug Administration accepts halving of the eGFR, expressed as doubling of serum creatinine levels, as a surrogate end point for the progression of renal disease in clinical trials; however, doubling of serum creatinine levels is a late event in chronic kidney disease (CKD) [4]. A decline in eGFR that is smaller than the doubling of serum creatinine concentration (e.g., a 30% reduction over 2 years) is strongly associated with the risk of end-stage renal disease (ESRD) and mortality [5]. In fact, 30–40% of declines in eGFR over 1–2 years are strongly associated with the risk of ESRD in Japanese patients with reduced eGFR, broadening global implications as a surrogate end point in clinical research [4].

Several interventional studies showed that together with albuminuria, urinary L-FABP decreased with the use of renoprotective therapy consisting of statin, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin 2 receptor blockers, renin inhibitors, and antihyperglycemic drugs in diabetic nephropathy of type 2 diabetes [6].

However, few studies have investigated the association between urinary L-FABP and eGFR. The relationship between urinary L-FABP and a renal dysfunction surrogate end point remains uncertain. Further, the effects of antihyperglycemic drugs, dipeptidyl peptidase-4 (DPP-4) inhibitors, or sodium glucose cotransporter-2 (SGLT-2) inhibitors on urinary L-FABP have not been sufficiently clarified.

This study aimed to investigate the association between urinary L-FABP and eGFR, the relationship between urinary L-FABP and a renal dysfunction surrogate end point, and the changes in urinary L-FABP with or without the additional administration of antihyperglycemic drugs using a cross-sectional study and a retrospective observational study in diabetic nephropathy of type 2 diabetes.

Materials and methods

Study subjects

A total of 227 patients with type 2 diabetes who underwent treatment at Ishinkai Group facilities (Ishinkai Yao General Hospital, Ishinkai Yao General Clinics, Yasunaka Clinic, and Yao Rehabilitation Hospital) between October 2016 and January 2017 were enrolled in the cross-sectional study to investigate the association of urinary L-FABP with blood and urine clinical parameters. During the observation period (October 2016–January 2019), a retrospective observational study involving all of the enrolled patients was designed to investigate the association between urinary L-FABP and the renal dysfunction surrogate end point. In the same period, 63 patients with available longitudinal data were recruited in a retrospective observational study aimed at determining the changes in blood and urine clinical parameters with or without the additional administration of antihyperglycemic drugs. The inclusion criteria were as follows: diagnosis of type 2 diabetes mellitus, age above 20 years, and continuation of hospital visits, regardless of sex, morbidity history, or severity of diabetic retinopathy. The exclusion criteria were as follows: nephrotic syndrome, concurrent renal replacement therapy including renal transplantation, acute-stage disease, malignant neoplasms, and ineligibility, as determined by physicians.

Measurement of urinary L-FABP

Urinary levels of L-FABP in spot urine samples were measured by chemiluminescent enzyme immunoassay (CLEIA) using the two-step sandwich method at an external laboratory (SRL Co., Tokyo, Japan). Urinary excretion levels of L-FABP were expressed as micrograms per gram of creatinine (μg/g Cr). The measurement range was 0.2–400 ng/mL, and values under the detection limit of 0.2 ng/mL were considered equal to 0 μg/g Cr.

Surrogate end point

The surrogate end point of renal dysfunction was defined as an eGFR reduction of 30% or more in 1–2 years.

Statistical analysis

Among the continuous variables, those that exhibited normal distribution are presented as mean ± SD (standard deviation), and those that did not were presented as median (interquartile range [IQR]). The Spearman's rank correlation coefficient was used to determine the relationship of urinary L-FABP with blood and urine clinical parameters. Multiple regression analysis was performed with urinary L-FABP as the dependent variable and several blood and urine clinical factors as the independent variables. The Kruskal–Wallis test was used to compare the levels of urinary L-FABP among categories of albuminuria or eGFR. The comparison between patients with or without eGFR reduction was performed to confirm the clinical factors using the Mann–Whitney *U* test. Receiver operating characteristic (ROC) curves for urinary L-FABP were plotted to predict eGFR decline. Cox regression analysis was used to determine the predictors of eGFR decline during the observation period. The comparison between patients receiving additional antihyperglycemic drugs and those who did not was performed using the Mann–Whitney U test. Logistic regression analysis was used to examine the changes in blood and urine clinical parameters with or without the additional administration of antihyperglycemic drugs. All statistical analyses were performed using EZR version 1.54 (Saitama Medical Center,

Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of R commander designed to include the statistical functions frequently used in biostatistics. *P*-values < 0.05 were considered as statistically significant.

Results

Baseline study characteristics

The clinical characteristics and laboratory data of the study subjects are shown in Table 1. The 227 subjects were predominantly male, with only 82 female subjects. Three CKD stages were defined based on eGFR or albuminuria. The eGFR (in mL/min/1.73 m^2) stages were as follows: G1 ($61 \leq$ eGFR ≤ 100), G2 ($31 \leq$ eGFR ≤ 60), and G3 (eGFR ≤ 30). Albuminuria levels (in mg/g Cr) were categorized in the following stages: A1 (u-Alb ≤ 29), A2 ($30 \leq$ u-Alb ≤ 299), and A3 ($300 \leq$ u-Alb). Most patients were in the mildest stages (G1 and A1) for both eGFR and albuminuria. Neither albuminuria nor urinary L-FABP showed a normal distribution; their medians were 22.6 mg/g Cr and 2.7 µg/g Cr, respectively.

Association of urinary L-FABP with renal functions

The Spearman's rank correlation coefficients of the relationships between baseline urinary L-FABP and baseline clinical parameters are presented in Table 2. Baseline urinary L-FABP was significantly associated with baseline eGFR ($\rho = -0.34$, $p < 0.001$) and baseline albuminuria ($\rho = 0.64$, $p < 0.001$). In the multivariate regression analysis, baseline urinary L-FABP was a significant and independent factor for eGFR reduction [$\beta = -0.348$, 95% confidence interval (CI) = −0.482 to −0.214, $p < 0.001$; Table 3). The Kruskal–Wallis test showed that urinary L-FABP levels

Table 1 Baseline clinical characteristics

Baseline clinical characteristics	Mean ± SD, median (IQR)
Laboratory findings	*n* = 227
Age (years)	66 ± 11
Gender (females%)	82 (36%)
Observation period (days)	513 ± 139
G1 (eGFR61 ~ 100)/G2 (31 ~ 60)/G3 (~ 30)	127 (56%)/79 (35%)/21 (9%)
A1 (u-Alb ~ 29)/A2 (30 ~ 299)/A3 (300 ~)	128 (56%)/63 (28%)/36 (16%)
RAS Blockade treatment, *n* (%)	99 (44%)
Lipid-lowering treatment, *n* (%)	123 (54%)
Plasma glucose (mg/dL)	151 ± 46
HbA1c (%)	7.4 ± 1.3
GA (%)	19.0 ± 4.9
BUN (mg/dL)	15.4 (6.3–112.0)
Cr (mg/dL)	0.85 (0.49–8.79)
eGFR (mL/min/1.73 m^2)	62 ± 22
Albuminuria (mg/gCr)	22.6 (1.7–4570)
Urinary-L-FABP (µg/gCr)	2.7 (0–224.0)
LDL-c (mg/dL)	104 ± 28
SBP (mmHg)	132 ± 13
DBP (mmHg)	77 ± 11
Alb (mg/dL)	4.4 ± 0.4
Hb (g/dL)	13.8 ± 1.9

Data are shown as mean ± standard deviation (SD), median [interquartile range (IQR)] or *n* (%)

RAS renin–angiotensin system, *HbA1c* hemoglobin A1c, *GA* glycoalbumin, *BUN* blood urea nitrogen, *Cr* creatinine, *eGFR* estimated glomerular filtration rate, *LDL-c* low-density lipoprotein-cholesterol, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *Alb* albumin, *Hb* hemoglobin

Table 2 Spearman's rank correlation coefficient was used to determine the relationship of baseline urinary L-FABP with several blood and urine clinical parameters (*n* = 227)

Urinary-L-FABP	*P*	*P*
Age	0.15	0.02
HbA1c	0.02	0.73
GA	0.05	0.5
Cr	0.35	< 0.001
eGFR	−0.34	< 0.001
Albuminuria	0.64	< 0.001
LDL-c	−0.15	0.03
SBP	0.12	0.06
DBP	−0.06	0.38
Alb	−0.2	< 0.01
Hb	−0.14	0.03

L-FABP, liver-type fatty acid-binding protein

Table 3 Multiple regression analysis was used to define the correlation of baseline urinary L-FABP with several blood and urine clinical parameters (*n* = 227)

Urinary-L-FABP	*B*	*T*	*p*
HbA1c	−1.179	−1.197	0.23
eGFR	−0.348	−5.107	< 0.001
Albuminuria	0.021	7.819	< 0.001
LDL-c	−0.034	−0.725	0.47
SBP	0.083	0.794	0.43
DBP	0.078	0.527	0.60

L-FABP, liver-type fatty acid-binding protein

were significantly higher as both G and A stages progressed (Fig. 1).

Relationship between urinary L-FABP and development of renal dysfunction

Out of 227 patients, 15 had an eGFR reduction of 30% or more during the observation period. The baseline urinary L-FABP was higher in the eGFR-decline group than in the no-decline group ($p < 0.001$; Table 4). The cut-off value of baseline urinary L-FABP on the ROC curve for eGFR decline was approximately 6.5 µg/g Cr [area under the ROC curve (AUC) 0.80, 95% CI 0.67–0.94; Fig. 2]. In the Cox regression analysis, baseline urinary L-FABP was a significant independent predictor of eGFR decline [hazard ratio (HR) = 1.050, 95% CI = 1.030–1.070, $p < 0.001$] and had the highest HR in the group with urinary L-FABP > 6.5 µg/g Cr (HR = 15.00, 95% CI = 3.640–61.40, $p < 0.001$; Table 5).

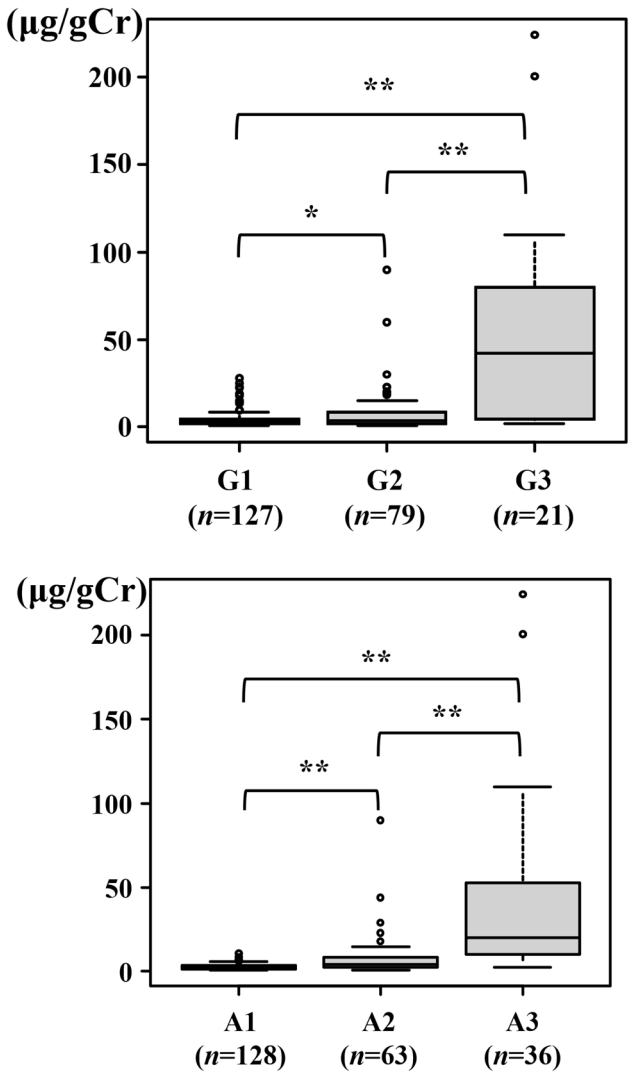

Fig. 1 Kruskal–Wallis test was used to compare urinary L-FABP among categories of albuminuria or eGFR. *L-FABP* urinary liver-type fatty acid-binding protein, *eGFR* estimated glomerular filtration rate

Changes in urinary L-FABP due to antihyperglycemic drugs

During the observation period, new antihyperglycemic drugs were additionally administered to 34 of the 63 patients being treated. Initially, 0–5 drugs were used; the number of single agent users was the highest, followed by a combination of two agents (data not shown). The newly administered drugs were biguanide (8 patients; 23%), DPP-4 inhibitors (7 patients; 20%), and SGLT-2 inhibitors (6 patients; 17%) in that order (data not shown). At dosage initiation, the eGFR of the new drug administration group was 67 ± 14, which was not significantly different from the value of 73 ± 25 of the non-additional drug group (data not shown). In the SGLT-2 inhibitor administration group, systolic blood pressure, glycosylated hemoglobin (HbA1c), eGFR, and albuminuria were unchanged; however, the change in urinary L-FABP was significantly reduced ($p = 0.01$; Table 6). In logistic regression analysis, administration of SGLT-2 inhibitors was associated with a statistically significant reduction in urinary L-FABP levels, independent of changes in systolic blood pressure, HbA1c, and eGFR (odds ratio = 0.75, 95% CI 0.56–0.99, $p = 0.04$). No statistically significant results were obtained in either the biguanide or DPP-4 inhibitor administration group.

Discussion

The cross-sectional study demonstrated that the level of urinary L-FABP deteriorated with increasing albuminuria or decreasing eGFR, and increased urinary L-FABP was a significant independent factor for eGFR reduction. In the retrospective observational study, urinary L-FABP was a significant independent factor for a surrogate end point of renal dysfunction. Furthermore, the administration of SGLT-2 inhibitors decreased urinary L-FABP levels without being affected by changes in systolic blood pressure, HbA1c, and eGFR (Table 7).

A previous study showed that a higher level of urinary L-FABP (> 8.4 µg/g Cr) at the start of the prospective study was associated with the progression of diabetic nephropathy in individuals with type 2 diabetes within an observation period of 4 years [3]. On the other hand, another prospective study showed that albuminuria was an independent factor associated with the eGFR-decline rate, although urinary L-FABP was not, in diabetic nephropathy of type 2 diabetes [7]. In our results, as in a previous report, an increase in urinary L-FABP was observed together with an increase in

Table 4 The Mann–Whitney U test was used to compare patients with or without a reduction of eGFR in terms of several blood and urine clinical parameters

Baseline parameters	No decline ($n=212$)	Decline ($n=15$)	p value
Age	67 (60–74)	65 (55–74)	0.71
Plasma glucose	142 (122–170)	139 (106–156)	0.15
HbA1c	7.2 (6.6–8.0)	6.7 (6.0–7.2)	< 0.01
GA	19.2 (16.8–21.7)	17.2 (16.2–20.6)	0.13
s-Cr	0.84 (0.70–1.03)	2.11 (1.66–5.11)	< 0.001
eGFR	66 (52–79)	20 (12–31)	< 0.001
Albuminuria	19.8 (7.7–77.3)	1054.6 (88.5–1864.4)	< 0.001
Urinary-L-FABP	2.87 (1.67–5.76)	20.4 (4.87–89.0)	< 0.001
LDL-c	101 (86–122)	98 (83–114)	0.55
SBP	130 (124–140)	135 (129–146)	0.23
DBP	74 (67–80)	80 (74–83)	0.35
Alb	4.4 (4.2–4.6)	3.7 (3.4–4.3)	< 0.001
Hb	14.0 (12.7–15.2)	11.3 (10.5–13.0)	< 0.001

eGFR Estimated glomerular filtration rate

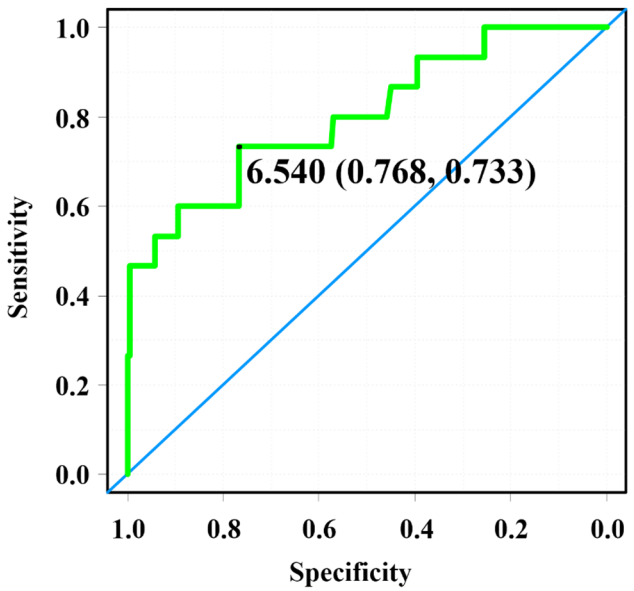

Fig. 2 Receiver operating characteristic (ROC) curve for urinary L-FABP in the progression of eGFR decline (AUC 0.80; 95% CI 0.67–0.94). *L-FABP* urinary liver-type fatty acid-binding protein, *eGFR* estimated glomerular filtration rate, *AUC* area under the curve, *CI* confidence interval

albuminuria, and urinary L-FABP was shown to increase with a decline in eGFR. Therefore, this study suggests that increased urinary L-FABP is a significant independent factor for eGFR reduction. The difference between our study and previous ones was that our study considered a wide range of patients with renal dysfunction not receiving renal replacement therapy including renal transplantation, while the previous study investigated only patients with mild diabetic nephropathy (albuminuria < 300 mg/day; eGFR > 60 mL/min/1.73 m^2) [7]. In our study, since patients with an eGFR ≤ 60 mL/min/1.73 m^2 were treated with antihypertensive drugs, statins, or uric acid-lowering drugs, risk factors for arteriosclerosis other than diabetes might have been involved in proximal tubular damage. Therefore, it may be necessary to take into account the effects of these medications on our results.

Additionally, our retrospective study found that baseline urinary L-FABP > 6.5 μg/g Cr was a significant independent factor for the renal dysfunction surrogate end point. A cut-off value of 6.5 μg/g Cr was extracted due to the use of a surrogate end point with a reduction of 30% or more in 1–2 years, with a shorter observation period and milder degree of renal dysfunction compared with those in previous studies. Since various reports have established that urinary L-FABP is a useful marker of diabetic nephropathy in the early and advanced stages [3, 8, 9], our results may be clinically meaningful.

Several reports have suggested that urinary L-FABP is improved by the use of antihyperglycemic drugs. Teneligliptin, but not sitagliptin, reduced urinary L-FABP in patients with type 2 diabetes and CKD, independent of decreasing albuminuria or restored glucose control [10]. The administration of linagliptin reduced urinary L-FABP after 3 months, regardless of changes in HbA1c [11]. Switching from other DPP-4 inhibitors (i.e., linagliptin) to anagliptin significantly decreased urinary L-FABP excretion without being affected by changes in HbA1c [12]. Interestingly, our results showed that urinary L-FABP was unchanged with the use of DPP-4 inhibitors; nonetheless, it significantly decreased with the use of SGLT-2 inhibitors. The DPP-4 inhibitors used in this study were sitagliptin, linagliptin, and vildagliptin, while teneligliptin and anagliptin were not used. The effect of DPP-4 inhibitors on urinary L-FABP may differ depending on the drug type. This study also showed that the reduction in urinary L-FABP levels due to

Table 5 Cox regression analysis was used to investigate predictors of eGFR decline

Parameter	Adjusted (multivariate) hazard ratio (95% CI)		
	Model 1 ($n=227$)	Model 2 ($n=87$)	Model 3 ($n=61$)
Urinary L-FABP	1.050† (1.030–1.07)	5.450* (1.500–19.90)	15.00† (3.640–61.40)
Age	0.980 (0.921–1.04)	0.980 (0.927–1.040)	0.982 (0.927–1.040)
Male	1.680 (0.353–8.01)	1.770 (0.423–7.410)	1.480 (0.314–6.950)
HbA1c	0.474 (0.197–1.14)	0.389* (0.181–0.834)	0.331** (0.150–0.731)
LDL-c	1.010 (0.978–1.03)	1.000 (0.976–1.020)	0.995 (0.970–1.020)
SBP	1.000 (0.955–1.05)	1.010 (0.968–1.050)	1.000 (0.959–1.050)
RAS blockade treatment	0.970 (0.223–4.22)	0.656 (0.180–2.400)	0.369 (0.085–1.610)
Lipid-lowering treatment	0.774 (0.183–3.27)	0.478 (0.141–1620)	0.562 (0.155–2.040)

Multivariate adjustments were performed according to several categories of baseline urinary L-FABP, some blood and urine clinical parameters, RAS blockade treatment, and lipid-lowering treatment. Baseline urinary L-FABP was categorized into three groups. Model 1 included all patients. Model 2 included patients with L-FABP ≥ 4.2 μg/g Cr, and Model 3 included patients with L-FABP ≥ 6.5 μg/g Cr

HR hazard ratio, *CI* confidence interval, *Cr* creatinine, *L-FABP* liver-type fatty acid-binding protein, *RAN* renin–angiotensin system.

*$p<0.05$, **$p<0.01$, †$p<0.001$

Table 6 The Mann–Whitney *U* test was used to compare patients with or without additional antihyperglycemic drugs in terms of several blood and urine clinical parameters

New additional drug	Yes ($n=34$)	No ($n=29$)	*p* value
ΔHbA1c	−0.3 (−0.9–0.2)	0.1 (−0.5 to 0.6)	0.13
ΔeGFR	−2.5 (−7.0–2.0)	−1.0 (−4.5 to 3.5)	0.20
ΔSBP	1.5 (−6.3–8.3)	4.0 (−2.0 to 9.5)	0.25
ΔAlbuminuria	−5.6 (−24.0–3.63)	−5.0 (−29.4 to 7.05)	0.94
Δurinary-L-FABP	−0.86 (−1.77–0.17)	−0.29 (−1.38 to 0.45)	0.43
DPP-4 inhibitors	Yes ($n=7$)	No ($n=56$)	*p* value
ΔHbA1c	−0.3 (−0.9 to -0.2)	0.1 (−0.7 to 0.6)	0.16
ΔeGFR	3.0 (−8.0 to 0.5)	−2.0 (−5.0 to 3.0)	0.35
ΔSBP	1.0 (0.0–5.5)	4.0 (−4.3 to 9.3)	0.82
ΔAlbuminuria	3.4 (−14.0 to 14.8)	−5.6 (−27.7 to 4.22)	0.32
Δurinary-L-FABP	−0.91 (−1.47 to −0.48)	−0.69 (−1.77 to 0.48)	0.66
SGLT-2 inhibitors	Yes ($n=6$)	No ($n=57$)	*p* value
ΔHbA1c	−0.95 (−1.30 to −0.15)	0.10 (−0.70 to 0.60)	0.07
ΔeGFR	−4.5 (−8.5 to −2.0)	−1.0 (−5.0 to 3.0)	0.12
ΔSBP	1.0 (−4.0 to 9.0)	4.0 (−4.0 to 9.0)	0.88
ΔAlbuminuria	−17.9 (−39.5 to −5.95)	−5.0 (−24.7 to 7.10)	0.17
Δurinary-L-FABP	−2.15 (−6.59 to −1.47)	−0.48 (−1.68 to 0.51)	0.01

Multivariate adjustments were performed according to several categories of baseline urinary L-FABP, some blood and urine clinical parameters, RAS blockade treatment, and lipid-lowering treatment. Baseline urinary L-FABP was categorized into three groups. Model 1 included all patients. Model 2 included patients with L-FABP ≥ 4.2 μg/g Cr, and Model 3 included patients with L-FABP ≥ 6.5 μg/g Cr

HR hazard ratio, *CI* confidence interval, *Cr* creatinine, *L-FABP* liver-type fatty acid-binding protein, *RAN* renin–angiotensin system

*$p<0.05$, **$p<0.01$, †$p<0.001$

the administration of SGLT-2 inhibitors was not affected by changes in systolic blood pressure, HbA1c, and eGFR. The SGLT-2 inhibitor used in this study was empagliflozin. In the EMPA-REG OUTCOME study, empagliflozin reduced the progression to macroalbuminuria by 38% compared with the placebo [13]. SGLT-2 inhibitors including empagliflozin prevented further eGFR decline in patients with type 2 diabetes and advanced dysfunction [14]. An experimental

Table 7 Logistic regression analysis was used to compare patients with or without administration of DPP-4 inhibitors or SGLT-2 inhibitors in terms of clinical characteristics and blood and urine parameters

Parameter	DPP-4 inhibitors		SGLT-2 inhibitors	
	Odds ratio (95% CI)		Odds ratio (95% CI)	
Age	1.02 (0.94–1.10)	1.02 (0.94–1.10)	0.85* (0.74–0.97)	0.82** (0.70–0.95)
Observation period(days)	1 (1.00–1.01)	1 (0.99–1.01)	1 (0.99–1.01)	1.01 (0.99–1.01)
ΔHbA1c	0.61 (0.23–1.63)	0.58 (0.22–1.49)	0.73 (0.15–3.45)	0.77 (0.14–4.35)
ΔeGFR	0.99 (0.89–1.10)	1 (0.91–1.10)	0.99 (0.85–1.15)	0.99 (0.82–1.20)
ΔSBP	1 (0.92–1.07)	0.99 (0.92–1.07)	1 (0.90–1.10)	0.99 (0.89–1.10)
ΔAlbuminuria	1.01 (0.99–1.02)		1 (0.98–1.01)	
Δurinary-L-FABP		1.04 (0.88–1.23)		0.75* (0.56–0.99)
AUC (95% CI)	0.71 (0.50–0.91)	0.69 (0.49–0.90)	0.89 (0.72–1.00)	0.92 (0.78–1.00)

*$p < 0.05$, **$p < 0.01$

study reported that the use of empagliflozin reduced urinary L-FABP in streptozotocin-induced diabetic rats [15]. In an in vitro model of human proximal tubular cells, empagliflozin reduced glucose-induced inflammatory and fibrotic markers by blocking glucose transport [16].

The protective effect of SGLT-2 inhibitors on the kidney has been explained by multiple mechanisms, including direct and indirect effects on the kidney. Among the direct effects, SGLT-2 inhibitors improved glomerular hyperfiltration, reduced renal oxygen consumption, and decreased renal inflammatory reactions. On the other hand, the effects of improved blood pressure or blood glucose, decreased uric acid levels, weight loss promotion or diuresis, and reduced insulin levels were among the indirect effects of SGLT-2 inhibitors [17]. Our study suggests that SGLT-2 inhibitors may directly reduce urinary L-FABP independent of blood pressure management, blood glucose management, and renal dysfunction.

Aging is associated with the progression of renal dysfunction. A reduction in peritubular capillary blood flow leads to tubular hypoperfusion and hypoxia and eventually to tubular atrophy and tubulointerstitial fibrosis, which is the main cause of aging-induced renal dysfunction. Urinary L-FABP reflects the degree of peritubular capillary blood flow and is an important factor for aging-induced renal dysfunction [2]. In a retrospective study, efficacy, renal safety, and tolerability of SGLT-2 inhibitors were similar in people over 70 years old compared to those 65–70 years of age, suggesting that its use should be considered even in the elderly [18]. This study was carried out shortly after the SGLT-2 inhibitor was launched, and the Japan Diabetes Society made recommendations regarding the use of SGLT-2 inhibitors for the purpose of safe use. Therefore, it is possible that safety was emphasized; thus, it was first intended for use in young individuals rather than for the elderly. To clarify the relationship between SGLT-2 inhibitor use and urinary L-FABP in elderly patients with type 2 diabetes, we believe that the accumulation of further data on the safety and efficacy of SGLT-2 inhibitor use is an issue for the future.

The results of this study were subject to some limitations. First, this was a retrospective observational study, and the sample size was not large. Second, the measurement of urinary L-FABP was a single spot urine measurement. Third, there were restrictions on the types of DPP-4 and SGLT-2 inhibitors that could be used in our medical facilities. Hence, prospective studies with a sufficient sample size of a wide-range age group are required to confirm our results.

In conclusion, our results suggest that urinary L-FABP may be associated with the future decrease in renal functions in type 2 diabetic nephropathy patients. Additionally, it could be used as a marker of the effectiveness of diabetic nephropathy treatment.

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Code availability Data are recorded in Excel® (Microsoft Office, Microsoft Corporation, Seattle, WA, USA) and are available upon reasonable request from the corresponding author.

Consent to participate The Ethics Committees of Ishinkai Yao General Hospital waived the requirement of written informed consent because data stored in the hospital database were analyzed anonymously for this retrospective study. Information about the research was disclosed to the research subjects (through posting on the hospital homepage), and the opportunity for the research subjects to refuse participation was guaranteed.

Consent for publication Not applicable.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics approval All procedures in the studies involved human participants; hence, they were performed in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB approval number 1103) and the 1964 Declaration of Helsinki and its later amendments. The Ethics Committees of Ishinkai Yao General Hospital approved the protocol of this study.

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