Clinical Kidney Journal, 2025, vol. 18, no. 4, sfaf056

https://doi.org/10.1093/ckj/sfaf056
Advance Access Publication Date: 12 March 2025
Original Article

ORIGINAL ARTICLE

Elevated urinary fatty acid-binding protein 4 level predicts future renal dysfunction and poor prognosis in Japanese patients with diabetes: a longitudinal cohort study

Marenao Tanaka [1,2,*], Tatsuya Sato [1,3,*], Tomohito Gohda [4], Nozomu Kamei [5,6], Maki Murakoshi [4], Erika Ishiwata [1], Kei Nakata [1], Yukinori Akiyama [7], Keisuke Endo [1], Wataru Kawaharata [1], Hiroki Aida [1], Toru Suzuki [1,8], Mitsunobu Kubota [9], Michiyoshi Sanuki [6], Yusuke Suzuki [4] and Masato Furuhashi [1]

[1]Department of Cardiovascular, Renal and Metabolic Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan, [2]Tanaka Medical Clinic, Yoichi, Japan, [3]Department of Cellular Physiology and Signal Transduction, Sapporo Medical University School of Medicine, Sapporo, Japan, [4]Department of Nephrology, Juntendo University Faculty of Medicine, Bunkyo-ku, Tokyo, Japan, [5]Department of Endocrinology and Metabolism, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Hiroshima, Japan, [6]Institute for Clinical Research, NHO Kure Medical Center and Chugoku Cancer Center, Kure, Japan, [7]Department of Neurosurgery, Sapporo Medical University School of Medicine, Sapporo, Japan, [8]Natori Toru Internal Medicine and Diabetes Clinic, Natori, Japan and [9]Department of Endocrinology and Diabetology, NHO Kure Medical Center and Chugoku Cancer Center, Kure, Japan

*The first two authors equally contributed to this work.
Correspondence to: Masato Furuhashi; E-mail: furuhasi@sapmed.ac.jp; Marenao Tanaka; E-mail: tanakamarenao@yahoo.co.jp

ABSTRACT

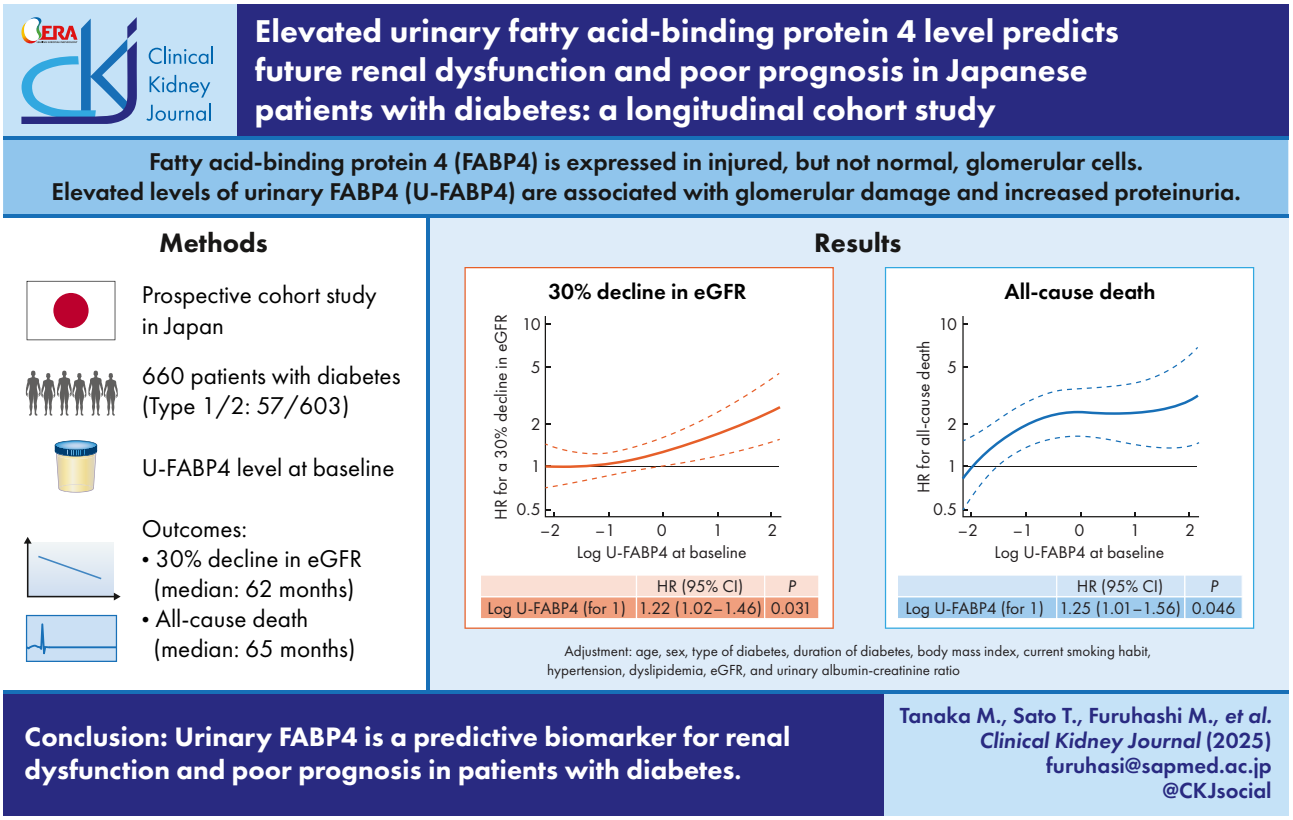
Background. Fatty acid-binding protein 4 (FABP4) is an adipokine secreted from adipocytes and macrophages and is also expressed in injured, but not normal, glomerular endothelial cells. Elevated levels of urinary FABP4 (U-FABP4) have been reported to be associated with glomerular damage and increased proteinuria.

Methods. The associations of levels of U-FABP4 at baseline with future events including renal dysfunction defined by a 30% decline in estimated glomerular filtration rate (eGFR) and all-cause death were investigated in 660 patients with diabetes (type 1/2, 57/603).

Received: 30.8.2024; Editorial decision: 13.2.2025

Results. During a follow-up period (median: 62 months), 90 patients (13.6%) developed renal dysfunction, and 66 patients (10.0%) died (median follow-up period 65 months). Kaplan–Meier survival curves showed that there were significant differences in cumulative incidences for a 30% decline in eGFR and all-cause death in patients divided by the tertiles of U-FABP4 level. Furthermore, multivariable Cox proportional hazard models with a restricted cubic spline showed that hazard ratios for a 30% decline in eGFR and all-cause death increased with a higher level of logarithmically transformed (log) U-FABP4 after adjustment for age, sex, type of diabetes, body mass index, current smoking habit, duration of diabetes, comorbidities of hypertension and dyslipidemia, eGFR, and the categorical classification of urinary albumin-creatinine ratio. The addition of log U-FABP4 to traditional risk factors significantly increased the discriminatory capacities for renal dysfunction in net reclassification improvement and integrated discrimination improvement and for all-cause death in NRI.
Conclusion. U-FABP4 is a predictive biomarker for future renal dysfunction and poor prognosis in patients with diabetes.

GRAPHICAL ABSTRACT



Keywords: diabetic kidney disease, fatty acid-binding protein 4, glomerular damage, mortality, prognosis

KEY LEARNING POINTS

What was known:

- Fatty acid-binding protein 4 (FABP4), which is mainly expressed in adipocytes and macrophages, is expressed in injured, but normal, glomerular cells.
- Elevated level of urinary FABP4 (U-FABP4) is associated with proteinuria and renal dysfunction in glomerular kidney diseases.

This study adds:

- Elevated U-FABP4 level was independently associated with future renal dysfunction defined by a 30% decline in estimated glomerular filtration rate in patients with diabetes.
- Elevated U-FABP4 level independently predicted all-cause mortality in patients with diabetes.

Potential impact:

- U-FABP4 is a promising predictive biomarker for both renal dysfunction and poor prognosis in patients with diabetes.

INTRODUCTION

The presence of diabetes has a major impact on healthy life expectancy as well as the occurrence of diabetes-related complications including cardiovascular and renal events [1, 2]. Recent advances in treatment strategies for achieving recommended glycemic management, blood pressure, and serum lipids have resulted in a reduction in the proportion of patients with diabetes [3]. However, the problems of diabetes-related cardiovascular, renal, and metabolic complications have not been fully overcome yet [4, 5]. Among the complications, diabetic kidney disease (DKD), defined as chronic kidney disease caused by diabetes with or without proteinuria/albuminuria, remains a major complication, leading to end stage renal disease (ESRD) and various cardiovascular events [6]. Therefore, early diagnosis and appropriate management of DKD are urgent issues for improving the healthy life expectancy of patients with diabetes [3].

Fatty acid-binding proteins (FABPs) are soluble proteins with a molecular weight of about 14-15 kDa that bind hydrophobic ligands such as long-chain fatty acids [7–9]. FABPs have been reported to function as chaperones of fatty acids, and some FABPs act as extracellularly secreted bioactive molecules [10, 11]. Among the FABPs, FABP1 is expressed in proximal tubular epithelial cells of the human kidneys [12, 13]. It has been reported that urinary FABP1 (U-FABP1) can be a marker of damaged proximal tubular epithelial cells in DKD [14]. However, since FABP1 is not expressed in glomeruli of the kidneys [12, 13], U-FABP1 does not directly reflect glomerular damage. On the other hand, albuminuria, a sensitive biomarker for an early stage of DKD, reflects abnormalities of both glomerular filtration and reabsorption in proximal tubular cells [15].

FABP4, classically known as adipocyte FABP, is mainly expressed in adipocytes and macrophages [7–10] and it can be a therapeutic target for insulin resistance and atherosclerosis [16, 17]. Previous studies showed that FABP4 is secreted from cells via a non-canonical pathway [18] and that circulating levels of FABP4 are increased in various cardiovascular and metabolic diseases including obesity-induced insulin resistance [19], diabetes [20], hypertension [21], dyslipidemia [22, 23], hyperuricemia [24], steatotic liver disease [25], coronary artery disease [22], carotid atherosclerosis [26], and chronic heart failure [27]. It has recently been reported that FABP4 is also expressed in injured vascular endothelial cells [28, 29].

Although FABP4 is not expressed in normal glomeruli of the kidneys, FABP4 has been reported to be ectopically expressed in glomerular endothelial cells of injured glomeruli [30]. It has also been reported that ectopic expression of FABP4 is associated with renal dysfunction and proteinuria in mice and humans [31, 32] and that urinary FABP4 (U-FABP4) is associated with albuminuria and annual decline in estimated glomerular filtration rate (eGFR) in a general population [33] and patients with diabetes [34], suggesting that U-FABP4 is a promising biomarker for glomerular damage. However, it remains unclear whether U-FABP4 is a predictive biomarker for future renal dysfunction and mortality in patients with diabetes. In the present study, we investigated the associations of U-FABP4 with future events of renal outcome and all-cause death and using a prospective cohort of Japanese patients with diabetes.

MATERIALS AND METHODS

The present study was a prospective cohort study using patients with diabetes and was approved by the ethics committees of Kure Medical Center and Chugoku Cancer Center (26–06) and Sapporo Medical University (3–1-77). Written informed consent was obtained from all the patients. The study conformed to the principles outlined in the Declaration of Helsinki.

Study patients

Japanese patients with diabetes were recruited at Kure Medical Center and Chugoku Cancer Center during the period from 1 July 2014 to 31 March 2016 ($n = 738$). A flow chart of the study patients is shown in Supplementary Fig. S1. At the recruitment, anthropometric and clinical characteristics were recorded, and samples of blood and urine were obtained from participants and were stored at −80°C until biochemical analyses. Prespecified exclusion criteria were the absence of data for U-FABP4 and patients with diabetes due to specific causes and gestational diabetes. Furthermore, patients with eGFR ≤15 ml/min at baseline were also excluded to investigate further progression of renal dysfunction. After exclusion, a total of 660 patients, including those with type 1 diabetes (T1D) ($n = 57$) and those with type 2 diabetes (T2D) ($n = 603$), who received checkups at least once until 31 March 2021 were enrolled in the present study. Most of the recruited patients were regularly followed up at least every 3 months. The clinical endpoints were set as a 30% decline in eGFR and all-cause death.

Measurements

Concentrations of FABP4 and FABP1 were measured by using enzyme-linked immunosorbent assay kits for FABP4 (BioVendor R&D, Modrice, Czech Republic) and FABP1 (CIMIC Co., Tokyo, Japan), respectively. Urinary albumin-to-creatinine ratio (U-ACR, mg/gCr) was used as a marker of microalbuminuria, and levels of U-ACR in patients with diabetes were categorized in accordance with the guidelines of the Japanese Society of Nephrology as follows [35]: stages A1 (U-ACR <30 mg/gCr), A2 (30 mg/gCr ≤ U-ACR <300 mg/gCr), and A3 (U-ACR ≥300 mg/gCr). eGFR was calculated using an equation for Japanese individuals [36]: eGFR (ml/min/1.73 m^2) = 194 × serum creatinine $^{(-1.094)}$ × age $^{(-0.287)}$ × 0.739 (if female). A self-administered questionnaire survey was performed to obtain information on current smoking habit, alcohol drinking habit, and family history of diabetes.

Statistical analysis

Variables are presented as means ± standard deviations for normal distributions or medians (interquartile ranges) for skewed variables. Normality of each variable was tested by the Shapiro–Wilk W test. Comparisons between two groups for parametric and nonparametric parameters were performed by Student's *t*-test and the Mann–Whitney *U*-test, respectively. The chi-square test was performed for intergroup differences in percentages of parameters. Clinical parameters were divided into three subgroups according to tertiles of U-FABP4 at baseline (T1–T3). One-way analysis of variance was used for detecting significant differences between data in multiple groups. To investigate whether U-FABP4 level affects outcomes step by step, the cumulative incidences of a 30% decline in eGFR and all-cause death were analyzed by the log-rank test of Kaplan–Meier survival curves in the three subgroups according to tertiles of U-FABP4 at baseline. Multivariable Cox proportional hazard models for a 30% decline in eGFR and all-cause death with a restricted cubic spline (spline knot 4) were analyzed after adjustment for confounders, which were determined by univariable analyses as well as possible candidates [37], including age, sex, type of

diabetes, body mass index (BMI), current smoking habit, duration of diabetes, comorbidities of hypertension and dyslipidemia, eGFR, and stage of U-ACR. Non-normally distributed variables were logarithmically transformed for regression analyses. Interactions of sex or type of diabetes with U-FABP4 for the endpoint of a 30% decline in eGFR or all-cause death were also investigated, and hazard ratios (HRs), 95% confidence intervals (CIs), and Akaike's information criterion (AIC) were calculated. Parameters with a lower AIC score constitute a better-fit model. To compare the discrimination, *C* statistics, analogous to the area under the curve (AUC) in receiver operating characteristic curve analysis, were investigated using the method from DeLong *et al*. [38]. Moreover, the different discriminatory value was investigated by using continuous net reclassification improvement (NRI) [39] and integrated discrimination improvement (IDI) [40]. A *P* value of <0.05 was considered statistically significant. All data were analyzed by using EZR [41] and R version 3.6.1.

RESULTS

Characteristics of the studied patients

Baseline characteristics of the enrolled patients ($n = 660$) and excluded patients ($n = 78$) with diabetes are shown in Supplementary Table S1. The enrolled patients were significantly older than the excluded patients and they had significantly higher BMI and systolic blood pressure and included a higher percentage of patients with hypertension than did the excluded patients. Levels of U-ACR and eGFR were comparable in the enrolled patients and excluded patients.

Baseline characteristics of the enrolled patients with T1D and those with T2D are shown in Table 1. The median duration of diabetes at baseline was 14 (interquartile range 7–22) years. Patients with T2D were significantly older than those with T1D. Patients with T2D had higher BMI, lower eGFR, and higher levels of total protein, triglycerides, and U-ACR, than those with T1D. The percentage of patients with dyslipidemia was higher in patients with T2D than in patients with T1D. Levels of serum FABP4 (S-FABP4), U-FABP1, and U-FABP4 were significantly higher in patients with T2D than in those with T1D.

Baseline characteristics of patients divided by tertiles (T1–T3) of U-FABP4 at baseline are shown in Table 2. Higher tertiles of U-FABP4 were accompanied by older patients, lower percentage of men, longer duration of diabetes, lower eGFR, and higher levels of S-FABP4, U-ACR, and U-FABP1. There were no significant differences in systolic blood pressure and BMI among the three subgroups.

Incidence rates and cumulative incidences for a 30% decline in eGFR and all-cause death during a follow-up period

Incidence rates for clinical endpoints of a 30% decline in eGFR and all-cause death are shown in Table 3. For a 30% decline in eGFR, the median follow-up period was 62 months, and follow-up summation was 34 637 patient-months. The number of patients who had only one checkup during the follow-up period was 13 (2.0%). Among the 660 enrolled patients, 90 patients (13.6%) progressed to a 30% decline in eGFR during the follow-up period. The incidence rate for a 30% decline in eGFR was 2.6 per 10 000 person-months. Baseline characteristics of patients divided by the presence and absence of a 30% decline in eGFR are shown in Supplementary Table S2. U-FABP4 level was significantly higher in patients with a 30% decline in eGFR during the follow-up period than in those without a 30% decline in eGFR. In Kaplan–Meier survival curves, there was a significant difference in cumulative incidences for a 30% decline in eGFR among the T1 (U-FABP4 $\leq$0.27 μg/gCr), T2 (U-FABP4 0.28–0.91 μg/gCr), and (T3) (U-FABP4 $\geq$0.92 μg/gCr) groups (log-rank test $P < .001$) (Fig. 1A).

For all-cause death, the median follow-up period was 65 months, and follow-up summation was 37 128 patient-months. Among the 660 enrolled patients, 66 patients (10.0%) died during the follow-up period. The incidence rate for all-cause death was 1.8 per 10 000 person-months. Baseline characteristics of patients divided by the presence and absence of all-cause death are shown in Supplementary Table S3. U-FABP4 level was significantly higher in patients with all-cause death during the follow-up period than in those without all-cause death. In Kaplan–Meier survival curves, there was a significant difference in cumulative incidences for all-cause death among the T1, T2, and T3 groups (log-rank test $P < .001$) (Fig. 1B). Cumulative incidences of the T2 and T3 groups were similar but markedly higher than that of the T1 group.

HRs for a 30% decline in eGFR and all-cause death in patients with diabetes

In univariable Cox regression analyses, current smoking habit, hypertension, eGFR, and U-ACR stage were significantly associated with a 30% decline in eGFR. On the other hand, age, sex, BMI, duration of diabetes, hypertension, eGFR, and U-ACR stage were significantly associated with all-cause death (Supplementary Table S4).

In multivariable Cox regression analysis after adjustment for age, sex, and type of diabetes (Model 1), a high level of logarithmically transformed (log) U-FABP4 was a significant risk factor for a 30% decline in eGFR [HR (95% CI): 1.53 (1.29–1.81)] and for all-cause death [HR (95% CI): 1.31 (1.07–1.61)] (Table 4). After additional incorporation of BMI, current smoking habit, duration of diabetes, comorbidities of hypertension and dyslipidemia, eGFR and stage of U-ACR into Model 1 (Model 2), a high level of log U-FABP4 was also a significant risk factor for a 30% decline in eGFR [HR (95% CI): 1.22 (1.02–1.46)] and for all-cause death [HR (95% CI): 1.25 (1.01–1.56)] (Table 4). The cubic spline of HR for a 30% decline in eGFR in Model 2 gradually increased with a higher level of log U-FABP4 (Fig. 1C). On the other hand, the cubic spline of HR for all-cause death in Model 2 rapidly and then gently increased with a higher level of log U-FABP4 (Fig. 1D).

After further additional incorporation of S-FABP4 into Model 2 (Model 3), a high level of log U-FABP4, but not that of log S-FABP4, was still a significant risk factor for a 30% decline in eGFR [HR (95% CI): 1.21 (1.01–1.45)] and for all-cause death [HR (95% CI): 1.25 (1.01–1.56)] (Supplementary Table S5). Further additional incorporation of U-FABP1 into Model 2 (Model 4) showed that the level of log U-FABP1, but not that of log U-FABP4, was significantly associated with a 30% decline in eGFR or all-cause death (Supplementary Table S5). As a related information, an elevated U-FABP1 level was independently associated with a 30% decline in eGFR and all-cause death after adjustment for age, sex, type of diabetes, BMI, current smoking habit, duration of diabetes, comorbidities of hypertension and dyslipidemia, eGFR, and stage of U-ACR in patients with diabetes (Supplementary Table S6).

In all Models 1–4, there were no significant interactions of sex or type of diabetes with log U-FABP4 for the adjusted HR of a 30% decline in eGFR and that of all-cause death (Table 4, Supplementary Table S5).

Table 1: Characteristics of enrolled patients with diabetes.

	All ($n = 660$)	T1D ($n = 57$)	T2D ($n = 603$)	P
Age, years	65 ± 13	61 ± 14	65 ± 13	.011
Sex, men	363 (55.0)	27 (47.4)	336 (55.7)	.265
BMI	25 ± 5	23 ± 4	25 ± 5	.001
Systolic blood pressure, mmHg	139 ± 18	135 ± 16	139 ± 18	.055
Diastolic blood pressure, mmHg	78 ± 12	78 ± 11	78 ± 12	.879
Current smoking habit	114 (17.5)	10 (17.9)	104 (17.5)	.990
Alcohol drinking habit	164 (25.2)	16 (28.6)	158 (24.9)	.523
Duration of diabetes, years	14 [7–22]	10 [4–19]	14 [7–22]	.068
Family history				
Diabetes	386 (58.5)	30 (52.6)	356 (59.0)	.399
Comorbidity				
Hypertension	488 (73.9)	38 (66.7)	450 (74.6)	.207
Dyslipidemia	161 (24.4)	3 (5.3)	445 (73.8)	<.001
Medication				
Anti-diabetic drugs				
Insulin	265 (40.2)	57 (100)	208 (34.5)	<.001
GLP-1 analogs	31 (4.7)	1 (1.8)	30 (5.0)	.507
Sulfonylureas	195 (29.5)	0 (0)	195 (32.3)	<.001
Biguanides	341 (51.7)	10 (17.5)	331 (54.9)	<.001
α-glucosidase inhibitors	110 (16.7)	4 (7.0)	106 (17.6)	.041
DPP-4 inhibitors	455 (68.9)	17 (29.8)	438 (72.6)	<.001
Glinides	49 (7.4)	0 (0)	49 (8.5)	.016
Pioglitazone	63 (9.5)	0 (0)	63 (10.4)	.004
SGLT2 inhibitors	11 (1.7)	0 (0)	11 (1.8)	.612
Biochemical data				
Total protein, g/dl	7.3 ± 0.5	7.1 ± 0.4	7.3 ± 0.5	.019
Blood urea nitrogen, mg/dl	17 ± 7	16 ± 6	17 ± 7	.231
Cr, mg/dl	0.80 [0.65–1.00]	0.70 [0.62–0.90]	0.80 [0.66–1.00]	.014
eGFR, ml/min/1.73 m^2	69 ± 24	76 ± 22	69 ± 24	.028
Uric acid, mg/dl	5.4 ± 1.4	4.7 ± 1.4	5.4 ± 1.3	<.001
Total cholesterol, mg/dl	182 ± 35	189 ± 31	181 ± 35	.099
LDL-C, mg/dl	106 ± 28	110 ± 23	105 ± 28	.169
HDL-C, mg/dl	53 ± 14	63 ± 18	52 ± 13	<.001
Triglycerides, mg/dl	105 [74–161]	75 [53–106]	108 [76–168]	<.001
Glucose, mg/dl	141 [118–172]	149 [118–213]	141 [119–171]	.305
Hemoglobin A1c, %	7.2 [6.6–7.9]	7.3 [6.7–8.2]	7.1 [6.6–7.9]	.195
S-FABP4, ng/ml	17.7 [11.8–25.1]	13.7 [9.6–16.7]	18.4 [12.2–25.4]	<.001
Urinalysis				
U-ACR, mg/gCr	24 [9–137]	11 [5–41]	26 [10–153]	<.001
A1 (<30 mg/gCr)	360 (54.5)	41 (71.9)	319 (52.9)	.008
A2 (≥30, <300 mg/gCr)	190 (28.8)	12 (21.1)	178 (29.5)	.221
A3 (≥300 mg/gCr)	110 (16.7)	4 (7.0)	106 (17.6)	.041
U-FABP1, μg/gCr	4.2 [2.5–9.3]	3.3 [1.8–5.5]	4.2 [2.5–9.9]	.023
U-FABP4, μg/gCr	0.50 [0.21–1.27]	0.41 [0.16–1.00]	0.67 [0.27–1.53]	<.001

Variables are expressed as number (%), means ± standard deviation or medians [interquartile ranges].
Cr, creatinine; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SGLT2, sodium-glucose co-transporter 2; S- , serum-; U-, urinary-.

Discriminatory capacity of the addition of U-FABP4 for predicting a 30% decline in eGFR or all-cause death

The addition of log U-FABP4 to traditional risk factors, including age, sex, type of diabetes, BMI, current smoking habit, duration of diabetes, comorbidities of hypertension and dyslipidemia, eGFR, and stage of U-ACR, significantly improved the discriminatory capacity for a 30% decline in eGFR in NRI (value 0.242, $P = .046$) and IDI (value 0.012, $P = .031$) (Table 5). On the other hand, the discriminatory capacity for all-cause death was significantly improved in NRI (value 0.300, $P = .024$) but not in IDI. There were no significant differences in the discriminatory capacity for a 30% decline in eGFR or all-cause death between values of AUC for traditional risk factors and those in addition to U-FABP4.

DISCUSSION

The present study showed that elevated U-FABP4 level predicted future renal dysfunction and mortality in patients with diabetes independently of conventional risk factors including age, sex, type of diabetes, BMI, current smoking habit, duration of diabetes, comorbidities of hypertension and dyslipidemia, eGFR, and U-ACR. Kaplan–Meier survival curves showed that there were significant differences in cumulative incidences for a 30% decline in eGFR and all-cause death in patients divided by the

Table 2: Characteristics of patients divided by the tertiles of U-FABP4 at baseline ($n = 660$).

	T1 (≤0.27) ($n = 220$)	T2 (0.28–0.91) ($n = 220$)	T3 (≥0.92) ($n = 220$)	P
Age, years	64 ± 12	64 ± 14	68 ± 14	.002
Sex, men	162 (64.5)	124 (56.4)	97 (44.1)	<.001
Type of diabetes, T2D	196 (89.1)	197 (89.5)	210 (95.5)	.030
BMI	25 ± 5	25 ± 4	25 ± 4	.535
Systolic blood pressure, mmHg	138 ± 17	139 ± 17	141 ± 19	.182
Diastolic blood pressure, mmHg	79 ± 11	77 ± 11	78 ± 12	.052
Current smoking habit	39 (18.0)	45 (20.7)	30 (13.9)	.169
Alcohol drinking habit	64 (29.5)	48 (22.1)	52 (24.0)	.184
Duration of diabetes, years	13 [6–20]	14 [7–24]	18 [9–24]	.001
Family history				
Diabetes	127 (57.7)	131 (59.5)	128 (58.2)	.922
Comorbidity				
Hypertension	156 (70.9)	163 (74.1)	169 (76.8)	.368
Dyslipidemia	59 (26.8)	46 (20.9)	56 (25.5)	.319
Medication				
Anti-diabetic drugs				
Insulin	81 (36.8)	89 (40.5)	95 (43.2)	.393
GLP-1 analogs	13 (5.9)	8 (3.6)	10 (4.5)	.526
Sulfonylureas	59 (26.8)	62 (28.2)	74 (33.6)	.253
Biguanides	128 (58.6)	104 (47.3)	109 (49.5)	.054
α-glucosidase inhibitors	37 (16.8)	31 (14.1)	42 (19.1)	.371
DPP-4 inhibitors	137 (62.3)	152 (69.1)	166 (75.5)	.012
Glinides	15 (6.8)	14 (6.4)	20 (9.1)	.505
Pioglitazone	21 (9.5)	19 (8.6)	23 (10.5)	.810
SGLT2 inhibitors	5 (2.3)	3 (1.4)	3 (1.4)	.691
Biochemical data				
Total protein, g/dl	7.3 ± 0.5	7.3 ± 0.5	7.3 ± 0.5	.420
Blood urea nitrogen, mg/dl	16 ± 6	17 ± 7	18 ± 7	.048
Cr, mg/dl	0.80 [0.70–1.00]	0.80 [0.65–1.00]	0.80 [0.62–1.10]	.497
eGFR, ml/min/1.73 m^2	73 ± 21	70 ± 25	64 ± 23	<.001
Uric acid, mg/dl	5.4 ± 1.4	5.3 ± 1.4	5.4 ± 1.4	.754
Total cholesterol, mg/dl	185 ± 35	179 ± 34	183 ± 36	.169
LDL-C, mg/dl	107 ± 27	104 ± 27	106 ± 29	.548
HDL-C, mg/dl	53 ± 14	52 ± 14	54 ± 14	.442
Triglycerides, mg/dl	115 [75–172]	98 [69–152]	102 [76–165]	.162
Glucose, mg/dl	139 [118–174]	144 [117–174]	141 [120–169]	.824
Hemoglobin A1c, %	7.1 [6.5–7.9]	7.2 [6.6–7.9]	7.2 [6.7–7.9]	.687
S-FABP4, ng/ml	15.6 [11.5–22.0]	17.1 [11.6–24.3]	19.9 [13.8–26.2]	<.001
Urinalysis				
U-ACR, mg/gCr	15 [7–38]	24 [10–136]	52 [12–401]	<.001
A1 (<30 mg/gCr)	151 (68.6)	118 (53.6)	91 (41.4)	<.001
A2 (≥30, <300 mg/gCr)	52 (23.6)	71 (32.3)	67 (30.5)	<.001
A3 (≥300 mg/gCr)	17 (7.7)	31 (14.1)	62 (28.3)	<.001
U-FABP1, μg/gCr	2.6 [1.7–4.0]	4.4 [2.8–8.5]	9.4 [4.1–28.0]	<.001
U-FABP4, μg/gCr	0.14 [0.09–0.21]	0.50 [0.38–0.68]	1.88 [1.27–3.29]	<.001

Variables are expressed as number (%), means ± standard deviation or medians [interquartile ranges].
Cr, creatinine; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SGLT2, sodium-glucose co-transporter 2; S- , serum-; U-, urinary-.

tertiles of U-FABP4 level. Furthermore, restricted cubic splines clearly showed that HR for a 30% decline in eGFR gradually increased with a higher level of log U-FABP4 and that HR for all-cause death increased rapidly and then gently increased with a higher level of log U-FABP4. Since progression of renal dysfunction is one of the important prognostic factors in patients with diabetes [42], the results of the present study support the notion that measurement of U-FABP4 is useful for estimation of the risk for both diabetes-related complications and mortality in patients with diabetes.

To the best of our knowledge, this study is the first study showing an association between U-FABP4 level and future prognosis. It was previously shown that elevated circulating FABP4 concentration is a predictive biomarker for all-cause death and cardiovascular death during a 12-year follow-up period in a general population [43]. However, U-FABP4 level was not investigated in the previous study [43]. The precise reason why U-FABP4 was a stronger risk marker than S-FABP4 for all-cause death in the present study remains unknown. However, patients with diabetes are more susceptible than the general population to the development of renal dysfunction [1]. In addition, the pathophysiology of DKD can be greatly influenced by glomerular endothelial cell damage [44]. Ectopic expression and subsequent secretion of FABP4 into urine due to glomerular damage may be

Table 3: Incidence rate of a 30% decline in eGFR and all-cause death ($n = 660$).

	30% decline in eGFR	All-cause death
Median of follow-up period, months	62 (31–70)	65 (43–72)
Follow-up summation, person-months	34 637	37 128
Number of events during the follow-up period	90	66
Incidence rate, value per 1000 person-months	2.6	1.8

Variables are expressed as number or medians (interquartile ranges).

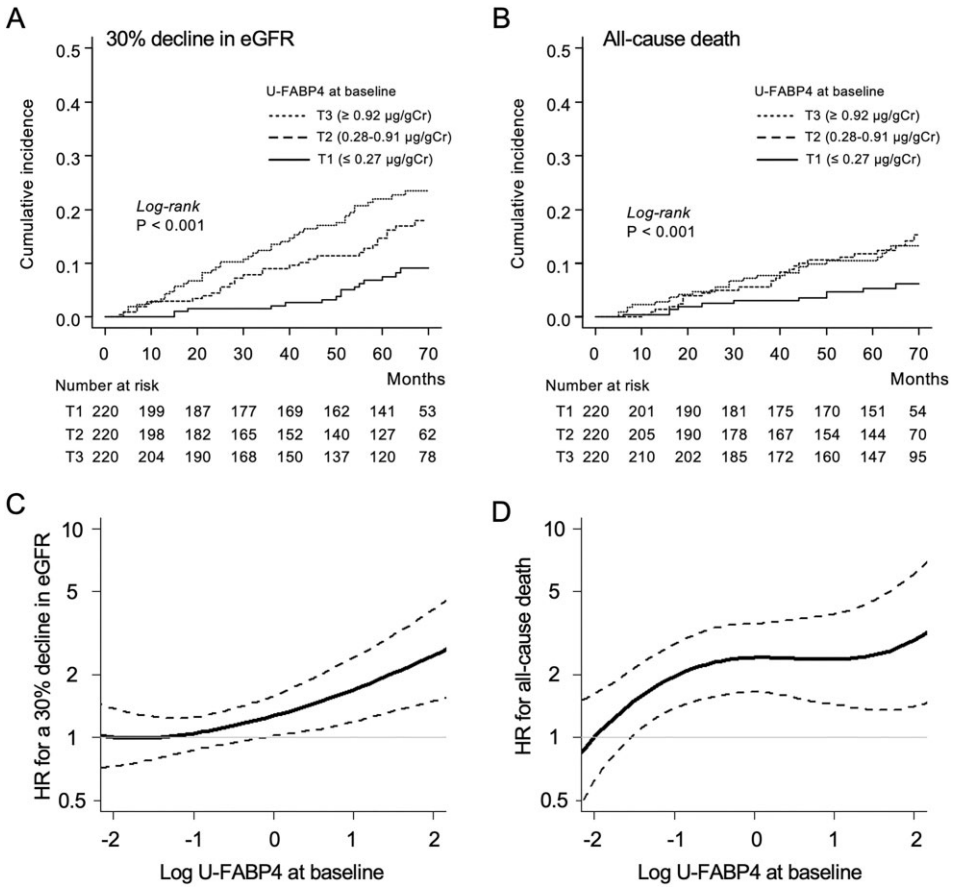


Figure 1: Effects of U-FABP4 for a 30% decline in eGFR and all-cause death. (**A**, **B**) Kaplan–Meier survival curves for cumulative incidences of a 30% decline in estimated glomerular filtration rate (eGFR) (A) and all-cause death (B) in the first tertile (T1, ≤ 0.27 μg/gCr), second tertile (T2, 0.28–0.91 μg/gCr), and third tertile (T3, ≥ 0.92 μg/gCr) of urinary fatty acid-binding protein 4 (U-FABP4) level at baseline. Solid, dashed, and dotted lines represent the T1, T2, and T3 groups, respectively. (**C**, **D**) HRs of logarithmically transformed (log) U-FABP4 for a 30% decline in eGFR (C) and all-cause death (D) in patients with diabetes were investigated in multivariable Cox proportional hazard models with a restricted cubic spline after adjustment for age, sex, type of diabetes, BMI, current smoking habit, duration of diabetes, comorbidities of hypertension and dyslipidemia, eGFR and stage of urinary albumin-creatinine ratio at baseline. Solid line: HR; dashed line: 95% confidence interval. The reference value of log U-FABP4 was −2.0 as the minimum value.

greater than those of FABP4 into blood. It has been shown that the presence of chronic kidney disease or DKD not only precedes ESRD but also increases the risk for cardiovascular events, leading to death even in early stages of DKD [35, 45, 46]. Therefore, level of U-FABP4 may directly reflect the progression of DKD, resulting in the association with high mortality in patients with diabetes.

Another reason for the discrepancy for all-cause death between levels of U-FABP4 and S-FABP4 may be the influence of adiposity and nutritional condition. S-FABP4 level has been reported to be independently associated with the amount of adipose tissue in the body [7–9]. In the present study, patients with diabetes who died during the follow-up had significantly lower BMI at baseline than did those who did not die. However, S-FABP4 levels were comparable between patients with diabetes who died and those who did not die (Supplementary Table S3), suggesting that S-FABP4 levels are underestimated in elder patients with diabetes who may have sarcopenia. On the other hand, it has been reported that U-FABP4 level is not significantly correlated with BMI [33, 34]. Therefore, U-FABP4 level would be a better predictor of prognosis than S-FABP4 level independent of adiposity especially in elder patients with diabetes.

Table 4: Multivariable Cox regression analyses for a 30% decline in eGFR and all-cause death.

	30% decline in eGFR				All-cause death			
	Model 1		Model 2		Model 1		Model 2	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
log U-FABP4 (per 1)	1.53 (1.29–1.81)	<.001	1.22 (1.02–1.46)	.031	1.31 (1.07–1.61)	.008	1.25 (1.01–1.56)	.046
Age (per 10 years)	0.98 (0.83–1.17)	.843	0.92 (0.73–1.16)	.473	2.02 (1.53–2.66)	<.001	1.71 (1.26–2.34)	<.001
Sex (men)	1.33 (0.86–2.05)	.198	0.86 (0.53–1.40)	.542	2.94 (1.65–5.22)	<.001	2.53 (1.40–4.60)	<.001
Type of diabetes (T2D)	1.39 (0.56–3.49)	.479	1.13 (0.40–3.22)	.815	0.51 (0.21–1.22)	.129	0.50 (0.20–1.23)	.130
BMI (per 1)			0.98 (0.93–1.04)	.516			0.94 (0.87–1.01)	.088
Current smoking habit			1.67 (0.95–2.91)	.072			1.31 (0.68–2.52)	.426
log (duration of diabetes) (per 1)			0.85 (0.66–1.10)	.210			0.98 (0.70–1.37)	.921
Hypertension			0.92 (0.49–1.70)	.782			1.24 (0.61–2.54)	.549
Dyslipidemia			0.99 (0.60–1.63)	.965			1.10 (0.58–2.06)	.773
eGFR (per 1 ml/min/1.73 m^2)			0.98 (0.97–0.99)	<.001			0.98 (0.96–0.99)	.012
U-ACR stage (per 1)			2.71 (1.97–3.73)	<.001			1.06 (0.73–1.53)	.767
AIC	1 086		947		764		734	
Interaction (log U-FABP4/sex)		.391		.154		.247		.206
Interaction (log U-FABP4/type of diabetes)		.424		.250		.251		.281

Table 5: Discriminatory capacity of U-FABP4 to traditional risk factors for a 30% decline in eGFR and all-cause death.

	AUC		IDI		Category-free NRI	
	Value (95% CI)	*P*	Value (95% CI)	*P*	Value (95% CI)	*P*
30% decline in eGFR						
Traditional model[a] (Reference)	0.769 (0.703, 0.836)					
Traditional model[a] + U-FABP4	0.777 (0.710, 0.844)	.282	0.012 (0.001, 0.023)	.031	0.242 (0.004, 0.479)	.046
All-cause death						
Traditional model[a] (Reference)	0.751 (0.689, 0.814)					
Traditional model[a] + U-FABP4	0.758 (0.696, 0.819)	.571	0.006 (-0.002, 0.015)	.170	0.300 (0.039, 0.561)	.024

[a]Traditional model includes age, sex, type of diabetes, BMI, current smoking habit, duration of diabetes, hypertension, dyslipidemia, eGFR, and the stage of urinary albumin-creatinine ratio. .

In a cross-sectional study [47], S-FABP4 concentration was shown to be independently associated with eGFR as well as levels of soluble tumor necrosis factor receptors (sTNFRs) including sTNFR1 and sTNFR2, which are potent markers for renal dysfunction [48, 49], in patients with diabetes. In the present study, S-FABP4 was not significantly associated with future renal dysfunction and all-cause death (Model 3, Supplementary Table S5). The reason for this discrepancy in results is unclear, but it might be explained by the possibility that specific expression of FABP4 in the kidneys directly reflects U-FABP4 rather than S-FABP4. It has been reported that stimulation of vascular endothelial cells with vascular endothelial growth factor or hydrogen peroxide induced the expression of FABP4 [29] and that FABP4 is secreted from cultured glomerular endothelial cells [32]. We also previously showed that U-FABP4 level and expression of FABP4 in glomeruli were independently associated with each other after adjustment of various related factors in patients with chronic glomerulonephritis [32]. Since the molecular weight of FABP4 is ∼14–15 kDa [7], a part of circulating FABP4 may cross the glomerular filtration barrier, leading to a source of U-FABP4. Indeed, U-FABP4 level was significantly, but not strongly, correlated with S-FABP4 level in the present study ($r = 0.186$, $P < .001$, data not shown). Therefore, U-FABP4 rather than S-FABP4 may reflect glomerular damage, presumably resulting in a promising predictive marker for a decline in eGFR in patients with diabetes.

It has been reported that U-FABP1 is associated with tubulointerstitial damage [13] and that U-FABP4 can reflect glomerular damage [30]. In the present study, an elevated U-FABP1 level was independently associated with a 30% decline in eGFR and all-cause death (Supplementary Table S6). Furthermore, only U-FABP1 was selected as a significant factor for future renal dysfunction and mortality in a model using both U-FABP4 and U-FABP1 as covariates (Model 4, Supplementary Table S5). One interpretation of the result is that not only glomerular damage but also tubulointerstitial damage contributes to major pathophysiological factors in the progression of DKD [50]. Another possible reason is that the effects of U-FABP4 on the outcomes were underestimated in the model since there might be a multicollinearity between levels of U-FABP1 and U-FABP4 [33, 34]. Indeed, there was a significant positive correlation between U-FABP4 and U-FABP1 in the present study ($r = 0.631$, $P < .001$, data not shown). Since FABPs including FABP4 and FABP1 are molecules that coordinate lipid responses in cells [7], the expression of FABPs might be influenced by the state of metabolic dysfunction including diabetes, partially affecting urinary excretion of FABP4 and FABP1. Nevertheless, simultaneous evaluation of U-FABP4 and U-FABP1 would be useful for prediction of renal outcomes, and the

development of novel formulas using levels of U-FABP4 and U-FABP1 may improve the accuracy for estimation of renal outcomes in DKD.

The present study has several limitations. First, since only Japanese people were enrolled in the present study, the generalizability of the findings to other ethnic groups would be limited by any genetic and environmental factors. Second, the possibility of sample selection bias cannot be ruled out since all patients were recruited form a single hospital. Third, it has been reported that several agents affect circulating levels of FABP4 [22, 51–54], although there has been no study focused on the regulation of U-FABP4 by treatment with drugs. Potential effects of unknown therapeutic agents affecting levels of U-FABP4 cannot be ruled out in the present study. Fourth, since the present study was started before showing beneficial effects of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 analogs on DKD [55], the number of patients treated with those drugs was small in the present study. Further exploration of how existing treatments might influence U-FABP4 levels could provide valuable context for future research directions. Finally, events for the development of ESRD and for cardiovascular death as clinical endpoints were not evaluated in the present study.

In conclusion, U-FABP4 is a promising predictive biomarker for both renal dysfunction and poor prognosis in patients with diabetes. Incorporating U-FABP4 measurement into clinical protocols as an indicator of early therapeutic intervention is expected to improve prognosis and healthy life expectancy in not only patients with DKD but also patients with diabetes who have not yet developed DKD. Further studies are needed to investigate whether U-FABP4 can be a useful biomarker in a large number of patients with diabetes including those who have ESRD.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

FUNDING

M.T. (22K08313), T.G. (23K07681), and M.F. (23K07993) were supported by grants from Japan Society for the Promotion of Science.

AUTHORS' CONTRIBUTIONS

M.T. and M.F. designed the study, performed data collection and statistical analyses, and wrote the paper. T.S., T.G., N.K., M.M., K.N., Y.A., K.E., W.K., H.A., T.S., and Y.S. performed data collection and discussed the data. E.I., M.K., and M.S. performed data collection. All authors approved the final version of manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Araki E, Goto A, Kondo T *et al*. Japanese Clinical Practice Guideline for Diabetes 2019. *Diabetol Int* 2020;**11**:165–223. https://doi.org/10.1007/s13340-020-00439-5
2. American Diabetes Association. Standards of Care in Diabetes-2023 abridged for primary care providers. *Clin Diabetes* 2022;**41**:4–31.
3. Tobias DK, Merino J, Ahmad A *et al*. Second international consensus report on gaps and opportunities for the clinical translation of precision diabetes medicine. *Nat Med* 2023;**29**:2438–57. https://doi.org/10.1038/s41591-023-02502-5
4. Sato T, Kouzu H, Yano T *et al*. Potential favorable action of sodium-glucose cotransporter-2 inhibitors on sudden cardiac death: a brief overview. *Front Cardiovasc Med* 2023;**10**:1159953. https://doi.org/10.3389/fcvm.2023.1159953
5. Ndumele CE, Neeland IJ, Tuttle KR *et al*. A synopsis of the evidence for the science and clinical management of cardiovascular-kidney-metabolic (CKM) syndrome: a scientific statement from the American Heart Association. *Circulation* 2023;**148**:1636–64. https://doi.org/10.1161/CIR.0000000000001186
6. Thomas MC, Brownlee M, Susztak K *et al*. Diabetic kidney disease. *Nat Rev Dis Primers* 2015;**1**:15018. https://doi.org/10.1038/nrdp.2015.18
7. Furuhashi M, Hotamisligil GS. Fatty acid-binding proteins: role in metabolic diseases and potential as drug targets. *Nat Rev Drug Discov* 2008;**7**:489–503. https://doi.org/10.1038/nrd2589
8. Furuhashi M, Saitoh S, Shimamoto K *et al*. Fatty acid-binding protein 4 (FABP4): pathophysiological insights and potent clinical biomarker of metabolic and cardiovascular diseases. *Clin Med Insights Cardiol* 2014;**8**:23–33.
9. Furuhashi M. Fatty acid-binding protein 4 in cardiovascular and metabolic diseases. *J Atheroscler Thromb* 2019;**26**:216–32. https://doi.org/10.5551/jat.48710
10. Furuhashi M, Ishimura S, Ota H *et al*. Lipid chaperones and metabolic inflammation. *Int J Inflam* 2011;**2011**:642612.
11. D'Anneo A, Bavisotto CC, Gammazza AM *et al*. Lipid chaperones and associated diseases: a group of chaperonopathies defining a new nosological entity with implications for medical research and practice. *Cell Stress Chaperones* 2020;**25**:805–20. https://doi.org/10.1007/s12192-020-01153-6
12. Kamijo A, Kimura K, Sugaya T *et al*. Urinary free fatty acids bound to albumin aggravate tubulointerstitial damage. *Kidney Int* 2002;**62**:1628–37. https://doi.org/10.1046/j.1523-1755.2002.00618.x
13. Kamijo A, Kimura K, Sugaya T *et al*. Urinary fatty acid-binding protein as a new clinical marker of the progression of chronic renal disease. *J Lab Clin Med* 2004;**143**:23–30. https://doi.org/10.1016/j.lab.2003.08.001
14. Kamijo-Ikemori A, Sugaya T, Kimura K. Novel urinary biomarkers in early diabetic kidney disease. *Curr Diab Rep* 2014;**14**:513. https://doi.org/10.1007/s11892-014-0513-1
15. Dickson LE, Wagner MC, Sandoval RM *et al*. The proximal tubule and albuminuria: really! *J Am Soc Nephrol* 2014;**25**:443–53. https://doi.org/10.1681/ASN.2013090950
16. Furuhashi M, Tuncman G, Gorgun CZ *et al*. Treatment of diabetes and atherosclerosis by inhibiting fatty-acid-binding protein aP2. *Nature* 2007;**447**:959–65. https://doi.org/10.1038/nature05844
17. Furuhashi M, Fucho R, Gorgun CZ *et al*. Adipocyte/macrophage fatty acid-binding proteins contribute to metabolic deterioration through actions in both macrophages and adipocytes in mice. *J Clin Invest* 2008;**118**:2640–50.

18. Mita T, Furuhashi M, Hiramitsu S *et al*. FABP4 is secreted from adipocytes by adenyl cyclase-PKA- and guanylyl cyclase-PKG-dependent lipolytic mechanisms. *Obesity* 2015;**23**:359–67. https://doi.org/10.1002/oby.20954
19. Ishimura S, Furuhashi M, Watanabe Y *et al*. Circulating levels of fatty acid-binding protein family and metabolic phenotype in the general population. *PLoS ONE* 2013;**8**:e81318. https://doi.org/10.1371/journal.pone.0081318
20. Furuhashi M, Sakuma I, Morimoto T *et al*. Independent and distinct associations of FABP4 and FABP5 with metabolic parameters in type 2 diabetes mellitus. *Front Endocrinol* 2020;**11**:575557. https://doi.org/10.3389/fendo.2020.575557
21. Ota H, Furuhashi M, Ishimura S *et al*. Elevation of fatty acid-binding protein 4 is predisposed by family history of hypertension and contributes to blood pressure elevation. *Am J Hypertens* 2012;**25**:1124–30. https://doi.org/10.1038/ajh.2012.88
22. Furuhashi M, Hiramitsu S, Mita T *et al*. Reduction of circulating FABP4 level by treatment with omega-3 fatty acid ethyl esters. *Lipids Health Dis* 2016;**15**:5. https://doi.org/10.1186/s12944-016-0177-8
23. Furuhashi M, Omori A, Matsumoto M *et al*. Independent link between levels of proprotein convertase subtilisin/kexin type 9 and FABP4 in a general population without medication. *Am J Cardiol* 2016;**118**:198–203. https://doi.org/10.1016/j.amjcard.2016.04.037
24. Furuhashi M, Matsumoto M, Murase T *et al*. Independent links between plasma xanthine oxidoreductase activity and levels of adipokines. *J Diabetes Investig* 2019;**10**:1059–67. https://doi.org/10.1111/jdi.12982
25. Tanaka M, Takahashi S, Higashiura Y *et al*. Circulating level of fatty acid-binding protein 4 is an independent predictor of metabolic dysfunction-associated fatty liver disease in middle-aged and elderly individuals. *J Diabetes Investig* 2022;**13**:878–88. https://doi.org/10.1111/jdi.13735
26. Furuhashi M, Yuda S, Muranaka A *et al*. Circulating fatty acid-binding protein 4 concentration predicts the progression of carotid atherosclerosis in a general population without medication. *Circ J* 2018;**82**:1121–9. https://doi.org/10.1253/circj.CJ-17-1295
27. Fuseya T, Furuhashi M, Yuda S *et al*. Elevation of circulating fatty acid-binding protein 4 is independently associated with left ventricular diastolic dysfunction in a general population. *Cardiovasc Diabetol* 2014;**13**:126. https://doi.org/10.1186/s12933-014-0126-7
28. Elmasri H, Karaaslan C, Teper Y *et al*. Fatty acid binding protein 4 is a target of VEGF and a regulator of cell proliferation in endothelial cells. *FASEB J* 2009;**23**:3865–73. https://doi.org/10.1096/fj.09-134882
29. Fuseya T, Furuhashi M, Matsumoto M *et al*. Ectopic fatty acid-binding protein 4 expression in the vascular endothelium is involved in neointima formation after vascular injury. *J Am Heart Assoc* 2017;**6**:e006377. https://doi.org/10.1161/JAHA.117.006377
30. Tanaka M, Furuhashi M, Okazaki Y *et al*. Ectopic expression of fatty acid-binding protein 4 in the glomerulus is associated with proteinuria and renal dysfunction. *Nephron Clin Pract* 2014;**128**:345–51. https://doi.org/10.1159/000368412
31. Tanaka M, Furuhashi M, Moniwa N *et al*. Significance of urinary fatty acid-binding protein 4 level as a possible biomarker for the identification of minimal change disease in patents with nephrotic-range proteinuria. *BMC Nephrol* 2020;**21**:459. https://doi.org/10.1186/s12882-020-02122-y
32. Tanaka M, Moniwa N, Nogi C *et al*. Glomerular expression and urinary excretion of fatty acid-binding protein 4 in IgA nephropathy. *J Nephrol* 2023;**36**:385–95. https://doi.org/10.1007/s40620-022-01551-2
33. Okazaki Y, Furuhashi M, Tanaka M *et al*. Urinary excretion of fatty acid-binding protein 4 is associated with albuminuria and renal dysfunction. *PLoS ONE* 2014;**9**:e115429. https://doi.org/10.1371/journal.pone.0115429
34. Tanaka M, Sato T, Gohda T *et al*. Urinary fatty acid-binding protein 4 is a promising biomarker for glomerular damage in patients with diabetes mellitus. *J Diabetes Investig* 2024; online ahead of print (26 December 2024). https://doi.org/10.1111/jdi.14388
35. Japanese Society of N. Essential points from evidence-based Clinical Practice Guidelines for Chronic Kidney Disease 2018. *Clin Exp Nephrol* 2019;**23**:1–15. https://doi.org/10.1007/s10157-018-1648-1
36. Matsuo S, Imai E, Horio M *et al*. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;**53**:982–92. https://doi.org/10.1053/j.ajkd.2008.12.034
37. Osanami A, Tanaka M, Furuhashi M *et al*. Increased LDL-cholesterol level is associated with deterioration of renal function in males. *Clin Kidney J* 2022;**15**:1888–95. https://doi.org/10.1093/ckj/sfac111
38. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;**44**:837–45. https://doi.org/10.2307/2531595
39. Pencina MJ, D'Agostino RB, Sr., Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med* 2011;**30**:11–21. https://doi.org/10.1002/sim.4085
40. Pencina MJ, D'Agostino RB, Pencina KM *et al*. Interpreting incremental value of markers added to risk prediction models. *Am J Epidemiol* 2012;**176**:473–81. https://doi.org/10.1093/aje/kws207
41. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013;**48**:452–8. https://doi.org/10.1038/bmt.2012.244
42. Neumiller JJ, Alicic RZ, Tuttle KR. Incorporating evidence and guidelines for personalized care of diabetes and chronic kidney disease. *Semin Nephrol* 2023;**43**:151427. https://doi.org/10.1016/j.semnephrol.2023.151427
43. Saito N, Furuhashi M, Koyama M *et al*. Elevated circulating FABP4 concentration predicts cardiovascular death in a general population: a 12-year prospective study. *Sci Rep* 2021;**11**:4008. https://doi.org/10.1038/s41598-021-83494-5
44. Kriz W, Lowen J, Grone HJ. The complex pathology of diabetic nephropathy in humans. *Nephrol Dial Transplant* 2023;**38**:2109–19. https://doi.org/10.1093/ndt/gfad052
45. Chronic Kidney Disease Prognosis C, Matsushita K, van der Velde M *et al*. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010;**375**:2073–81.
46. Hallan SI, Matsushita K, Sang Y *et al*. Age and association of kidney measures with mortality and end-stage renal disease. *JAMA* 2012;**308**:2349–60. https://doi.org/10.1001/jama.2012.16817
47. Tanaka M, Gohda T, Kamei N *et al*. Associations between circulating levels of FABP4 and TNF receptors are more evident in patients with type 2 diabetes mellitus than in patients with type 1 diabetes mellitus. *Endocr Connect* 2024;**13**:e240343. https://doi.org/10.1530/EC-24-0343

48. Murakoshi M, Kamei N, Suzuki Y *et al*. Circulating tumor necrosis factor-related biomarkers predict kidney function decline in Japanese patients with diabetes: an observational cohort study. *Diabetes Res Clin Pract* 2023;**206**:111017. https://doi.org/10.1016/j.diabres.2023.111017
49. Gohda T, Murakoshi M, Shibata T *et al*. Circulating TNF receptor levels are associated with estimated glomerular filtration rate even in healthy individuals with normal kidney function. *Sci Rep* 2024;**14**:7245. https://doi.org/10.1038/s41598-024-57265-x
50. Nath KA. Tubulointerstitial changes as a major determinant in the progression of renal damage. *Am J Kidney Dis* 1992;**20**:1–17. https://doi.org/10.1016/S0272-6386(12)80312-X
51. Furuhashi M, Mita T, Moniwa N *et al*. Angiotensin II receptor blockers decrease serum concentration of fatty acid-binding protein 4 in patients with hypertension. *Hypertens Res* 2015;**38**:252–9. https://doi.org/10.1038/hr.2015.2
52. Furuhashi M, Hiramitsu S, Mita T *et al*. Reduction of serum FABP4 level by sitagliptin, a DPP-4 inhibitor, in patients with type 2 diabetes mellitus. *J Lipid Res* 2015;**56**:2372–80. https://doi.org/10.1194/jlr.M059469
53. Furuhashi M, Sakuma I, Morimoto T *et al*. Treatment with anagliptin, a DPP-4 inhibitor, decreases FABP4 concentration in patients with type 2 diabetes mellitus at a high risk for cardiovascular disease who are receiving statin therapy. *Cardiovasc Diabetol* 2020;**19**:89. https://doi.org/10.1186/s12933-020-01061-0
54. Furuhashi M, Matsumoto M, Hiramitsu S *et al*. Possible increase in serum FABP4 level despite adiposity reduction by canagliflozin, an SGLT2 inhibitor. *PLoS ONE* 2016;**11**:e0154482. https://doi.org/10.1371/journal.pone.0154482
55. Palmer SC, Tendal B, Mustafa RA *et al*. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ* 2021;**372**:m4573. https://doi.org/10.1136/bmj.m4573

Received: 30.8.2024; Editorial decision: 13.2.2025