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REVIEW

Urinary L-FABP: A Novel Biomarker for Evaluating Diabetic Nephropathy Onset and Progression. A Narrative Review

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ABSTRACT

Patients with diabetes mellitus (DM) are at risk of developing diabetic nephropathy (DN), a condition whose onset and progression are linked to increased morbidity and mortality. Therefore, early recognition is crucial. Presently, this relies on the albumin excretion rate (AER) and glomerular filtration rate (GFR). Nevertheless, DN eventually affects patients with normal AER and GFR. Thus, further easy-to-handle biomarkers of DN onset/worsening are needed. Liver-type fatty acid-binding protein (L-FABP) has been associated with renal damage and could help predict/diagnose DN. We performed a literature selection to evaluate the performance of urinary excretion of such biomarker (urinary-L-FABP:uL-FABP) in predicting/diagnosing DN and its progression in diabetes. We evaluated 635 publications, 21 of which were included. Of these, 14 have cross-sectional design/arms and ten longitudinal design/arms. Cross-sectional studies showed uL-FABP to correlate with DN onset and severity in type-1 DM and type-2 DM, besides being higher than in healthy controls in the case of normoalbuminuria. Longitudinal studies showed baseline uL-FABP to predict DN onset in normoalbuminuric patients with T1DM and DN progression independently of diabetes type. The results suggest that uL-FABP is a marker of tubular damage detectable before increased albumin excretion and can represent the earliest sign of DN. Indeed, it discloses its onset and

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often predicts its severity in T2DM and patients with T1DM. Currently, uL-FABP can be routinely assessed and, being available as a point-of-care fast-test kit, may also become an easy-to-handle diagnostic tool for outpatients. In conclusion, uL-FABP represents a user-friendly biomarker of DN and can even predict DN progression in T2DM and T1DM over time.

Keywords: Diabetic nephropathy; Liver-type fatty acid-binding protein; Urinary biomarker

Key Summary Points
Diabetic nephropathy (DN) is the first cause of chronic kidney disease and end-stage renal disease worldwide, the detection of its onset and progression are crucial. Cost-effective early biomarkers of DN are advisable and needed.
Liver-type fatty acid-binding protein (L-FABP) has been associated with renal damage and has been reported to help predict/diagnose DN even before the onset of albuminuria.
We performed a review of the literature reporting on the diagnostic performance of urinary L-FABP as a potential point-of-care diagnostic tool for DN in patients with type 1 and type 2 diabetes.
The scientific evidence reviewed supports the idea that urinary L-FABP represents an easy-to-handle biomarker of DN in type 2 and type 1 diabetes, even predictive of its progression over time.

INTRODUCTION

Patients with type 1 and type 2 diabetes mellitus (T1DM and T2DM) are at high risk of developing diabetic nephropathy (DN). This complication is the most common cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD), affecting approximately half of these patients [1]. DN significantly increases the risk of cardiovascular disease (CVD) and mortality and often necessitates costly, quality-of-life-disrupting renal replacement therapies, such as dialysis or kidney transplantation. Accordingly, its early prediction is crucial for timely interventions to stop or slow its natural progression [2]. For these reasons, monitoring renal function through a fast, reliable, and easy-to-handle method in T1DM and T2DM is clinically crucial [1]. Generally, laboratory findings of DN range from microalbuminuria to macroalbuminuria and increased plasma creatinine/decreased glomerular filtration rate (GFR) [1]. Compared to plasma creatinine, albuminuria is time- and cost-effective for outpatients, requiring only a commercial dipstick for a urine spot test. However, since about 20% of diabetic patients with CKD may be normoalbuminuric [3, 4], repeated efforts have been made to find a suitable urinary DN biomarker without microalbuminuria [5, 6]. DN is one of the most common complications of diabetes, accounting for 25–50% of T1DM and 45–57% of patients with T2DM, more than half (52.5%) of whom suffer from moderate-to-severe disease (stage 3-4) [7, 8]. The most widely used method to assess impaired renal function is AER in terms of spot urine albumin/creatinine ratio (ACR) [9, 10]. Despite being fast and cost-effective, such measurement is only partially reliable, as several patients with DN do not display increased AER [11]. Also, the present best eGFR calculator (CKD-EPI) in people with diabetes has the bias of depending only on creatinine, age, and sex, so eGFR underestimation is quite likely to occur [12, 13].

Liver-type fatty-acid binding protein (L-FABP), also known as FABP1, is an intracellular carrier protein of free fatty acids expressed in several organs, such as the liver, intestine, lungs, pancreas, and kidneys [14]. Its increased expression correlates with local and systemic inflammation and, within the kidney, is predominantly found in proximal tubules [14]. Increased levels of urinary and serum L-FABP have been correlated with intestinal ischemia, ischemic damage caused by renal transplantation or cardiac bypass surgery, obesity, and also with hepatic tumorigenesis [15–18]. High urinary L-FABP (uL-FABP) levels are associated with tubule-interstitial

damage [19]. Moreover, there is increasing evidence that uL-FABP excretion is associated with the protein-to-creatinine ratio, thus correlating with DN onset and progression [20]. Finally, by detecting the positive effects of therapeutic intervention on DN, uL-FABP can be used as an accurate marker of individual responsiveness to reno-protective treatment protocols [21–23].

With the above-mentioned indications, the healthcare system in Japan reimburses its clinical use. Considering it a highly desirable early marker of DN for widespread utilization, we performed a review of the literature with the aim of evaluating uL-FABP in terms of diagnostic performance to detect the onset and predict the progression of DN in patients with T2DM and T1DM.

METHODS

Two authors (MM and SG) searched the literature through the most relevant electronic databases (MEDLINE/PubMed, SCOPUS, EMBASE, Web of Science) by entering the following Boolean string: "L-FABP AND diabetes AND nephropathy OR L-FABP AND diabetes AND kidney disease OR liver-type fatty acid-binding protein AND diabetes AND nephropathy OR liver-type fatty acid-binding protein AND diabetes AND kidney disease" keywords. Also, a free-text search was performed by entering the same keywords. We retrieved 90 papers *in-extenso* from Medline/PubMed, 78 from EMBASE, 354 from Scopus, and 113 from Web of Science until September 2022. After removing duplicates, the authors reviewed all identified articles and discarded those not pertinent to the aim. In particular, the inclusion criteria were original papers published in English on the diagnostic performance of urinary L-FABP for predicting DN in humans. Conversely, the exclusion criteria for the study design were papers published in non-English language or unrelated to diabetes or L-FABP, non-human studies, reviews, abstracts, missing DN-related data, studies reporting data that duplicated those already included in the review, and interventional studies exclusively evaluating the effects of a specific therapy, therefore not aimed at the diagnostic performance of L-FABP. The PRISMA flow diagram is shown in Fig. 1.

We selected 21 cross-sectional and/or longitudinal studies for inclusion in this review. Due to their inhomogeneity in terms of statistical analysis and data presentation, we refrained from performing a meta-analysis and preferred to extract their most significant results and summarize them into dedicated tables.

Patients are classified as normoalbuminuric with an ACR < 30 mg/g creatinine, microalbuminuric with an ACR of 30–299 mg/g creatinine, and macroalbuminuric with an ACR ≥ 300 mg/g creatinine. By definition, patients with diabetic nephropathy (DN) had albuminuria, reduced glomerular filtration rate (GFR), or both [1]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

SEARCH RESULTS

In the 21 selected studies (Tables 1 and 2), L-FABP measurement primarily relied on commercially available, clinically validated enzyme-linked immunosorbent assay (ELISA) kits and DN assessment on albumin excretion rate (AER) or albumin-to-creatinine ratio (ACR) [9]. We assessed uL-FABP's ability to detect DN onset and predict DN progression by analyzing cross-sectional and longitudinal evaluations.

The included studies had an exclusively cross-sectional design in 11 cases [20–22, 24–31], an exclusively longitudinal design in seven cases [32–38], and a both cross-sectional and longitudinal evaluation in three cases [39–41].

CHARACTERISTICS OF THE INCLUDED STUDIES

Cross-Sectional Studies

Fourteen studies reported cross-sectional results (ten on T2DM and four on patients with T1DM). The ten studies on patients with T2DM enrolled 3126 adults with T2DM ranging from

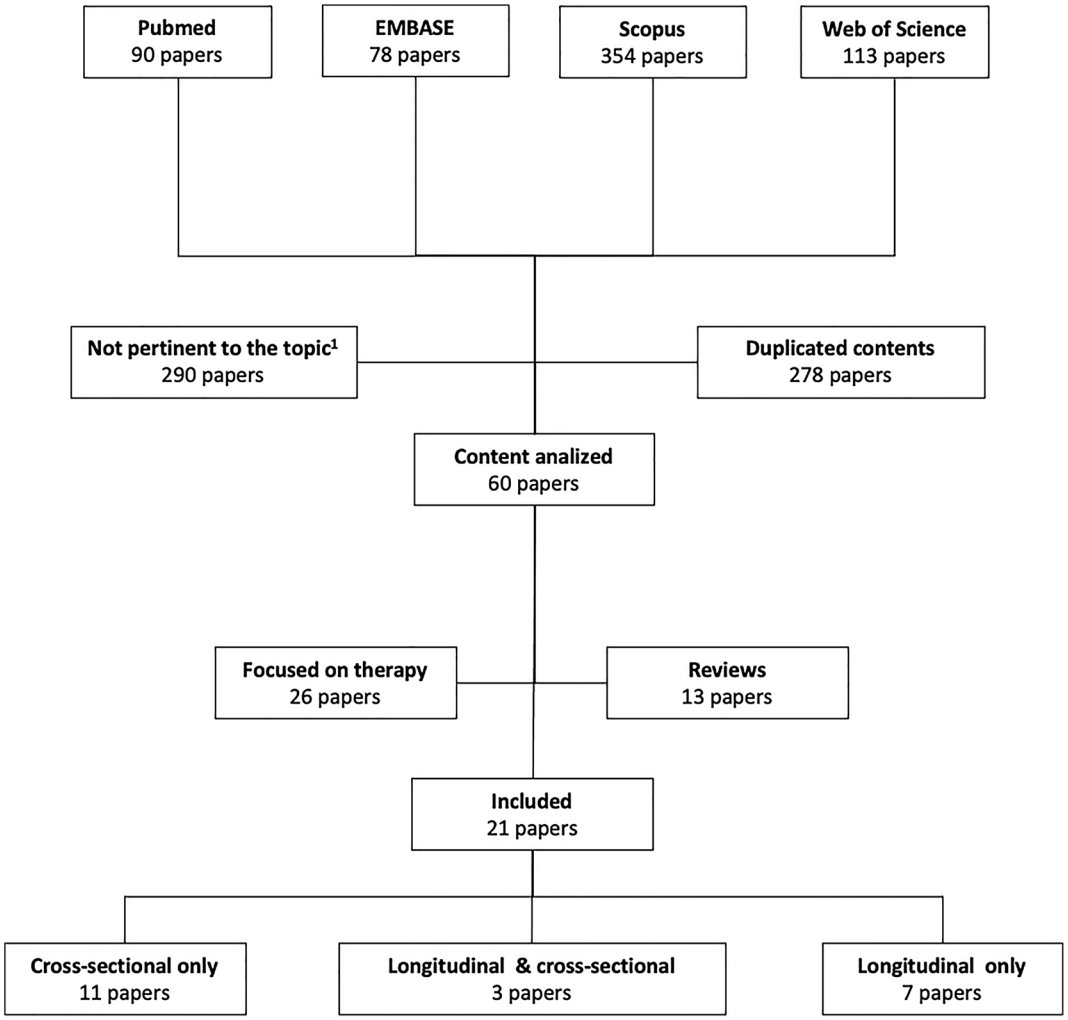

Fig. 1 PRISMA flow diagram for the selection of the papers included in the present review [1]. The papers were considered "not pertinent to the topic" when conducted exclusively on animal/cellular experimental models, unavailable in extenso, in a non-English language, not including patients with diabetes, data on DN, and presented as editorials or non-original publications. The included studies had an exclusively cross-sectional design in 11 cases [9–11, 14–21], an exclusively longitudinal design in seven cases [22–28], and both cross-sectional and longitudinal evaluation in three cases [29–31]

normoalbuminuria, micro-albuminuria, macro-albuminuria, and DM-related CKD [20, 21, 24–27, 29, 30, 40, 41]. Five papers also included 574 healthy control (HC) subjects without T2DM or CKD [20, 21, 25, 27, 30, 40]. The geographical provenience of the studies was the Far East (12 studies) and Northern Europe (two studies from Germany).

The four studies that dealt with patients with T1DM included 2440 subjects and 327 controls as a whole [22, 28, 31, 39]. The geographical provenience areas were Northern Europe (two studies), Egypt, and South Korea (see Table 1 for further details).

The cross-sectional analyses measured uL-FABP using commercial and self-made non-commercial ELISA kits or enzyme-chemiluminescent immunosorbent assay (ECLIA) kits (see Table 1 for details on which kit was used in each study). uL-FABP levels were found to be significantly higher in normoalbuminuric T1DM and patients with T2DM than in HC in five of six

Table 1 Cross-sectional studies correlating L-FABP to DN in type 1 and type 2 diabetes mellitus in chronological order of publication

Author, year, [Ref. #]	Type of DM	Country	No. of patients (severity of DN)	Control group (*n*)	DN severity	Endpoints	Type of sample	Type of urinary L-FABP tests (vendor)	Results	Statistics
Suzuki, 2005, [24]	2	Japan	356 (216*/64#/46†/30‡)	No	Normoalbuminuric Microalbuminuric Macroabuminuric Renal failure	Correlation with DN (ACR)	First-morning urine	ELISA (CMIC Co. Tokyo, Japan)	1) Increase with an increase in urinary albumin and 2) Renal failure levels	1) $p < 0.001$ 2) $p < 0.001$
Nakamura, 2005, [21]	2	Japan	58 (12*/20#/14†/12‡)	Yes (20)	Normoalbuminuric Microalbuminuric Macroabuminuric Renal failure	Correlation with DN (AER)	24-h urine	ELISA (ns)	1) Normoalbuminuric = controls 2) Increase with an increase in urinary albumin levels	1) $p < 0.05$ 2) $p < 0.001$
Nielsen, 2009, [22]	1	Denmark	103 (58*/45#)	Yes (57)	Normoalbuminuric Microalbuminuric	Correlation with DN (AER)	First-morning urine	ELISA) (ns)	1) Normoalbuminuric > Controls 2) Increase with an increase in urinary albumin levels	1) $p < 0.05$
von Eynatten, 2010, [25]	2	Germany	130 (ns)	Yes (40)	Any DN with CrClearance > 60 ml/min	Correlation with DN (AER) and anemia	24-h urine	ELISA (CMIC Co. Tokyo, Japan)	1) DN group > controls 2) Correlated with AER 3) Correlated with anemia	1) $p < 0.001$ 2) OR: 1.432 (1.087–2.078) 3) OR: 6.060 (1.652–22.232)
Kamijo-Ikemori, 2011, [40]	2	Japan	140 (64*/30#/27†/12‡)	Yes (412)	Normoalbuminuric Microalbuminuric Macroabuminuric Renal failure	Correlation with DN (eGF, AER)	Spot urine	ELISA (CMIC Co. Tokyo, Japan)	1) Normoalbuminuric > Control group, 2) Increase with an increase in urinary albumin and with renal failure	$p < 0.05$

Table 1 continued

Author, year, [Ref. #]	Type of DM	Country	No. of patients (severity of DN)	Control group (*n*)	DN severity	Endpoints	Type of sample	Type of urinary L-FABP tests (vendor)	Results	Statistics
Panduru, 2013, [40]	1	Finland	2246 (1549*/334#/363†)	Yes (208)	Normoalbuminuric Microalbuminuric Macroalbuminuric	Correlation with DN (AER)	24-h urine	ELISA (Roche Diagnostics GmbH, Mannheim, Germany)	1) Normoalbuminuric > controls 2) Increase with an increase in urinary albumin levels	HR 4.10 (95% CI 2.31–7.27; $p = 0.001$)
Kim, 2014, [40]	2	South Korea	118 (#†49.2%/‡42.4%)	No	Any DN	Correlation with DN (NAPCR)	Random spot urine	ELISA (CMIC Co. Tokyo, Japan)	LFABP correlated with NAPCR	$R = 0.43$; $p = 0.001$
Holzscheiter, 2014, [27]	nr	Germany	263 [overall - 29 (11%) diabetes]	59	Any DN	Correlation with DN (AER)	First-morning urine	ECLIA (Roche Diagnostics GmbH, Mannheim, Germany)	uLFABP showed better diagnostic performance in detecting tubular injury	
Viswanathan, 2015, [20]	2	South India	65 (22*/22#/21†)	Yes (13)	Macroalbuminuric	Correlation with DN (eGFR)	Spot urine	Solid phase ELISA (HK404, Hycult Biotechnology, Uden, The Netherlands)	1) Increase with an increase in urinary albumin levels	$p = 0.005$
Abd El Dayem, 2016, [28]	1	Egypt	62	Yes (30)	Normoalbuminuric Microalbuminuric	Correlation with DN (ACR)	First-morning urine	ELISA (Biovendor Laboratory Medicine, Brno, Czech Republic)	1) Normoalbuminuric > controls 2) Normoalbuminuric < macroalbuminuric 3) Corr. with albumin/creatinine ratio	1) $p < 0.0001$ 2) $p < 0.0001$ 3) $r = 0.82$; $p = 0.0001$

Table 1 continued

Author, year, [Ref. #]	Type of DM	Country	No. of patients (severity of DN)	Control group (*n*)	DN severity	Endpoints	Type of sample	Type of urinary L-FABP tests (vendor)	Results	Statistics
Ito, 2017, [41]	2	Japan	788	No	Normoalbuminuric Albuminuric	Correlation with DN (ACR) and metabolic status	nr	ELISA (CMIC Co. Tokyo, Japan)	L-FABP correlated with 1) eGFR in normoalbuminuric 2) ACR in albuminuric	1) OR: 0.98 (0.96–1.00); $p = 0.01$
Gohda, 2018, [29]	2	Japan	314 (No-CKD:241; NA-DKD:73)	No	Normoalbuminuric	Correlation with DN (eGFR)	nr	ELISA (CMIC Co. Tokyo, Japan)	L-FABP correlated with ACR	$R = 0.35$ < 0.001
Ngan, 2020, [30]	2	Vietnam	106 (*41/#47/†18)	Yes (30)	Normoalbuminuric Microalbuminuric Macroabuminuric	Correlation with DN (ACR/eGFR)	First-morning urine	LEIA (Sekisui Medical Co., Ltd, Japan)	1) Normoalbuminuric > controls 2) L-FABP correlated with eGFR better than EGR	1) $p < 0.001$ 2) AUC:0.98 vs. 0.78
Suh, 2015, [31]	1	South Korea	29 (*20/#9)	Yes (32)	Normoalbuminuric Microalbuminuric	Correlation with DN (ACR/eGFR)	Random spot urine	ELISA R&D Systems (Minneapolis, MN, USA)	1) Normoalbuminuric = controls 2) Microalbuminuric < macroalbuminuric 3) LFABP correlated with HbA1c	2) $p = 0.03$ 3) $p = 0.005$

ns not specified, *ELISA* enzyme-linked immunosorbent assay, *CLEIA* Chemi-luminescent enzyme immunosorbent assay, *LEIA* latex-enhanced immunoturbidimetric assay, *HR* hazard ratio, *CI* confidence interval, *DN* diabetic nephropathy, *AER* albumin excretion rate, *UAE* urinary albumin excretion, *NAPCR* non-albumin protein-to-creatinine ratio, *ACR* albumin-to-creatinine ratio, *eGFR* electronically calculated glomerular filtration rate, *NA-DKD* normo-albuminuric diabetic kidney disease, *CKD* chronic kidney disease

*Normoalbuminuric

#Microalbuminuric

†Macroalbuminuric

‡Renal failure

studies concerning T2DM and all four on T1DM. Moreover, in all the studies included in this analysis, independently of being measured on random spot urine, first-morning urine, or 24-h urine samples, uL-FABP significantly correlated with albuminuria or DN as measured by eGFR AER or ACR.

T2DM Cross-Sectional Studies

The cross-sectional studies that enrolled the higher number of patients with T2DM were from Japan, i.e., Suzuki et al. 2005 [24] and Ito et al. 2017 [41]. Suzuki et al. recruited 356 adult outpatients with T2DM from the Division of Nephrology and Hypertension of a tertiary center in Tokyo, Japan, and stratified them into four ACR classes. Two hundred sixteen patients had normoalbuminuria, 64 microalbuminuria, 46 macroalbuminuria, and 30 renal failure. Being the study from 2005, by design, the authors referred to the 2004 American Diabetes Association position statement on nephropathy in diabetes [42]. Therefore, they defined patients with a serum creatinine concentration ≥ 2.0 mg/dl as having renal failure; those with serum creatinine ≤ 2.0 mg/dl were classified as normoalbuminuric if ACR was ≤ 30 mg/g creatinine, as microalbuminuric if ACR was 30–299 mg/g creatinine, and as having clinical albuminuria if ACR was ≥ 300 mg/g creatinine. The authors found that in patients with macroalbuminuria and renal failure, uL-FABP (measured on first-morning urine spot samples) was significantly increased compared to those with normo- and micro-albuminuria ($p < 0.001$). Moreover, the difference between macroalbuminuric and renal failure patients was also statistically significant ($p < 0.001$). In univariate and multivariate analysis, the only variables significantly associated with uL-FABP were urinary albumin (directly) and eGFR by MDRD (inversely). The authors concluded that uL-FABP might be associated with advanced kidney disease in T2DM [24]. In the other study from Ito et al., uL-FABP was measured in random spot urine samples in 788 outpatients with T2DM reporting for routine screening to the Department of Diabetes, Metabolism and Kidney Disease of a tertiary center in Tokyo, Japan. Four hundred sixty-six patients had normoalbuminuria, 218 microalbuminuria, and 104 macroalbuminuria. In this study, which also included a longitudinal evaluation, the authors found that uL-FABP (ELISA Kit, CMIC Co. Tokyo, Japan) significantly correlated with HbA1c levels, systolic blood pressure, and eGFR in normoalbuminuric patients and with serum HDL cholesterol, ACR, and renin–angiotensin system (RAS) inhibitors treatment in micro-/macro-albuminuric ones. The authors concluded that uL-FABP correlated with part of the metabolic derangements of T2DM normoalbuminuric patients (levels of HbA1c and systolic blood pressure) and vascular complications in albuminuric subjects [41].

T1DM Cross-Sectional Studies

Regarding T1DM studies, the study enrolling the higher number of patients was the one from Panduru et al. [39]. This paper reported part of the Finnish Diabetic Nephropathy Study (FinnDiane). In this multicenter nationwide study based in Finland, 2246 adult patients with T1DM were evaluated and compared to a cohort of 208 healthy controls. A total of 1549 patients had normoalbuminuria, 334 had microalbuminuria, and 363 had macroalbuminuria. At the cross-sectional baseline analysis, 24-h uL-FABP levels, as measured by an ELISA commercial kit (Cobas Elecsys 411 Immunoanalyzer, Roche Diagnostics GmbH, Mannheim, Germany) on spot urine samples, were significantly higher in patients with T1DM with normal AER than controls, in microalbuminuric than normoalbuminuric patients, and macroalbuminuric than microalbuminuric patients ($p < 0.001$, for each). The study also included a longitudinal evaluation (discussed below). From their results, the authors concluded that uL-FABP, i.e., a parameter closely associated with structural and functional tubular damage, was a reliable predictor of disease progression in patients with T1DM at all DN stages, even with normal AER [39].

Longitudinal Studies

Ten of the selected studies included a longitudinal observation of uL-FABP, intending to

Table 2 Longitudinal studies correlating L-FABP to DN progression in type 1 and type 2 diabetes mellitus

Author, year, [Ref. #]	Type of DM	Country	No. of patients	Follow-up (years)	DN baseline Severity	Endpoints	Type of sample	Type of L-FABP tests	Results	Notes
Nielsen, 2010, [32]	1	Denmark	165	18	Non-albuminuric	Increase in albuminuria	24-h urine	ELISA (ns)	Baseline u-LFABP predicted: Microalbuminuria* Macroalbuminuria# Mortality§	*HR:2.21 (1.1–4.6) #HR2.6 (1.2–5.4) §HR:3 (1.3–7.0)
Panduru, 2013, [32]	1	Finland	2246	6-10	All stages of DN (No dialysis or transplant)	Progression of albuminuria; need of dialysis or transplant	24-h urine	ELISA (Roche Diagnostics GmbH, Mannheim, Germany)	Baseline u-LFABP predicted Progression from: Normoalbuminuria* Macroalbuminuria#	*OR 2.97 (1.50–5.90) #1.17 (1.10–1.24)
Nielsen, 2011, [33]	1	Denmark	63	3	Macroalbuminuric (GFR > 60 ml/min)	Decline in GFR	nr	ELISA (Roche, Penzberg, Germany)	u-LFABP was not related to GFR decline	$R = 0.1, p = 0.5$
Kamijo-Ikemori, 2011, [40]	2	Japan	104	4	All stages of DN (No dialysis or transplant)	Increase in albuminuria and creatinine	Spot urine	ELISA (CMIC Co. Tokyo, Japan)	u-LFABP related to DN progression	HR: 9.46 (2.24–39.92)

Table 2 continued

Author, year, [Ref. #]	Type of DM	Country	No. of patients	Follow-up (years)	DN baseline Severity	Endpoints	Type of sample	Type of L-FABP tests	Results	Notes
Araki, 2013, [34]	2	Japan	618	12 (11–15)	No-albuminuric Micro-albuminuric	Dialysis CV events	24-h urine	ELISA (ns)	u-LFABP related to dialysis occurrence and CVD events	HR: 2.16 (95% CI 1.23–3.79)
Abd El Dayem, 2017, [35]	1	Egypt	48	3	NR	Progression to/of albuminuria	First-morning urine	ELISA Biovendor Laboratory Medicine, Brno, Czech Republic)	u-LFABP>10.3 related to DN progression	AUROC:0.941 (0.862-0.982) Sens: 09.0 Spec: 87.7 PPV: 6.65
Ito, 2017, [41]	2	Japan	668	6 months	Normoalbuminuric Albuminuric	Progression to/of albuminuria	nr	ELISA (CMIC Co. Tokyo, Japan)	1) u-LFABP increased in normoalbuminuric patients 2) Influenced by HbA1c changes	1) $p < 0.01$ 2) $p < 0.01$
Ishizu, 2020, [36]	1 and 2	Japan	201 (61-T1DM 178-T2DM)	2	All stages of DN (no dialysis or transplant)	Progression of DN (eGFR)	First-morning urine	CLEIA (ns)	1) u-LFABP was associated with eGFR at baseline 2)	1) OR: 2.3 (p = 0.007)

Table 2 continued

Author, year, [Ref. #]	Type of DM	Country	No. of patients	Follow-up (years)	DN baseline Severity	Endpoints	Type of sample	Type of L-FABP tests	Results	Notes
Fufaa, 2015, [37]	2	American Pima Indians	260	14	Normoalbuminuric Microalbuminuric Macroalbuminuric	Development of ESRD	First-morning urine	ELISA (CMIC Co. Tokyo, Japan)	1) u-LFABP/Cr was associated with ESRD (inversely) 2) LFABP higher in macroalbuminuria	1) HR: 0.40 (0.19-0.83) 2) $p < 0.001$
Ide - 2022, [37]	2	Japan	2685	5	All stages of DN (no dialysis)	Progression of DN (eGFR)	Random spot urine	ELISA (CMIC Co. Tokyo, Japan)	LFABP predicted ESRD in baseline albuminuric patients	HPR:2.32 (1.84–2.93) < 0.0001

HR hazard ratio, *AUROC* area under the receiving operator curve, *GFR* glomerular filtration rate, *DN* diabetic nephropathy, *CV* cardiovascular, *ELISA* enzyme-linked immuno-sorbent assay, *CLEIA* chemiluminescent enzyme immuno-assay, *ESRD* end-stage renal disease, *Cr* creatinine

evaluate the prognostic performance of such a test on DN onset and evolution. Their features are summarized in Table 2.

Five studies dealt with T2DM [34, 37, 38, 40, 41], four with T1DM [32, 33, 35, 39], and one included T1DM and patients with T2DM [36]. Overall, the authors analyzed 833 T1DM and 4513 patients with T2DM (with a follow-up time ranging from 6 months to 18 years) by measuring uL-FABP on 24-h urine samples, spot urine, or first-morning urine samples according to the above-mentioned ELISA or ECLIA methods. All of the studies had the endpoint to evaluate uL-FABP predictive value on CKD onset and progression by assessing the rate of albuminuria increase and GFR/eGFR decline, ESRD onset, or the requirement for dialysis or kidney transplant. All of the studies, within their specific endpoints, found that uL-FABP could predict DN onset and progression.

T2DM Longitudinal Studies

In particular, the study enrolling the highest number of patients with T2DM, recently published by Ide et al., recruited 2685 subjects from the "Fukuoka Diabetes Registry" study, i.e., a multicenter prospective longitudinal study, included 5131 adults (aged ≥ 20 years) with T2DM in the Fukuoka Prefecture, Japan with (i) eGFR ≥ 15 ml/min/1.73 m^2 at baseline; (ii) ≥ 3 annual eGFR recordings during a 5-year follow-up; (iii) simultaneous measurement of urinary NGAL, KIM-1, L-FABP, and albumin [38]. A total of 1634 (60.85%) patients had normal, and 1051 (39.15%) increased albuminuria at baseline. The latter were significantly older, had longer diabetes durations, higher BMI, blood pressure, HbA1c, and proportion of RAS inhibitor use, and, as an even more relevant issue, lower eGFR, and increased urinary L-FABP. During the 5-year follow-up, an over 30% decline in eGFR was observed in 17% of the participants. At multivariable analyses adjusted for age, sex, diabetes duration, BMI, blood pressure, smoking, HbA1c, RAS-inhibitors utilization, and eGFR as confounding factors, uL-FABP turned out to be capable of predicting an over 30% eGFR decline only in those with baseline ACR ≥30 mg/gCr (HR: 2.78–2.24–3.45 95% CI) independently of ACR and eGFR baseline levels. Moreover, the three combined urinary markers of tubular injury (NGAL + KIM-1 + uL-FABP) increased the predictive power of the above association (HR: 7.00–4.69–10.47 95% CI). The authors concluded that the three tubular injury markers might help identify and aggressively treat high-risk albuminuric East Asian patients to reduce the ESRD onset [38].

The other studies on T2DM were also published principally in Japan [34, 36, 40, 41], with only one on American Pima Indians [37]. As stated above, all the longitudinal studies demonstrated, within their endpoints, an association between L-FABP and DN progression (see Table 2).

T1DM Longitudinal Studies

Similarly, the previously mentioned large study from Panduru et al., involving north-European subjects included in the Finn-Diane cohort, analyzed longitudinally uL-FABP ability to predict DN progression in patients with T1DM for a median follow-up of 5.8 years [39]. In detail, 68.97% of the 2246 patients in the study were normoalbuminuric, 14.87% micro-albuminuric, and 16.16% were macro-albuminuric. The definition of DN progression relied on shifting from one stage to the following based on AER or developing ESRD (i.e., the need for dialysis or a kidney transplant). At univariate and Cox regression analyses, L-FABP independently predicted the progression from normoalbuminuria to microalbuminuria (HR: 2.97–1.49-5.89 95% CI, $p < 0.002$), from microalbuminuria to macroalbuminuria (HR: 1.40–1.10–1.79 95% CI, $p = 0.006$) and from macroalbuminuria to ESRD (HR: 1.24–1.19-1.28 95% CI, $p < 0.001$), and the association persisted after adjusting for potentially interfering medications (except for antihypertensive drugs, including ACE inhibitors). The authors concluded that uL-FABP was an independent predictor of progression across all stages of DN in patients with T1DM [39].

The other studies on T1DM are from Europe [32], Egypt [35], and Japan [36]. All of the studies demonstrated a correlation between L-FABP levels and DN progression variously evaluated, except the one from Nielsen, on 63 Danish

T1DM macroalbuminuric patients, in which uL-FABP was not correlated to GFR decline (see Table 2) [33].

DISCUSSION

As extensively discussed in the Introduction, there is a strong need for a sensitive DN biomarker, possibly endowed with reliable disease progression-predicting capacity, especially in the early stages, to enable clinicians to slow down and even stop it with adequate treatment [43, 44]. Indeed, we must point out that DN cannot be reverted after reaching its clinically detectable phase. Therefore, early diagnosis is crucial to start the best pharmacological and lifestyle interventions against its progression toward advanced stages until dialysis or transplant [45, 46]. uL-FABP is a marker of renal tubular damage, a condition emerging in the early stages of DN and promoting renal disease progression [47, 48]. In addition, uL-FABP is also available as a POC (point-of-care) fast spot urine test (e.g., the simplified kit, Dip-test, CMIC Co Ltd, Tokyo, Japan). Such formulation is affordable and does not need costly equipment or procedures, which makes it particularly suited for population screening programs, especially in low-income settings [49]. The majority of cross-sectional studies including a control group, analyzed in the present review, showed that, in the presence of DN, uL-FABP levels were significantly higher in T1DM and patients with T2DM with normal AER than in healthy controls, thus suggesting that it could detect renal impairment in patients with diabetes earlier than AER.

Moreover, those papers also spotted a significant correlation with the DN severity, being uL-FABP levels progressively increased along with different renal impairment stages (normo- > micro- > macro-albuminuric > CKD with increased serum creatinine). This feature was confirmed both in T1DM and T2DM cohorts. Of particular note, the study from Ito et al., including a large cohort of patients with T2DM studied by cross-sectional and longitudinal analysis, reported that uL-FABP also correlated with T2DM metabolic and cardiovascular risk factors (namely HbA1c, HDL, and blood pressure) [41].

Finally, according to the ten longitudinal studies, including T1DM and patients with T2DM with a follow-up time ranging from 6 months to 18 years, uL-FABP was able to predict DN onset and progression. In this particular field, the study conducted in Japan by Ide et al. on patients with T2DM is of great notice [38]. In this registry study, including a large cohort of patients (2685 subjects) with all DN stages, uL-FABP did not predict DN in normoalbuminuric patients. This finding was likely because a ≥ 30 increase in % eGFR over 5 years of follow-up was the clinical endpoint chosen to spot DN onset and progression. Therefore, it is difficult to imagine (and also desirable) that a significant proportion of patients could reach such a worsening starting from a normal glomerular filtration rate, given the progress made in the diagnosis and prevention of complications in diabetes. However, the paper demonstrated that uL-FABP was able to predict a significant eGFR decline (≥ 30%) in already albuminuric subjects, even after adjusting for confounding factors such as age, sex, diabetes duration, blood pressure, smoking, HbA1c, therapy (RAS inhibitors), and baseline eGFR. This finding is significant because uL-FABP increase is a typical expression of tubular damage, probably one of the first histologically relevant signs in DN pathophysiology. Subsequently, after the first damage step, the pathophysiological course of DN most often switches to glomerular involvement and impaired barrier function with albuminuria, overt proteinuria, increased serum creatinine levels, and reduced GFR [50]. Therefore, the fact that this tubular damage marker was shown to predict the onset and progression of glomerular involvement is important and indicates that uL-FABP can detect renal impairment progression in microalbuminuric patients with T2DM and that its diagnostic power is also relevant in advanced DN stages as a predictor of disease progression over time [38].

Longitudinal T1DM cohorts replicated these findings. This concept applies particularly to the study by Panduru et al., whose endpoints were probably more likely to be verifiable from a pathophysiological point of view by defining DN progression as the switch from one stage to

another (normo-, micro-, macro-albuminuria, and ESRD) instead of an increase in eGFR. With this definition of DN progression, uL-FABP could predict it in all patients with T1DM (including normoalbuminuric subjects) after adjusting for confounding factors such as interfering medications [39].

Taken as a whole, the results of these studies demonstrated that uL-FABP could be a promising biomarker not only in the early DN stages (characterized only by initial tubular damage) but also when glomerular damage has occurred, as a valuable predictor of disease progression, both in T1DM and T2DM.

Moreover, uL-FABP is also available as a fast point-of-care kit, not requiring a laboratory facility to collect and analyze urine and serum samples. Instead, it can easily be performed at the time of an outpatient visit. Therefore, uL-FABP could be considered a reliable and easy-to-handle candidate for screening programs in low-income settings and whenever a quick evaluation of the renal status of diabetic outpatients is required, and a laboratory is not readily accessible.

Several other urinary biomarkers have been studied as potential diagnostic tools for DN. These include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), *N*-acetyl-beta-D-glucosaminidase (NAG), alpha-1 microglobulin (A1M), beta 2-microglobulim (B2-M), and retinol-binding protein (RBP), to cite the most studied [51]. Each of these biomarkers has strengths and weaknesses, and varying degrees of accessibility based on the availability of commercial kits. However, an extensive analysis of the comparative performance with respect to uL-FABP is difficult due to the almost total absence (except in one case [37]) of direct comparative studies and would also be beyond the scope of this work.

The present review has some limitations. First of all, as already mentioned in the Methods section, the studies included were quite different in study design, statistical analysis, and data presentation; therefore, it was impossible to perform a meta-analysis of the pooled data. In particular, regarding the topic of the study design, it has to be mentioned that urinary L-FABP measurements were carried out by using several different laboratory assays (i.e., commercial and non-commercial ELISA, ECLIA, and LEIA assays) on different types of urine samples (i.e., random spot, first-morning spot, and 24-h urine). This fact may have introduced a bias in efficiently comparing each study's results. However, we must also point out that, despite these differences, all the analyzed studies reported consistent results on uL-FABP's capacity to predict DN.

Moreover, the geographical provenience of the included patients was almost entirely limited to East Asian (mostly Japanese) and north-European patients. Therefore, more studies are needed on other ethnicities to confirm the reported results of this review. Furthermore, as already mentioned, other biomarkers of tubular renal impairment have been proposed in DN [52, 53]. However, as it has already been pointed out, a direct comparison (or even an association) between these molecules and L-FABP was only reported in one study [37]. Therefore, no inference was possible on the possible different efficacy of those biomarkers other than reporting that, in a specific study, pooling biomarkers improved the predictive performance of the tests. Another limitation to be considered is that all the evaluated studies reported their results referring to the diagnosis of DN (which implicitly infers the presence of a glomerular damage) instead of that of "diabetic kidney disease" (DKD), which is a clinical diagnosis based on the presence of proteinuria, decreased eGFR, or both in diabetes, and can be caused by diverse causes (i.e., hypertensive nephrosclerosis or unresolved acute kidney failure) other than glomerular damage. Because of this, and even if L-FABP has demonstrated to predict renal alterations also when increased albuminuria is not present, we cannot conclude that L-FABP is a good predictor of DKD. However, since the major cause of DKD is DN, this fact could strengthen the idea of the usefulness of L-FABP in DN diagnosis, particularly at the normoalbuminuric stages [54, 55].

Finally, it must be mentioned that the diagnostic performance of uL-FABP in DN was already the subject of two reviews published in the past. The first, published in 2016 by Fiseha and Tamir [51], was a narrative review on the performance of several urinary biomarkers. It was focused precisely on the diagnosis of early DN, in

which a chapter was dedicated to uL-FABP. Like us, those authors concluded that uL-FABP could be a good biomarker of early DN. However, the study was only partially focused on uL-FABP and, being published in 2016, was therefore missing the studies published subsequently. The other review was published by Zhang et al. in 2022 [56]. This paper reported a series of metanalyses on the diagnostic performance of uL-FABP in predicting various stages of DN. Those authors also reached the conclusion of a good performance of such biomarker in predicting DN. However, they included only 13 of the 21 studies we evaluated. This was probably due both to the technical needs related to the execution of the metanalyses and the publication date. Moreover, the heterogeneity measurements of their pooled analyses were not below an I-square of 80%, probably demonstrating our belief that a metanalysis on this topic may not be sufficiently accurate. For these reasons, we believe that the present work has new elements that further strengthen the indication of the clinical usefulness of uL-FABP in the early diagnosis of DN.

CONCLUSIONS

In conclusion, uL-FABP assessment by mean of commercially available and clinically validated kits on either 24-h, first-morning, or random spot samples, showed excellent performance in predicting renal impairment in both T1DM and T2DM and, therefore, proving to be a good candidate for a role as a reliable and easy-to-use, point-of-care early biomarker of DN onset and progression.

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Declarations

Conflict of Interest. Sandro Gentile and Felice Strollo are Editorial board members of *Diabetes Therapy* and were not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Ersilia Satta, Giuseppina Guarino, Carmine Romano, Luisa Borgia, and Raffaele Marfella and have no financial interests (no personal, financial, commercial, or academic conflicts of interest) to declare concerning the present study. The corresponding author, Mario Masarone, is a consultant for ESTOR SpA regarding this study.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. Afkarian M, Zelnick LR, Hall YN, Heagerty PJ, Tuttle K, Weiss NS, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988–2014. JAMA. 2016;316:602–10.

2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–305.

3. Rigalleau V, Lasseur C, Raffaitin C, Beauvieux MC, Barthe N, Chauveau P, et al. Normoalbuminuric renal-insufficient diabetic patients: a lower-risk group. Diabetes Care. 2007;30:2034–9.

4. Robles-Osorio ML, Sabath E. Tubular dysfunction and non-albuminuric renal disease in subjects with type 2 diabetes mellitus. Rev Invest Clin. 2014;66:234–9.

5. Jain S, Rajput A, Kumar Y, Uppuluri N, Arvind AS, Tatu U. Proteomic analysis of urinary protein markers for accurate prediction of diabetic kidney disorder. J Assoc Physicians India. 2005;53:513–20.

6. Nauta FL, Boertien WE, Bakker SJL, van Goor H, van Oeveren W, de Jong PE, et al. Glomerular and tubular damage markers are elevated in patients with diabetes. Diabetes Care. 2011;34:975–81.

7. Levin A, Tonelli M, Bonventre J, Coresh J, Donner J-A, Fogo AB, et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. Lancet. 2017;390:1888–917.

8. Caramori ML, Rossing P. Diabetic Kidney Disease. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, et al. (eds.). *Endotext*. South Dartmouth (MA) 2000.

9. American Diabetes A. Standards of medical care in diabetes–2009. Diabetes Care. 2009;32(Suppl 1):S13-61.

10. Remuzzi G, Schieppati A, Ruggenenti P. Clinical practice. nephropathy in patients with type 2 diabetes. N Engl J Med. 2002;346:1145–51.

11. Chen C, Wang C, Hu C, Han Y, Zhao L, Zhu X, et al. Normoalbuminuric diabetic kidney disease. Front Med. 2017;11:310–8.

12. Salem NAB, El Helaly RM, Ali IM, Ebrahim HAA, Alayooti MM, El Domiaty HA, et al. Urinary cyclophilin A and serum cystatin C as biomarkers for diabetic nephropathy in children with type 1 diabetes. Pediatr Diabet. 2020;21:846–55.

13. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Annal Intern Med. 2009;150:604–12.

14. 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.

15. Thuijls G, van Wijck K, Grootjans J, Derikx JP, van Bijnen AA, Heineman E, et al. Early diagnosis of intestinal ischemia using urinary and plasma fatty acid binding proteins. Ann Surg. 2011;253:303–8.

16. Shi J, Zhang Y, Gu W, Cui B, Xu M, Yan Q, et al. Serum liver fatty acid binding protein levels correlate positively with obesity and insulin resistance in Chinese young adults. PLoS One. 2012;7:e48777.

17. Portilla D, Dent C, Sugaya T, Nagothu KK, Kundi I, Moore P, et al. Liver fatty acid-binding protein as a biomarker of acute kidney injury after cardiac surgery. Kidney Int. 2008;73:465–72.

18. Ku CY, Liu YH, Lin HY, Lu SC, Lin JY. Liver fatty acid-binding protein (L-FABP) promotes cellular angiogenesis and migration in hepatocellular carcinoma. Oncotarget. 2016;7:18229–46.

19. Kamijo A, Sugaya T, Hikawa A, Okada M, Okumura F, Yamanouchi M, et al. Urinary excretion of fatty acid-binding protein reflects stress overload on the proximal tubules. Am J Pathol. 2004;165:1243–55.

20. Viswanathan V, Sivakumar S, Sekar V, Umapathy D, Kumpatla S. Clinical significance of urinary liver-type fatty acid binding protein at various stages of nephropathy. Indian J Nephrol. 2015;25:269–73.

21. Nakamura T, Sugaya T, Kawagoe Y, Ueda Y, Osada S, Koide H. Effect of pitavastatin on urinary liver-type fatty acid-binding protein levels in patients with early diabetic nephropathy. Diabetes Care. 2005;28:2728–32.

22. Nielsen SE, Sugaya T, Tarnow L, Lajer M, Schjoedt KJ, Astrup AS, et al. Tubular and glomerular injury in diabetes and the impact of ACE inhibition. Diabetes Care. 2009;32:1684–8.

23. Abe M, Maruyama N, Okada K, Matsumoto S, Matsumoto K, Soma M. Effects of lipid-lowering therapy with rosuvastatin on kidney function and oxidative stress in patients with diabetic nephropathy. J Atheroscler Thromb. 2011;18:1018–28.

24. Suzuki K, Babazono T, Murata H, Iwamoto Y. Clinical significance of urinary liver-type fatty acid-binding protein in patients with diabetic nephropathy. Diabetes Care. 2005;28:2038–9.

25. von Eynatten M, Baumann M, Heemann U, Zdunek D, Hess G, Nawroth PP, et al. Urinary L-FABP and anaemia: distinct roles of urinary markers in type 2 diabetes. Eur J Clin Invest. 2010;40:95–102.

26. Kim SS, Song SH, Kim IJ, Kim WJ, Jeon YK, Kim BH, et al. Nonalbuminuric proteinuria as a biomarker for tubular damage in early development of nephropathy with type 2 diabetic patients. Diabetes/Metab Res Rev. 2014;30:736–41.

27. Holzscheiter L, Beck C, Rutz S, Manuilova E, Domke I, Guder WG, et al. NGAL, L-FABP, and KIM-1 in comparison to established markers of renal dysfunction. Clin Chem Lab Med. 2014;52:537–46.

28. Abd El Dayem S, El Bohy Ael M, El Shehaby A. Value of the intrarenal arterial resistivity indices and different renal biomarkers for early identification of diabetic nephropathy in type 1 diabetic patients. J Pediatr Endocrinol Metab. 2016;29:273–9.

29. Gohda T, Nishizaki Y, Murakoshi M, Nojiri S, Yanagisawa N, Shibata T, et al. Clinical predictive biomarkers for normoalbuminuric diabetic kidney disease. Diabetes Res Clin Pract. 2018;141:62–8.

30. Ngan DTT, Binh NG, Lan LTH, Nguyen CTT, Huong PT. Evaluation of urinary L-FABP as an early marker for diabetic nephropathy in type 2 diabetic patients. J Med Biochem. 2019;39:224–30.

31. Suh J-S, Kim S-H, Cho KS, Jung I-A, Cho WK, Jeon YJ, et al. Urinary markers in the early stage of nephropathy in patients with childhood-onset type 1 diabetes. Pediatr Nephrol. 2015;31:623–31.

32. Nielsen SE, Sugaya T, Hovind P, Baba T, Parving H-H, Rossing P. Urinary liver-type fatty acid-binding protein predicts progression to nephropathy in type 1 diabetic patients. Diabetes Care. 2010;33:1320–4.

33. Nielsen SE, Andersen S, Zdunek D, Hess G, Parving H-H, Rossing P. Tubular markers do not predict the decline in glomerular filtration rate in type 1 diabetic patients with overt nephropathy. Kidney Int. 2011;79:1113–8.

34. Araki S-I, Haneda M, Koya D, Sugaya T, Isshiki K, Kume S, et al. Predictive effects of urinary liver-type fatty acid-binding protein for deteriorating renal function and incidence of cardiovascular disease in type 2 diabetic patients without advanced nephropathy. Diabetes Care. 2013;36:1248–53.

35. Abd El Dayem SM, El Bohy AEM, Hamed M, Ahmed S. Follow up of value of the intrarenal resistivity indices and different renal biomarkers for early identification of diabetic nephropathy in type 1 diabetic patients. Open Access Maced J Med Sci. 2017;5:188–92.

36. Ishizu M, Mori H, Ohishi M, Kuroda A, Akehi Y, Yoshida S, et al. Urinary adiponectin excretion is an early predictive marker of the decline of the renal function in patients with diabetes mellitus. J Diabetes Complicat. 2021;35:107848.

37. Fufaa GD, Weil EJ, Nelson RG, Hanson RL, Bonventre JV, Sabbisetti V, et al. Association of urinary KIM-1, L-FABP, NAG and NGAL with incident end-stage renal disease and mortality in American Indians with type 2 diabetes mellitus. Diabetologia. 2014;58:188–98.

38. Ide H, Iwase M, Ohkuma T, Fujii H, Komorita Y, Oku Y, et al. Usefulness of urinary tubule injury markers for predicting progression of renal dysfunction in patients with type 2 diabetes and albuminuria: The Fukuoka Diabetes Registry. Diabetes Res Clin Pr. 2022;186:109840.

39. Panduru NM, Forsblom C, Saraheimo M, Thorn L, Bierhaus A, Humpert PM, et al. Urinary liver-type fatty acid-binding protein and progression of diabetic nephropathy in type 1 diabetes. Diabetes Care. 2013;36:2077–83.

40. Kamijo-Ikemori A, Sugaya T, Yasuda T, Kawata T, Ota A, Tatsunami S, et al. Clinical significance of urinary liver-type fatty acid-binding protein in diabetic nephropathy of type 2 diabetic patients. Diabetes Care. 2011;34:691–6.

41. Ito H, Yamashita H, Nakashima M, Takaki A, Yukawa C, Matsumoto S, et al. Current metabolic status affects urinary liver-type fatty-acid binding protein in normoalbuminuric patients with type 2 diabetes. J Clin Med Res. 2017;9:366–73.

42. Molitch ME, DeFronzo RA, Franz MJ, Keane WF. Nephropathy in diabetes. Diabetes care. 2004;27:S79-s83.

43. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. New Engl J Med. 2003;348:2285–93.

44. Pourshabanan P, Momeni A, Mahmoudnia L, Kheiri S. Effect of pioglitazone on decreasing of proteinuria in type 2 diabetic patients with nephropathy. Diabetes Metab Syndr: Clin Res Rev. 2019;13:132–6.

45. Beaubien-Souligny W, Leclerc S, Verdin N, Ramzanali R, Fox DE. Bridging Gaps in diabetic nephropathy care: a narrative review guided by the lived experiences of patient partners. Can J Kidney Health Dis. 2022;9:20543581221127940.

46. Stengel B, Muenz D, Tu C, Speyer E, de Pinho AN, Combe C, et al. Adherence to the kidney disease: improving global outcomes CKD guideline in nephrology practice across countries. Kidney Int Rep. 2021;6:437–48.

47. Guo J-K, Marlier A, Shi H, Shan A, Ardito TA, Du Z-P, et al. Increased tubular proliferation as an adaptive response to glomerular albuminuria. J Am Soc Nephrol. 2012;23:429–37.

48. Zeni L, Norden AGW, Cancarini G, Unwin RJ. A more tubulocentric view of diabetic kidney disease. J Nephrol. 2017;30:701–17.

49. Sato R, Suzuki Y, Takahashi G, Kojika M, Inoue Y, Endo S. A newly developed kit for the measurement of urinary liver-type fatty acid-binding protein as a biomarker for acute kidney injury in patients with critical care. J Infect Chemother. 2015;21:165–9.

50. Liu H, Feng J, Tang L. Early renal structural changes and potential biomarkers in diabetic nephropathy. Front Physiol. 2022;13:1020443.

51. Fiseha T, Tamir Z. Urinary markers of tubular injury in early diabetic nephropathy. Int J Nephrol. 2016;2016:1–10.

52. Żyłka A, Dumnicka P, Kuśnierz-Cabala B, Gala-Błądzińska A, Ceranowicz P, Kucharz J, et al. Markers of glomerular and tubular damage in the early stage of kidney disease in type 2 diabetic patients. Mediat Inflamm. 2018;2018:1–12.

53. Priyadarshini G, Rajappa M. Predictive markers in chronic kidney disease. Clin Chim Acta. 2022;535:180–6.

54. Suneja M. Diabetic nephropathy and diabetic kidney disease. J Diabetes Mellit. 2021;11:359–77.

55. De Cosmo S, Viazzi F, Pacilli A, Giorda C, Ceriello A, Gentile S, et al. Predictors of chronic kidney disease in type 2 diabetes. Medicine. 2016;95:e4007.

56. Zhang L, Xue S, Wu M, Dong D. Performance of urinary liver-type fatty acid-binding protein in diabetic nephropathy: a meta-analysis. Front Med. 2022;9:914587.