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REVIEW ARTICLE

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Review of potential biomarkers of inflammation and kidney injury in diabetic kidney disease

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Abstract

Diabetic kidney disease is expected to increase rapidly over the coming decades with rising prevalence of diabetes worldwide. Current measures of kidney function based on albuminuria and estimated glomerular filtration rate do not accurately stratify and predict individuals at risk of declining kidney function in diabetes. As a result, recent attention has turned towards identifying and assessing the utility of biomarkers in diabetic kidney disease. This review explores the current literature on biomarkers of inflammation and kidney injury focussing on studies of single or multiple biomarkers between January 2014 and February 2020. Multiple serum and urine biomarkers of inflammation and kidney injury have demonstrated significant association with the development and progression of diabetic kidney disease. Of the inflammatory biomarkers, tumour necrosis factor receptor-1 and -2 were frequently studied and appear to hold most promise as markers of diabetic kidney disease. With regards to kidney injury biomarkers, studies have largely targeted markers of tubular injury of which kidney injury molecule-1, beta-2-microglobulin and neutrophil gelatinase-associated lipocalin emerged as potential candidates. Finally, the use of a small panel of selective biomarkers appears to perform just as well as a panel of multiple biomarkers for predicting kidney function decline.

KEYWORDS
biomarkers, diabetic kidney disease, inflammation, kidney injury, kidney injury Molecule-1 [KIM-1], tumour necrosis factor receptor [TNFR]

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1 | INTRODUCTION

1.1 | Background

The prevalence of diabetes continues to increase rapidly worldwide with the number estimated to reach almost 700 million by 2045.[1] Globally, diabetes is amongst the leading cause of chronic kidney disease (CKD) and end stage kidney disease (ESKD).[2,3] Diabetic kidney disease (DKD) affects up to 40% of people with diabetes and is associated with significant morbidity and mortality, particularly from ESKD and cardiovascular disease (CVD).[4,5]

Estimated glomerular filtration rate (eGFR) and albuminuria are established markers of kidney function.[6–8] However, in recent times their utility has come under increasing scrutiny with growing body of evidence questioning their reliability as markers of DKD.[4,9–13] It is now well recognised that DKD can occur without an increase in albuminuria and subsequently progress towards ESKD, making albuminuria a less sensitive marker of disease progression.[9,14–16] Additionally, microalbuminuria, regarded as an early indicator of DKD, is prone to fluctuations between normoalbuminuria and a poor determinant of early kidney function decline in type-1 diabetes (T1D).[10,14,17] On the other hand, eGFR does not accurately reflect measured GFR (mGFR), especially when the mGFR is >60 ml/min/1.73 m^2, which can lead to potential misclassification of kidney function.[18] The use of serum creatinine as a surrogate marker for eGFR has also been questioned with some studies suggesting a potential role for cystatin C on its own or in combination with creatinine.[19,20] Thus, there is a critical need for improved biomarkers of kidney function to reliably predict DKD development and progression.[21]

1.2 | Biomarkers of diabetic kidney disease

In recent years, considerable attention has turned towards the discovery and identification of biomarkers in DKD. Multiple biomarkers have been reported to demonstrate an association with eGFR and albuminuria or enhanced predictive or diagnostic performance over eGFR and albuminuria (Table 1). These have primarily been biomarkers implicated in inflammation and kidney injury pathways of DKD.[21–23] Studies of biomarkers have either involved evaluation of single or multiple panels of candidate markers.[21] More recently, novel advances in the field of genomics, proteomics and metabolomics have transformed the landscape of biomarker discovery and have proved to be promising in DKD.[6] These novel approaches enable for considerable amount of information pertaining to the molecular basis of the disease to be studied, making them attractive tools for understanding complex biological systems.[24] One such example is the urinary CKD273 proteomic classifier panel comprising of 273 peptides which has demonstrated significant potential in diabetes for predicting renal outcomes.[25,26]

This review aims to examine recent studies of inflammatory and kidney injury biomarkers in DKD and to establish markers demonstrating most potential.

2 | METHODS

Studies are sourced from Ovid MEDLINE database using the following MeSH terms; diabetic nephropathies, renal insufficiency, chronic renal insufficiency, chronic kidney failure, diabetes mellitus type 1 and type 2, biological factors, biomarkers, diagnosis, and disease progression. Keywords were also used as part of the search strategy which can be found in the Appendix (Supplementary Material S1).[27] The search was conducted with the assistance of a clinical librarian at Austin Health. Initial search was performed in August 2019 and was further refined in February 2020. Results were limited to studies conducted in humans, reported in English, and published between January 2014 and February 2020. Hand searching of the literature was conducted to source for articles not picked up by the search strategy. Cross-sectional or longitudinal studies on biomarkers of inflammation and kidney injury in people with type-1 or type-2 diabetes and DKD were included. Studies were excluded if participants were aged <18 years, had kidney transplant or renal replacement therapy or if studies only assessed genetic or other non-protein markers. Articles pertaining to genomics, metabolomics and proteomics were also excluded except for those involving evaluation of inflammatory or kidney injury proteins.

3 | RESULTS

Overall, from 1534 papers retrieved, 89 were shortlisted. Out of the 89 studies, 48 were cross-sectional studies, 37 were longitudinal cohort studies and 4 had both cross-sectional and longitudinal components (Figure 1).

4 | DISCUSSION

4.1 | Diabetic kidney disease: Pathogenesis, diagnosis and risk factors

The pathogenesis of DKD is complex and involves the interplay of multiple biochemical processes leading to structural and functional impairment of the kidneys.[28] Such impairment is usually brought on by sustained, poorly managed hyperglycaemia which instigates many of the downstream mechanisms implicated in DKD progression, for instance, oxidative stress and hypoxia (Figure 2).[28–30] The pathogenesis of DKD is still rapidly evolving and represents a growing area in diabetes research. Ultimately, kidney injury ensues characterised by glomerular sclerosis, mesangial expansion and tubulointerstitial fibrosis.[31] Clinically, this manifests as albuminuria and reduced eGFR (Figure 2).[28–31]

Diabetic kidney disease is diagnosed with albumin–creatinine ratio ≥30 mg/g corresponding to the presence of micro- or macroalbuminuria and/or eGFR <60 ml/min/1.73 m^2 equivalent to CKD stages 3, 4 or 5 (Figure 3).[7,31,32] Albuminuria and reduced eGFR needs to be present in two measurements 3 months apart.[31,32] There

TABLE 1 Outline of biomarkers associated with diabetic kidney disease, January 2014 to February 2020

Inflammatory markers		
TNFR1	TNFRSF27	IL-8
TNFR2	TNFSF15	IL-9
TNF-α	CRP	YKL-40
ICAM-1	IL-10	ANGPTL2
VCAM-1	IL-6	IL-19
CD27	GDF-15	CD36
IL-17F	PAI-1	IL-2RA
CCL15	E-selectin	TWEAK
Eotaxin	PTX-3	CCL4
VAP-1	ALCAM	Promarker D panel (*ApoA4*, *CD5L*, *C1QB*, *IBP-3*)
IL-18	MCP-1	
Kidney injury markers		
Glomerular markers	*Tubular Markers*	*Others*
Glypican-5	KIM-1	VDBP
Nephrin	NGAL	BTP
Podocin	L-FABP	CAF
Transferrin	E-cadherin	Smad1
Immunoglobulin G	Cystatin C	AQP5
Immunoglobulin M	DcR2	Megalin
	Netrin-1	RBP
	MIOX	α-1 microglobulin
	NAG	Cyclophilin A
	Periostin	GAL
	B2M	Uromodulin
	OPN	
Anti-inflammatory markers		
Adipocytokines (Adiponectin, DPP-4, vaspin, omentin)	Vitamin C	Vitamin D
Endothelial/Vascular markers		
VEGF	Endocan	Selectin
Angiopoietin 2	Fibrinogen	
Endostatin	LRG1	
Fibrosis markers		
MMPs		
Oxidative stress markers		
Protein carbonylation	Ischaemia modified albumin	Heme oxygenase-1
Others		
EGF	Adrenomedullin	ACE-2
Copeptin	Soluble Klotho	NEP
Bilirubin	Uric acid	SUPAR
Cathelicidin	Betatrophin	FGF21
CD147	Placenta Growth factor	FGF23

(Continues)

TABLE 1 (Continued)

Osteoprotegrin	hs-Troponin	Haptoglobin
PEDF	HGF	SDMA/ADMA
CTGF	NT-proCNP	

Abbreviations: ACE-2, angiotensin converting enzyme-2; ALCAM, activated leucocyte cell adhesion molecule; ANGPTL2, angiopoietin-like protein 2; ApoA4, apolipoprotein A-IV; AQP5, aquaporin 5; B2M, beta-2 microglobulin; BTP, beta-trace protein; CAF, C-terminal fragment of Agrin; CCL, chemokine ligand; CD, cluster of differentiation; CD5L, CD5 antigen like; C1QB, complement C1q subcomponent subunit B; CRP, C-reactive protein; CTGF, connective tissue growth factor; DcR2, decoy receptor 2; DPP-4, dipeptidyl peptidase-4; EGF, epidermal growth factor; FGF, fibroblast growth factor; GAL, beta-galactosidase; GDF-15, growth differentiation factor-15; HGF, hepatocyte growth factor; hs, high sensitivity; IBP-3, insulin like growth factor binding protein-3; ICAM-1, intercellular cell adhesion molecule-1; KIM-1, kidney injury molecule-1; IL, interleukin; L-FABP, liver-type fatty acid-binding protein; LRG1, leucine rich alpha-2 glycoprotein 1; MCP-1, monocyte chemoattractant protein −1; MIOX, myo-inositol oxygenase; MMPs, matrix metalloproteinases; NAG, N-acetyl beta-D-glucosaminidase; NEP, neprilysin; NGAL, neutrophil gelatinase-associated lipocalin; NT-proCNP, amino terminal pro C-type natriuretic peptide; OPN, osteopontin; PAI-1, plasminogen activator inhibitor-1; PEDF, pigment epithelium derived factor; PTX-3, pentraxin-3; RBP, retinol binding protein; SDMA/ADMA, symmetric dimethylarginine/asymmetric dimethylarginine; SUPAR, soluble urokinase plasminogen activator receptor; TNFα, tumour necrosis factor-α; TNFR, tumour necrosis factor receptor; TNFRSF27, tumour necrosis factor receptor superfamily 27; TNF-SF15, tumour necrosis factor superfamily 15; TWEAK, tumour necrosis factor-like weak inducer of apoptosis; VAP-1, vascular adhesion protein-1; VCAM-1, vascular cell adhesion molecule-1; VDBP, vitamin-D binding protein; VEGF, vascular endothelial growth factor; YKL-40, chitinase 3-like protein 1.

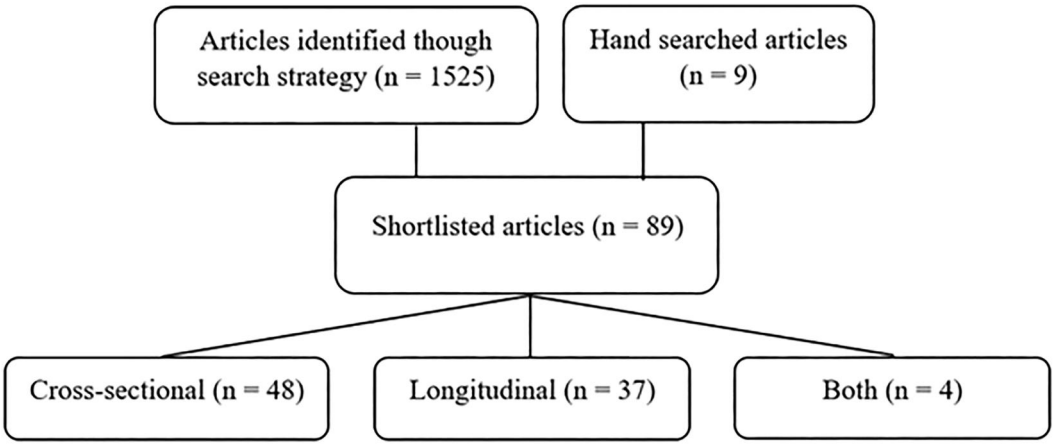

FIGURE 1 Flowchart depicting the outcome of literature search

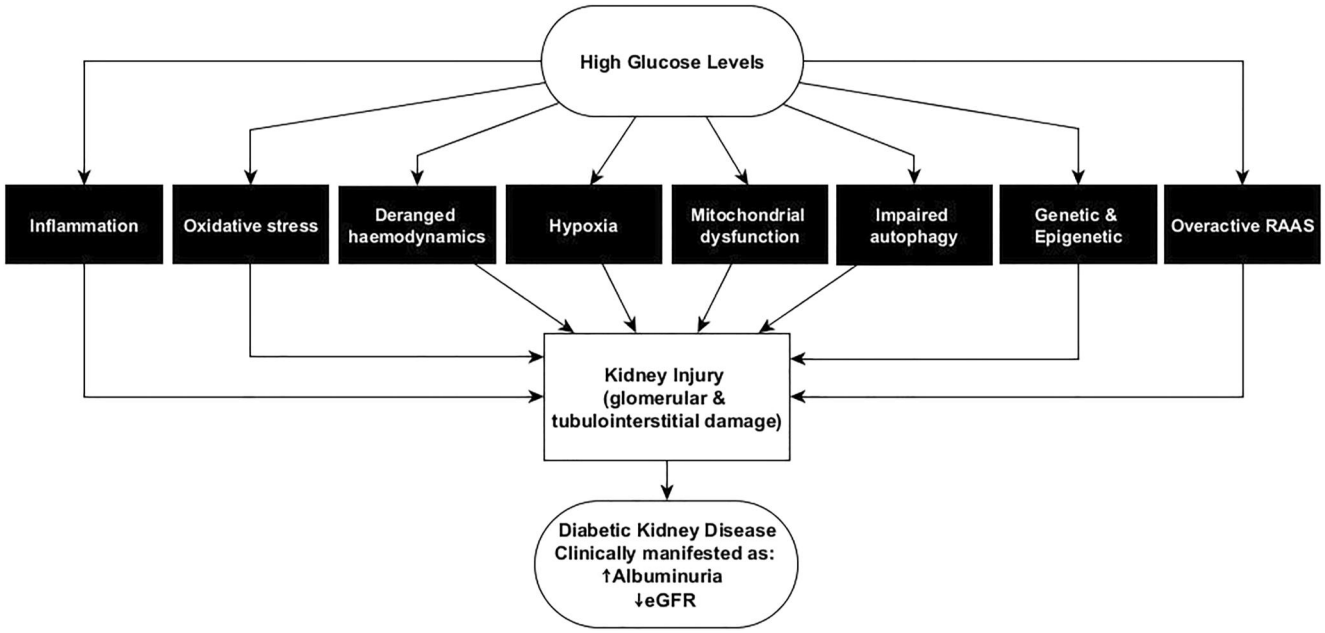

FIGURE 2 Pathways leading to diabetic kidney disease.[28–31] eGFR, estimated glomerular filtration rate; RAAS, renin angiotensin aldosterone system

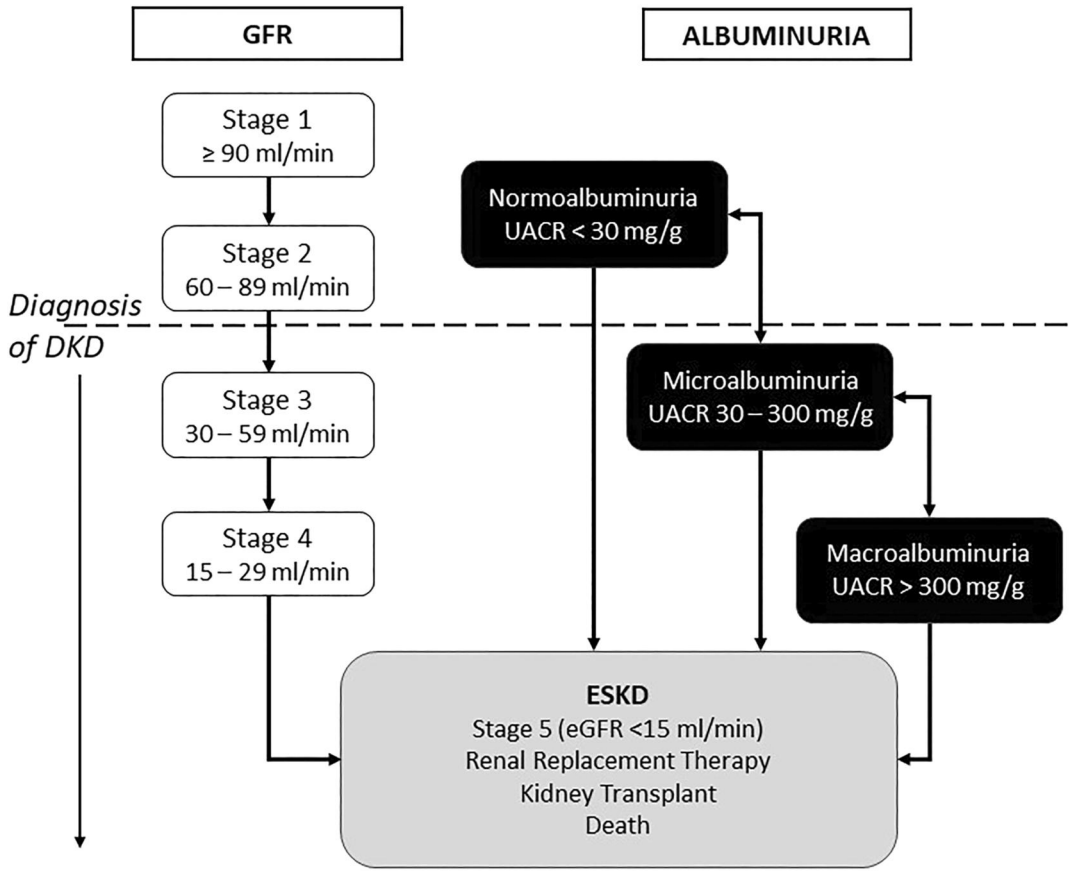

FIGURE 3 Relationship of glomerular filtration rate and albuminuria with respect to the development of end stage kidney disease. DKD, diabetic kidney disease; ESKD, end stage kidney disease; GFR, glomerular filtration rate; UACR, urine albumin–creatinine ratio

are multiple established and potential risk factors that predispose an individual to developing DKD; these include age, sex, baseline kidney function (*eGFR and albuminuria*), glycated haemoglobin level, blood pressure, duration of diabetes, family history, body mass index, smoking status, dyslipidaemia, elevated baseline GFR, variability in serum creatinine and ethnicity.[7,33–35] These risk factors are commonly referred to as clinical predictors or variables in research as they are typically acquired in the clinical setting and often readily available.[33] Studies have found that models comprising of such risk factors can accurately predict the development of renal events in diabetes and CKD.[36–38] Biomarkers that outperform or enhance the accuracy of these clinical predictors are highly sought after, and the current lack of biomarkers in clinical use may be ascribed to the robustness of these clinical factors.[21]

4.2 | Inflammatory biomarkers in DKD

Inflammation is recognised as a crucial player in the pathogenesis of DKD.[22,29] Various molecules are implicated in the inflammatory response with pro-inflammatory cytokines, chemokines, adhesion molecules and various growth and nuclear factors making up the molecular signature of inflammation.[23,39] Some of the biomarkers studied are the adhesion molecules, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), inflammatory cytokines including tumour necrosis factor receptors (TNFRs), C-reactive protein (CRP), monocyte chemoattractant protein-1 (MCP-1), interleukins-1,6,8,17,18,19 and numerous others (Table 1). The extensive set of biomarkers indicate not only the presence of, but also the complexity of inflammatory processes involved in DKD, making this an attractive avenue to search for novel biomarkers.[23] Multiple studies have investigated the association of inflammatory biomarkers with DKD, as well as, assessing the predictive or diagnostic ability of such markers.

4.2.1 | Cross-sectional studies

With regards to cross-sectional studies, research investigating the relationship of inflammatory biomarkers CRP and ICAM-1 with DKD has been inconsistent. In two studies involving participants with type-2 diabetes (T2D), significantly higher levels of ICAM-1 were reported in macroalbuminuria and microalbuminuria compared to normoalbuminuria and controls, $p = 0.001$[40,41] (Table 2). In contrast, no significant difference in ICAM-1 was observed in T1D subjects with microalbuminuria and normoalbuminuria, $p > 0.05$[42] (Table 2).

TABLE 2 Cross-sectional studies of inflammatory biomarkers in diabetic kidney disease, January 2014 to February 2020

Author and Year	Biomarkers	Sample size ± controls	Study characteristics (diabetes type, age, sex, region)	Population distribution	Exclusion criteria	Findings
Karimi et al. 2018[40]	ICAM-1	*N* = 147 + 40 healthy controls	T2D Mean age >50 years 53.1% males Iran	T2D subjects divided into two groups: Microalbuminuria and without microalbuminuria	Severe systemic diseases	Serum ICAM-1 levels higher in diabetic patients compared to controls and higher in diabetic patients with microalbuminuria compared to without, $p = 0.001$
Abu Seman et al. 2015[41]	ICAM-1	*N* = 90 + 90 normal glucose tolerance controls	T2D Mean age >55 years 50.5% males Malaysia (*multiethnic population*)	T2D subjects divided into two groups: Macroalbuminuria or ESKD requiring dialysis and normoalbuminuria	-	Plasma ICAM-1 levels higher in diabetes compared to controls and within diabetes group found to be higher in macroalbuminuria group compared to normoalbuminuria, $p = 0.001$
Polat et al. 2016[42]	ET-1 ICAM-1 VCAM-1	*N* = 73 + 100 age, sex matched healthy controls	T1D Mean age >30 years 50.7% males Turkey	Subjects divided into three groups: Without microalbuminuria (Group I), with microalbuminuria (Group II) and control group (Group III)	Smoking history, coronary heart disease, CHF, PAD, renal failure or CLD	Serum ICAM-1 higher in diabetic group versus controls, $p < 0.05$. No significant difference between diabetic groups Serum VCAM-1 higher in Group II versus Group I and Group III (*controls*) and correlates with albuminuria, $p < 0.05$
Liu et al. 2015[43]	VCAM-1 ICAM-1	*N* = 1950	T2D 57.5 ± 10.8 years 50.3% males Singapore (multi-ethnic population)	Subjects distributed based on biomarker concentration	Age <21 or >90 years, pregnancy, cancer and active inflammation, fasting glucose <4.5 or >15 mM or HbA1c > 12%, NSAIDs use, steroids use	Plasma VCAM-1 independently associated with eGFR, $p < 0.001$ and UACR, $p = 0002$ while no significant association reported for ICAM-1 with eGFR, $p = 0.506$ and albuminuria, $p = 0.061$
Pojskic et al. 2018[44]	CRP	*N* = 69	T2D Mean age >60 years 34.8% males Bosnia and Herzegovina	Subjects divided into two groups: Normoalbuminuria and microalbuminuria	T1D, new onset T2D, acute or chronic systemic inflammatory diseases, infectious or sepsis	Serum high sensitivity-CRP higher in microalbuminuria group compared to normoalbuminuria $p = 0.005$ Raised hs-CRP associated with increased risk of microalbuminuria (*OR=1.115 [1.014-1.225]; p = 0.025*)

TABLE 2 (Continued)

Author and Year	Biomarkers	Sample size ± controls	Study characteristics (diabetes type, age, sex, region)	Population distribution	Exclusion criteria	Findings
Bashir et al. 2014[45]	CRP	*N* = 50	T2D Mean age 51.1 years 80% males Pakistan	Subjects divided into four groups based on BMI: Underweight, normal, overweight and obese	Severe HTN, CVD, statin use, renal failure	22 of 50 subjects had microalbuminuria CRP raised in 14 of 22 cases of microalbuminuria while in those without microalbuminuria CRP was raised in 2 of 26 cases ($p < 0.00$)
Uzun et al. 2016[46]	PTX-3 CRP IL-1 TNF-α	*N* = 106	T2D Mean age >50 years 42.5% males Turkey	Subjects divided into three groups: eGFR>60 and microalbuminuria (Group 1) eGFR > 60 and macroalbuminuria (Group 2) and eGFR < 60 and macroalbuminuria (Group 3)	Age <18 or >65 years, T1D, AKI or renal diseases other than DKD, advanced liver disease, increased transaminase levels, autoimmune disorders, cancer, CVD or respiratory diseases, active systemic infections or inflammatory or ischaemic vascular disease	Serum PTX-3, IL-1 and TNF-α levels higher with worsening DKD, Group 3 > Group 2 > Group 1 ($p < 0.05$) No significant difference observed for high sensitivity-CRP ($p > 0.05$)
Carlsson et al. 2016[47]	TNFR1 TNFR2	*N* = 607	T2D Mean age 61 years 66% males Sweden	140 subjects had DKD defined as eGFR <60 ml/min/1.73 m^2 and/or microalbuminuria	Cancer, cognitive impairment, myocardial infarct, stroke	TNFR1 (*OR 1.60 [1.32-1.93]*; $p < 0.001$) and TNFR2 (*OR 1.43 [1.19-1.71]*; $p < 0.001$) associated with increased risk of DKD Both biomarkers had significant correlation with eGFR ($R = -0.21$; $p < 0.001$) and weak correlation with albuminuria
Gomez-Banoy et al. 2016[48]	TNFR1 TNFR2	*N* = 92	T2D Mean age >65 years 56.5% males Colombia	Subjects divided into two groups: Reduced eGFR (<60 ml/min) and normal eGFR (>60 ml/min)	Age < 18, active autoimmune or neoplastic diseases, psychiatric disorders requiring medications, pregnancy	TNFR1 and 2 significantly raised in the reduced eGFR group ($p < 0.001$) TNFR1 a risk factor for developing eGFR <60 ml/min, OR 1.152, $p = 0.034$

(Continues)

TABLE 2 (Continued)

Author and Year	Biomarkers	Sample size ± controls	Study characteristics (diabetes type, age, sex, region)	Population distribution	Exclusion criteria	Findings
Doody et al. 2018[49]	TNFR1	*N* = 4207	T2D Mean age >60 years 60% males Ireland	-	Patients with normal glycaemic control	High TNFR1 levels above 2061 pg/ml significantly associated with reduced eGFR and elevated UACR $p < 0.01$ High TNFR1 associated with increased risk of developing CKD stage 3 or worse, OR 6.51 (4.25–9.99), $p < 0.001$
Perlman et al. 2015[50]	39 inflammatory proteins	*N* = 71 + 25 age, sex, race matched controls	T2D Mean age ~65 years Males > Females USA	T2D subjects divided into stages of CKD: CKD 1/2—eGFR >60 CKD 3—eGFR 30–59 CKD 4—eGFR 15–29 CKD 5—eGFR <15	-	Serum MCP-1, FGF-2, VEGF and EGF raised over controls in all CKD stages, $p < 0.05$ Serum GM-CSF, IL-1-α, IL-1RA, IL-6 and MIP1β increased with disease progression to stage 4–5 and then decreased, $p < 0.05$ Serum IL2RA progressively increased at all stages, $p < 0.05$
Senthilkumar et al. 2018[51]	IL-6	*N* = 82	T2D Mean age >45 years Sex proportion not stated India	Subjects divided into two groups: Group A or control included subjects without nephropathy and group B, or cases included subjects with nephropathy	Pregnancy, malignancy, CVD, active infectious disease, rheumatoid arthritis, SLE and other inflammatory diseases	Serum IL-6 increased in cases compared to controls, $p = 0.023$ IL-6 not correlated with eGFR, $p = 0.064$
Li et al. 2017[52]	IL-19	*N* = 200 + 50 healthy age and sex matched controls	T2D 60 ± 10.3 years 54.5% males China	T2D subjects distributed based on albuminuria stages (normo-, micro- and macro-albuminuria)	T1D, previous diagnosis of urolithiasis, proteinuria confounders, presence of viral hepatitis or liver cirrhosis, history of CVD, chronic lung disease, acute or chronic infections	Serum IL-19 significantly higher in diabetes compared to controls, $p < 0.001$ and higher with worsening albuminuria stage, $p < 0.05$ IL-19 independently associated with diabetic nephropathy after adjusting for age, gender, HTN and blood fat, $p = 0.01$
Vasanthakumar et al. 2015[53]	IL-9 IL-17 TGF-β	*N* = 162 + 88 normal glucose tolerance controls	T2D Mean age >50 years 58.6% males India	Subjects divided into two groups: T2D without DKD and with DKD (*based on albuminuria*)	T1D and previous diagnosis with urolithiasis, presence of viral hepatitis or liver cirrhosis, history of CHF, chronic lung disease, acute or chronic infections	Serum IL-17 lower in DKD while TGF-beta levels higher in DKD, $p < 0.001$ IL-17 (*OR 1.03 [1.002–1.06]; p = 0.03*) and IL-9 (*OR 1.5 [1.05–2.14]; p = 0.03*) significant associated with DKD risk, after adjusting for age and gender

TABLE 2 (Continued)

Author and Year	Biomarkers	Sample size ± controls	Study characteristics (diabetes type, age, sex, region)	Population distribution	Exclusion criteria	Findings
Sulaj, et al. 2017[54]	ALCAM or CD166	*N* = 136 + 34 non-diabetic controls	T2D Mean age >50 years 75.7% males Germany	T2D subjects divided into two groups: Normo-albuminuria and DKD (*defined as presence of microalbuminuria*)	Pre-existing non-diabetic kidney disease, age <30 or >70 years, diabetes duration <3 years, psychiatric disorders, use of alcohol/drugs, malignancy or blood disorders, CHF, ACS	Serum ALCAM levels raised in diabetes compared to non-diabetics, $p < 0.0001$ and higher in normoalbuminuria compared to microalbuminuria, $p < 0.0001$ ALCAM corelates with CKD stages, $p < 0.001$ and eGFR, $p < 0.05$
Shiju, et al. 2015[55]	CD36	*N* = 60 + 20 normal glucose tolerance controls	T2D Mean age >40 years 78.3% males India	T2D subjects divided into three groups: Normo-, micro- and macro-albuminuria	Pre-existing history of renal disease other than DKD, CVD, cancer, haematuria, hypothyroidism or any known inflammatory or infectious disease	Plasma and urine CD36 raised in diabetic group with micro- and macro-albuminuria, $p < 0.05$ CD36 correlated with eGFR and albuminuria, $p < 0.05$
Mir et al. 2017[56]	IL-18	*N* = 69	T2D Age 45–75 years 51.5% males Iran	Subjects divided into two groups: With nephropathy and age, sex matched controls without nephropathy (*based on presence of albuminuria*)	Non-T2D, non-consent, cancer, chronic inflammatory diseases, blood disorder, immunosuppressed diabetics, CRP positive, active infections or HTN	Serum IL-18 elevated in T2D patients with nephropathy compared to controls, $p < 0.001$
Liu et al. 2018[57]	IL-8 TWEAK	*N* = 124 + 30 healthy controls	T2D Mean age >50 years 45.2% males China	T2D subjects divided into three groups based on degree of albuminuria: Normo-, micro- and macro-albuminuria	Infectious disease, acute infections, CHF, hyperthyroidism, tumours, immune system disease, haematological disorders, hepatic and renal insufficiency	Serum IL-8 levels higher in T2D than controls and progressively higher with albuminuria stage, $p < 0.05$ Soluble TWEAK levels lower in T2D than controls and progressively lower with albuminuria stage, $p < 0.05$ IL-8 independent risk factor for micro- and macro-albuminuria, (*OR 2.1*, $p = 0.002$) while sTWEAK a protective factor (*OR 0.85*, $p < 0.001$)
Ishii et al. 2019[58]	ANGPTL2	*N* = 220	Diabetes type not specified Mean age 57.8 years 63.2% males Japan	Subjects divided into three groups based on levels of ANGPTL2	-	High levels of ANGPTL2 associated with reduced eGFR, $p = 0.049$ but not higher albuminuria, $p = 0.543$

(Continues)

TABLE 2 (Continued)

Author and Year	Biomarkers	Sample size ± controls	Study characteristics (diabetes type, age, sex, region)	Population distribution	Exclusion criteria	Findings
Caner et al. 2014[59]	IL-33	$N = 74 + 26$ healthy controls	Diabetes type not specified Mean age 55.3 years 40% males Turkey	Subjects with diabetes mellitus divided into two groups: Normal kidney functions and nephropathy (micro-albuminuria)	-	IL-33 higher in diabetes compared to controls, $p < 0.05$ No difference in IL-33 level between the 2-diabetes group
Kolseth et al. 2017[60]	Multiple inflammatory mediators and marker of endothelial dysfunction	$N = 28$	T1D Mean age >45 years 53.6% males Norway	Subjects divided into two groups: Renal failure (eGFR <40 ml/min) and normal renal function (eGFR >60 ml/min)	Ongoing RRT, eGFR between 40 and 60 ml/min, haemoglobin <10 mg/dl, ongoing infection, CRP above 15 mg/ml and immunosuppressive treatment	Plasma PAI-1, syndecan-1, VEGF, IL-1β, IL-1RA and CCL4 were significantly elevated in the renal failure group, $p < 0.05$

Biomarkers abbreviations: ALCAM, activated leucocyte cell adhesion molecule; ANGPTL2, angiopoietin-like protein 2; CCL4, chemokine ligand 4; CD166, cluster of differentiation 166; CD36, cluster of differentiation 36; CRP, C-reactive protein; EGF, epidermal growth factor; ET-1, endothelin-1; FGF-2, fibroblast growth factor-2; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM-1, intercellular cell adhesion molecule-1; IL-1, interleukin-1; IL-1-β, interleukin-1-beta; IL-1-α, interleukin-1-alpha; IL-6, interleukin-6; IL-9, interleukin-9; IL-8, interleukin-8; IL-17, interleukin-17; IL-18, interleukin-18; IL-19, interleukin-19; IL-33, interleukin-33; IL-1RA, interleukin-1 receptor antagonist; IL-2RA, interleukin-2 receptor alpha; MCP-1, monocyte chemoattractant protein-1; MIP1β, macrophage inflammatory protein-1 beta; PAI-1, plasminogen activator inhibitor-1; PTX-3, pentraxin-3; TGF-β, transforming growth factor-beta; TNF-α, tumour necrosis factor-α; TNFR1, tumour necrosis factor receptor-1; TNFR2, tumour necrosis factor receptor-2; TWEAK, tumour necrosis factor-like weak inducer of apoptosis; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

Other abbreviations: ACS, acute coronary syndrome; AKI, acute kidney injury; BMI, body mass index; CHF, congestive heart failure; CKD, chronic kidney disease; CLD, chronic liver disease; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; HbA1c, glycated haemoglobin; HTN, hypertension; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; PAD, peripheral artery disease; RRT, renal replacement therapy; SLE, systemic lupus erythematosus; T1D, type-1 diabetes; T2D, type-2 diabetes; UACR, urine albumin–creatinine ratio; USA, United States of America.

Additionally, a study involving 1950 T2D subjects found no association of ICAM-1 with both eGFR, $p = 0.506$ and albuminuria, $p = 0.061$[43] (Table 2). Similar observation was also noted for CRP. Two studies found significant association of CRP with microalbuminuria while another study found no significant difference in the levels of CRP between T2D participants with eGFR <60 ml/min/1.73 m^2 and macroalbuminuria, versus those with eGFR >60 ml/min/1.73 m^2 and microalbuminuria, $p > 0.05$[44–46] (Table 2). No significant correlation of CRP with eGFR ($r = -0.063$, $p = 0.59$) and albuminuria ($r = -0.212$, $p = 0.065$) was also noted.[46]

The inconsistent findings observed for these biomarkers can be attributed to several factors. Firstly, majority of studies have consisted of a relatively small sample size of <200 participants, highlighting reduced study power and validity of results.[40–42,44–46] Additionally, discrepancies across studies with regards to demographic and clinical characteristics such as age, sex, ethnicity and diabetes duration may also influence the outcome of studies given their significance as risk factors in DKD.[33,34,61] Furthermore, unclear and poorly defined exclusion criteria in some studies could introduce potential sources of confounders[40,41,45] (Table 2). Hence, the significance of CRP and ICAM-1 as biomarkers in DKD is yet to be completely established.

Aside from ICAM-1 and CRP, the other frequently cited inflammatory biomarkers are MCP-1, IL-6 and TNFRs (Tables 2 and 3). Unlike with ICAM-1 and CRP, consistent association was observed for these biomarkers with impaired kidney function in diabetes. For instance, a Japanese study reported significant association of both TNFR1 (OR 2.32; $p < 0.001$) and TNFR2 (OR 2.40; $p < 0.001$) with eGFR <60 ml/min/1.73 m^2[62] (Table 3). This was also noted in three independent studies from Colombia, Sweden and Ireland (combined OR > 1.15; $p < 0.05$)[47–49] (Table 2). Note that these studies primarily involved participants with T2D and >60 years of age which may explain the consistency of association observed with eGFR <60 ml/min/1.73 m^2.[47–49,62] However, the congruency in findings across various countries coupled with larger sample size of >300 participants in most studies strengthens the association of TNFRs with DKD.[47–49,62] With respect to MCP-1, association was observed with progressive increase in albuminuria, $p < 0.001$ and varying stages of eGFR compared to controls, $p < 0.05$[50,63] (Tables 2 and 3). With IL-6, significantly higher levels were reported in participants with DKD compared to those without, $p = 0.023$[51] (Table 2). IL-6 was also found to increase progressively with worsening stages of eGFR, $p < 0.05$.[50] Note that these studies of MCP-1 and IL-6 were generally small, with <100 participants, hence, further evidence in larger cohorts is recommended to prove significance as biomarkers in DKD.[50,51,63]

Other inflammatory biomarkers studied, namely the adhesion molecules VCAM-1 and activated leucocyte cell adhesion molecule (ALCAM), cluster of differentiation 36 (CD36) which is expressed by various cells including monocytes and platelets, pentraxin 3 (PTX-3) an acute phase inflammatory protein, and the cytokines IL-1, 8, 9, 17, 18 and 19, have also exhibited significant association with DKD[43,46,52–57] (Table 2). However, given majority of these markers were studied infrequently, further research to validate their associations are warranted. A key limitation of cross-sectional studies is that they do not assess the performance of biomarkers over time, particularly with regards to attaining pre-specified renal outcomes. This is important because it limits the clinical utility of these biomarkers.

4.2.2 | Longitudinal cohort studies

Renal outcomes or endpoints assessed in longitudinal studies vary between studies and comprise of either clinical and/or surrogate endpoints.[65] ESKD is an example of a clinical endpoint defined as either eGFR <15 ml/min/1.73 m^2, undergoing renal replacement therapy (RRT) or kidney transplant.[66] It represents the late stage of DKD and is often referred to as a hard outcome in literature.[21,65,66] Examples of surrogate endpoints include; declining eGFR slope trajectory, annual eGFR decline of ≥5 ml/min/1.73 m^2/year, incident CKD defined as eGFR <60 ml/min/1.73 m^2, eGFR decline of ≥20%, 30%, 40% or 50% over the study period and progression to higher stages of albuminuria.[65,67–69] Majority of longitudinal studies in recent years have targeted the TNFR super family (TNFRSF), particularly, TNFR-1 and TNFR-2 (Tables 4 and 5).

With respect to ESKD, a notable publication by Niewczas et al.[70] identified 17 kidney risk inflammatory signature (KRIS) proteins of which five, namely TNFR-1, TNFRSF-27, IL-17F, TNFSF-15 and chemokine ligand 15 (CCL15) were found to predict progression to ESKD over 10 years, with a combined hazard ratio (HR) > 1.20, $p < 0.1$. Of the five markers, TNFR-1 exhibited the strongest predictive power for ESKD improving the C-statistic from 0.81 to 0.84 which was validated in three independent cohorts including both T1D and T2D participants[70] (Table 4). The C-statistic or area under the receiver operating characteristic (AUROC) is a value ranging from 0.5 to 1 where any value close to 1 implies that a biomarker or prediction model is effective at discriminating individuals at high risk of developing the endpoint or outcome of interest.[99]

Various other studies have also arrived to similar conclusions on the predictive ability of TNFRs for ESKD in diabetes, for instance, Skupien et al.,[71] Pavkov et al.[72] and Yamanouchi et al.[73] (Table 4). These studies have involved participants from the Joslin and Pima Indian cohort like in Niewczas et al. (Table 4). However, studies involving cohorts from Finland, France and Spain, have all reported enhanced performances of TNFRs for predicting ESKD[74–76] (Table 4). Additionally, in a study involving Indigenous Australian participants with diabetes, increased levels of TNFR-1 was associated with elevated risk of combined surrogate and hard renal outcome (*eGFR decline* ≥ 30% *to eGFR* < 60 ml/min/1.73 m^2 *and progress to RRT or death*) after adjusting for age, sex, eGFR and albuminuria, HR 3.8, $p = 0.03$.[77] This further validates the robustness of TNFRs as a strong candidate biomarker across diverse population backgrounds. Importantly, most of the studies mentioned here have utilised cohorts with impaired baseline kidney function, CKD stage 3 or worse and/or presence of macroalbuminuria[70,71,73–76] (Table 4). This has to do with the nature of ESKD as an endpoint which requires studies to have either a large sample size or longer follow-up duration.[100] Therefore, studies with smaller sample

TABLE 3 Cross-sectional studies that have assessed both inflammatory and kidney injury biomarkers in diabetic kidney disease, January 2014 to February 2020

Author and Year	Biomarkers	Sample Size ± controls	Study characteristics (diabetes type, age, sex, region)	Population distribution	Exclusion criteria	Findings
Gohda et al. 2018[62]	OPG BNP L-FABP TNF-α TNFR1 TNFR2	$N = 314$	T2D Mean age >60 years 52.9% males Japan	Subjects divided into two groups: eGFR ≥ 60 and eGFR < 60	T1D or other types of diabetes, micro- and macro-albuminuria, missed check-ups for fundoscopy, missing values	All biomarkers except for L-FABP were higher in the reduced eGFR group, $p < 0.001$ TNFR1 (*OR 2.32*, $p < 0.001$) and TNFR2 (*OR 2.40*, $p < 0.001$) associated with reduced renal function (eGFR < 60)
Shoukry, et al. 2015[63]	MCP-1 VDBP	$N = 75 + 25$ healthy age, sex matched controls	T2D Mean age >50 years 68% males Egypt	T2D subjects divided into three groups: Normo- micro- and macro-albuminuria	DKA or hypoglycaemic coma, urinary system disorder, liver, autoimmune and inflammatory diseases, pregnancy, infections, haematological, neoplastic, rheumatological, endocrine (except diabetes), CVD, use of statins, anti-hypertensive, and immune suppressants	Urine MCP-1 and VDBP significantly higher with worsening albuminuria and when compared to controls, $p < 0.001$ Urine MCP-1 and VDBP correlated with UACR and eGFR, $p < 0.001$ Both demonstrated ability to predict DKD, AUROC of 0.99 for MCP-1 and 0.95 for VDBP respectively, $p < 0.001$
Al-Rubeaan et al. 2017[64]	22 biomarkers (serum, plasma and urine)	$N = 467$	T2D Mean age 55.6 years 45.4% males Saudi Arabia	Subjects distribution: Normo-, micro- and macro-albuminuria	Current smokers, pregnant, suffering from other causes of kidney impairment or having ESKD	12 biomarkers; transferrin, OPN, RBP, IL-18, cystatin C, resistin, YKL-40, TNF-α, IL-6, VCAM-1, adiponectin and NGAL significantly increased in micro- and macro-albuminuria versus normo-albuminuria, $p < 0.05$ Only transferrin had AUROC of >0.7 for detecting micro-albuminuria and only seven biomarkers; transferrin, OPN, RBP, IL-18, cystatin C, resistin and NGAL had AUROC > 0.7 for detecting macro-albuminuria

Biomarkers abbreviations: BNP, brain natriuretic peptide; IL-6, interleukin-6; IL-18, interleukin-18; L-FABP, L-type fatty acid binding protein; MCP-1, monocyte chemoattractant protein-1; NGAL, neutrophil gelatinase-associated lipocalin; OPG, osteoprotegrin; RBP, retinol binding protein; TNF-α, tumour necrosis factor-alpha; TNFR1, tumour necrosis factor receptor-1; TNFR2, tumour necrosis factor receptor-2; VCAM-1, vascular cell adhesion molecule-1; VDBP, vitamin D-binding protein; YKL-40, chitinase 3-like protein 1.

Other abbreviations: AUROC, area under receiver operating characteristic; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; OR, odds ratio; T1D, type-1 diabetes; T2D, type-2 diabetes; UACR, urine albumin–creatinine ratio.

TABLE 4 Longitudinal studies of inflammatory biomarkers in diabetic kidney disease, January 2014 to February 2020

Author and Year	Biomarkers	Study characteristics	Baseline eGFR[a] and albuminuria[b]	Follow-up period	Renal outcomes	Findings
Niewczas et al. 2019[70]	17 plasma inflammatory biomarkers (KRIS)	**3 cohorts**: 219 T1D ***Joslin***: Mean age 45 years, 52% males, USA 144 T2D ***Joslin***: Mean age 60 years, 35% males, USA 162 T2D ***Pima Indians***: Mean age 45 years, 72% males, USA	***Joslin***: CKD stage 3 and macro-albuminuria on average ***Pima Indians***: CKD stage 1 and macro-albuminuria on average	8–11 years in all three cohorts	ESKD	5 KRIS proteins namely TNFR-1, TNFRSF27, IL-17F, TNFSF15 and CCL15 predicted 10-year risk of ESKD, combined HRs >1.20, $p < 0.1$ TNFR1 and TNFRSF27 had highest HR of 1.87 [1.41–2.46] and 1.57 [1.26–1.94] respectively, $p < 0.05$ TNFR1 addition improved C-statistic from 0.81 (baseline *model*: *age*, *sex*, *diabetes duration*, *HbA1c*, *GFR*, *ACR*, *SBP*, *BMI*) to 0.84
Skupien et al. 2014[71]	TNFR2	$N = 349$ T1D Median age 38 years 55% males USA—***Joslin***	CKD stage 1–3 Macroalbuminuria	5–18 years	Rate of renal decline to ESKD based on serial eGFR measurement and time to onset of ESKD	Serum TNFR2 associated with increased risk of kidney function decline and ESKD. C-statistic of 0.79 highest for TNFR2 followed by 0.72 for ACR and 0.62 for HbA1c. When combined, C-statistic = 0.86
Pavkov et al. 2015[72]	TNFR1 TNFR2	$N = 193$ T2D Median age 46 years 29% males USA—***Pima Indians***	CKD stage 1 and 2 Normo-, micro- and macro-albuminuria	Median 9.5 years	ESKD	Both TNFRs associated with increased risk of ESKD, HR 1.6 [1.1–2.2] for TNFR1 and 1.7 [1.2–2.3] for TNFR2 C-index increased from 0.858 (*model*: *age*, *gender*, *HbA1c*, *MAP and ACR*) to >0.870. Addition of mGFR further improved C-statistic by 0.007, $p = 0.006$
Yamanouchi et al. 2017[73]	TNFR1 TNFR2	**2 cohorts**: 279 T1D ***Joslin***: Median age 44 years, 48% males and USA 221 T2D ***Joslin***: Median age 61 yeaear, 61% males and USA	***Both cohorts***: CKD stage 3 Micro- and macro-albuminuria	3 years	ESKD or eGFR decline ≥40% or death	Identified cut-off for serum TNFR-1 in predicting patients at high risk of developing ESKD in both T1D and T2D of >4.3 ng/ml with sensitivity of >70% Similar performance reported for TNFR2
Forsblom et al 2014[74]	TNFR1	$N = 459$ T1D Mean age 42 years 56% males	CKD stage 2, 3 and 4	Median of 9.4 years	ESKD or death	TNFR1 significant predictor of ESKD along with raised HbA1c and shorter diabetes duration, $p < 0.001$

(Continues)

TABLE 4 (Continued)

Author and Year	Biomarkers	Study characteristics	Baseline eGFR[a] and albuminuria[b]	Follow-up period	Renal outcomes	Findings
		Finland	Macroalbuminuria			TNFR1 improved prediction of ESKD over clinical variables (*eGFR, HbA1C and diabetes duration*). C-index increased from 0.84 to 0.87
Saulnier et al. 2014[75]	TNFR1	*N* = 522 T2D Mean age 70 years 57% males France	CKD stage 3	Median of 2 years	Time to onset of all-cause mortality	High serum TNFR-1 associated with increased risk of all-cause mortality including ESKD, HR 2.98 (1.70–5.23) $p < 0.0001$
			Macroalbuminuria		Time to onset of ESKD or dialysis or sustained doubling of serum creatinine from baseline	Incidence rate for ESKD at high (4th quartile) TNFR1 was 88.8 per 1000 person-years
Fernandez-Juarez et al. 2017[76]	TNFR1 TNFR2	*N* = 101 T2D Mean age 69 years 76% males Spain	CKD stage 2 and 3 Macroalbuminuria	Median of 32 months	ESKD or >50% increase of baseline serum creatinine or death	High levels of TNFR1 significantly associated with increased risk of progression to renal outcome, *HR 2.60 (1.11–6.34)*, $p = 0.03$
Barr et al. 2018[77]	TNFR1	*N* = 194 + 259 without diabetes Not specified Mean age 45 years 38% males Australia	CKD stage 1–5	Median of 3 years	eGFR decline trajectory Combined renal outcome (eGFR decline ≥ 30% to eGFR < 60 ml/min/1.73 m^2 and death from renal causes or RRT)	Doubling of serum TNFR1 from baseline associated with increased risk of combined renal outcome in participants with diabetes, *HR* 3.8 (1.1-12.8), $p = 0.03$
			Normo-, micro- and macro-albuminuria			High TNFR1 levels associated with greater decline in eGFR trajectory in participants with diabetes, $p = 0.004$
Saulnier et al. 2017[78]	TNFR1 (*plus 2 other non-inflammatory or kidney injury markers*)	*N* = 1135 T2D Mean age 64 years 57% males France	CKD stage 1, 2 and 3	Up to 11.8 years	*Renal function loss* = eGFR decline ≥40% from baseline	TNFR1 associated with increased risk of outcome 1) HR 1.8, $p < 0.0001$ and 2) OR 2.3, $p < 0.0001$
			Normo-, micro- and macro-albuminuria		*Rapid renal function decline* = decline in annual eGFR slope of ≤−5 ml/min/1.73 m^2/yr	TNFR1 alone improved C-statistic for outcome 1) from 0.702 to 0.739, $p < 0.0001$ and outcome 2) from 0.726 to 0.780, $p < 0.0001$.
Aryan et al. 2018[79]	CRP	*N* = 1301 T2D Mean age 55 years 47% males Iran	CKD stage 2 and 3	Mean of 7.5 years	Development of DKD (*micro-albuminuria or eGFR < 60*)	Baseline high sensitivity CRP predicts development of DKD in T2D improving C-statistic from 0.76 (*baseline model: diabetes duration, HbA1c, SBP, anti-hypertensive medications and waist circumference*) to 0.85

TABLE 4 (Continued)

Author and Year	Biomarkers	Study characteristics	Baseline eGFR[a] and albuminuria[b]	Follow-up period	Renal outcomes	Findings
			Baseline albuminuria not specified			High sensitivity CRP is associated with increased risk of DKD, *HR 1.045 (1.035–1.056), p < 0.001*
Ishii et al. 2019[58]	ANGPTL2	*N* = 145 *Not stated* Mean age <50 years 45% males Japan	CKD stage 1–5	Median of 7-years	Progression to higher stages of albuminuria towards ESKD	Baseline serum ANGPTL2 is an independent risk factor for progression of albuminuria during the follow-up period, *OR 2.64 (1.14-6.11), p = 0.023.*
Longitudinal component			Normo-, micro- and macro-albuminuria			AUROC of 0.87 for predicting albuminuria progression
Roy et al. 2015[80]	28 plasma inflammatory biomarkers	*N* = 356 T1D Mean age ~25 years ~40% males USA	CKD stage 1 and 2	Mean of 6-years	Development of eGFR <60 or ESKD	Elevated plasma ICAM-1 predicted progression to macroalbuminuria, OR 4.72 (1.55–14.4), *p* = 0.006
			Normo- and micro-albuminuria		Development of macroalbuminuria	Elevated plasma eotaxin predicted progression to eGFR <60 or ESKD, OR 7.66 (2.38–24.6), *p* = 0.001
Li et al. 2016[81]	VAP-1	*N* = 604 T2D Mean age ~60 years ~50% males Taiwan	CKD stage 1–3 Normo-, micro- and macro-albuminuria	Median 12.36 years	ESKD	Serum VAP-1 is predictive of ESKD, adjusted HR 1.55 (1.12–2.14) and AUROC of 0.82 which when combined with eGFR, HbA1c and proteinuria increased to 0.94
Frimodt-Moller et al. 2018[82]	GDF-15	*N* = 200 T2D Mean age 59 years 76% males Denmark	CKD stage 1 and 2 Microalbuminuria	Median 6.1 years	eGFR decline >30% at any time point during follow-up	GDF-15 associated with increased risk of eGFR decline, HR 1.7 (1.1–2.5), *p* = 0.018. Addition of GDF-15 to clinical variables improves risk prediction rIDI of 30%
Preciado-Puga et al. 2014[83]	CRP TNF-α IL-6	*N* = 157 T2D Mean age 52 years 30% males Mexico	CKD stage 2 (average eGFR >60) Normo-, micro- and macro-albuminuria	1 year	Progression of complication in T2D	Serum TNF-α associated with increased risk of complication progression in T2D, *p* < 0.008 High sensitivity CRP only had marginal increase after 1 year while IL-6 not significant

(Continues)

TABLE 4 (Continued)

Author and Year	Biomarkers	Study characteristics	Baseline eGFR[a] and albuminuria[b]	Follow-up period	Renal outcomes	Findings
Peters et al. 2017[84]	*Promarker D*: ApoA4 CD5L C1QB IBP3	*N* = 345 T2D Mean age 67 years 52% males Australia	CKD stages 1–4 Normo- and micro-albuminuria	4 years	Rapidly declining eGFR trajectory Incident CKD (eGFR <60 ml/min) eGFR decline ≥30% eGFR decline ≥5 ml/min/1.73 m^2/yr	ApoA4, CD5L, C1QB, IBP3 (*Promarker D panel*) found to improve prediction of renal outcomes. AUROC improved from 0.75 to 0.82, $p = 0.039$ for rapidly declining eGFR trajectory.
Baker et al. 2018[85]	CRP	*N* = 1396 T1D Mean age 27 years 52% males USA	CKD stage 1	28 years (*subdivided into two windows: 3 years and 10 years*)	Development of eGFR <60	TNFR-1 and 2, E-selectin, and fibrinogen significantly associated with increased risk of progression to eGFR <60 after adjustment for clinical variables at both 3-year and 10-year window, combined *HRs > 1.2, p < 0.05*
	Fibrinogen		Normoalbuminuria		Development of macroalbuminuria	TNFR-2, E-selectin and PAI-1 significantly associated with increased risk of developing macroalbuminuria at 10-year window after adjusting for variables, combined *HRs > 1.15, p < 0.05*. No biomarkers associated at 3 years window
	IL-6					
	TNFR 1 and 2					
	ICAM-1					
	VCAM-1					
	E-selectin					
	PAI-1					

Biomarkers abbreviations: ANGPTL2, angiopoietin-like protein 2; ApoA4, apolipoprotein A-IV; C1QB, complement C1q subcomponent subunit B; CCL15, chemokine ligand-15; CD5L, CD5 antigen like; CRP, C-reactive protein; GDF-15, growth differentiation factor-15; IBP-3, insulin like growth factor binding protein-3; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; IL-17F, interleukin-17F; KRIS, kidney risk inflammatory signature; PAI-1, plasminogen activator inhibitor-1; TNFR-1, tumour necrosis factor receptor-1; TNFR2, tumour necrosis factor receptor-2; TNFSF15, tumour necrosis factor super family-15; TNFRSF27, tumour necrosis factor receptor super family-27; TNF-α, tumour necrosis factor alpha; VAP-1, vascular adhesion protein-1; VCAM-1, vascular cell adhesion molecule-1.

Other abbreviations: ACR, albumin–creatinine ratio; AUROC, area under receiver operating characteristic; BMI, body mass index; CKD, chronic kidney disease; DKD, diabetic kidney disease; eGFR, estimated GFR; ESKD, end stage kidney disease; GFR, glomerular filtration rate; HbA1c, glycated haemoglobin; HR, hazard ratio; MAP, mean arterial pressure; mGFR, measured GFR; OR, odds ratio; rIDI, relative integrated discrimination improvement; RRT, renal replacement therapy; SBP, systolic blood pressure; T1D, type-1 diabetes; T2D, type-2 diabetes; USA, United States of America.

[a]eGFR expressed in terms of CKD stages, 1, 2, 3, 4 and 5 which corresponds with ≥90, 60–89, 30–59, 15–29 and <15 ml/min/1.73 m^2, respectively.

[b]Albuminuria expressed in terms of stages, Normoalbuminuria (ACR <30 mg/g), Microalbuminuria (30–300 mg/g) and Macroalbuminuria (>300 mg/g).

TABLE 5 Longitudinal studies that have assessed both inflammatory and kidney injury biomarkers in diabetic kidney disease, January 2014 to February 2020

Author and Year	Biomarkers	Study characteristics	Baseline eGFR[a] and albuminuria[b]	Follow-up period	Renal outcomes	Findings
Colombo, et al. 2020[86]	22 serum/urine biomarkers	*N* = 1629 T1D Median age 48 years 51% males Scotland	CKD stage 1,2 and 3 Normo-, micro- and macro-albuminuria	Median of 5.1 years	eGFR progression to <30 ml/min/1.73 m^2 Final eGFR	A panel of serum biomarkers (*TNFR1, KIM-1, CD27, α-1-microglobulin, syndecan-1, cystatin C, MMP-8, clusterin and thrombomodulin*) outperform clinical variables for predicting outcomes, R^2 0.743 versus 0.702, AUROC 0.953 versus 0.876 Of serum biomarkers, TNFR1, KIM-1 and CD27 exhibited strongest association, $p < 0.001$
Coca SG, et al. 2017[87]	TNFR1 TNFR2 KIM-1	**2-Cohorts**: 380 T2D ***ACCORD*** mean age 62 years, ~51% males 1256 T2D ***NEPHRON-D*** Mean age ~63 years Population from USA and Canada	***ACCORD***: CKD stage 1 and 2 Normo- and micro-albuminuria ***NEPHRON-D:*** CKD stage 2 and 3 Macroalbuminuria	***ACCORD***: Mean of 5 years for ***NEPHRON-D:*** Median of 2.2 years	***ACCORD***: eGFR decline of ≥40% and eGFR <60 ml/min/1.73 m^2 ***NEPHRON-D***: Decline in the eGFR ≥30 ml/min/1.73 m^2 if the eGFR was ≥60 ***or*** a decrease of ≥50% if the eGFR was <60 ***or*** ESKD	***ACCORD***: TNFR1 OR of 2.44 (1.48–4.04), TNFR2 OR of 3.17 (1.65–6.08) and KIM-1 OR of 2.42 (1.66–3.53) with respect to renal outcome ***NEPHRON-D***: C-statistic increased from 0.68 (*clinical model*) to 0.722 for TNFR1, 0.709 for TNFR2 and 0.735 for KIM-1, $p < 0.05$. When all combined C-statistic improved to 0.752 OR 2.4 (1.7–3.3) for TNFR1, 1.9 (1.4–2.8) for TNFR2 and 1.7 (1.5–2.1) for KIM-1
Pena et al. 2015[88]	28 blood biomarkers	*N* = 82 T2D Mean age 63 years 53% males Netherlands	CKD stage 1, 2 and 3 Normo-, micro- and macro-albuminuria	Median of 4 years	eGRR decline defined as < −3 ml/min/1.73 m^2/year	MMP-7, TEK and TNFR1 independently associated with eGFR decline after adjustment for clinical variables, $p < 0.05$. These 3 biomarkers did not significantly improve C-index/statistic, $p = 0.262$ 13 biomarkers representing various pathways improved C-index from 0.835 to 0.896, $p = 0.008$. Of the 13 markers **TNFR1** and **YKL-40** are the only inflammatory markers
Agarwal et al. 2014[89]	*Kidney Injury Markers:* Cystatin C Nephrin Podocalyxin B2M NGAL L-FABP	*N* = 67 + 20 age-matched controls T2D Mean age 67 years 98% males USA	CKD stage 2, 3 and 4 Normo-, micro- and macroalbuminuria	2–6 years	eGFR decline/slope progression over time Progression to ESKD or dialysis or death	None of the kidney injury or inflammatory biomarkers were significantly associated with achieving the outcomes after adjustment for baseline eGFR and UACR, $p > 0.05$ FGF23 (*marker of mineral metabolism*) was most significantly associated with eGFR slope, OR 2.1, $p < 0.05$, while

(Continues)

TABLE 5 (Continued)

Author and Year	Biomarkers	Study characteristics	Baseline eGFR[a] and albuminuria[b]	Follow-up period	Renal outcomes	Findings
	Inflammatory Markers: TNFR1 TNFR2 MCP-1 Tenascin C					VEGF (*marker of angiogenesis*) associated with ESKD, OR 1.4, $p < 0.05$
Heinzel et al. 2018[90]	*Kidney Injury Markers:* KIM-1 UMOD Cystatin C *Inflammatory Markers:* VCAM-1 TNFR1 YKL-40 CCL2	$N = 481$ T2D Mean age 64 years 53% males Austria, Hungary and Scotland	CKD stage 1 and 2 Normoalbuminuria	>2 years	eGFR slope (*subjects divided by rate of eGFR decline; stable or fast progressors*)	Low predictive power for individual biomarkers, all had AUROC of <0.65 for identifying eGFR progressors Biomarkers did not contribute much to the prediction ($R^2 < 1$) compared to model consisting of clinical variables, especially after adjusting for baseline eGFR
Hwang et al. 2017[91]	NGAL KIM-1 TNFR1 TNFR2	$N = 35$ T1D and T2D Median age 50 years 80% males Korea	CKD stage 2 and 3 Albuminuria not specified	Median follow-up of 24.2 months	Annual decline in eGFR slope	Tissue expression of NGAL was independently associated with eGFR slope decline, $p = 0.038$. No correlation for TNFRs and eGFR slope decline. KIM-1 association dependent on urine protein-creatinine ratio
Mayer et al. 2017[92]	9 serum biomarkers **YKL-40** GH1 HGF MMP-2,7,8,13 Tyrosine kinase **TNFR-1**	$N = 1765$ T2D Mean age >55 years >50% males -	Subjects divided according to eGFR (<60 and ≥ 60 ml/min/1.73 m^2) Normo-, micro- and macro-albuminuria	1–3 years	Annual eGFR slope decline	Studied biomarkers able to predict declining eGFR at eGFR <60 ml/min (*MMP-2, 7, 13,* ***TNFR1*** *and TIE2*) and ≥60 ml/min (*MMP-2, 7, 8 and GH1*), R^2 of 33.4% and 15.2% respectively. When combined with clinical variables R^2 improved to 64% and 35% respectively
Satirapoj et al. 2018[93]	MCP-1 EGF	$N = 83$ T2D Mean age 66 years 64% males Thailand	CKD stages 1–5 Micro- and macro-albuminuria	23 months	GFR decline ≥25% per year from baseline	Urine MCP-1 and EGF predicted renal outcome, AUROC 0.73 and 0.68 respectively, although not as good as ACR which had AUROC of 0.84 MCP-1 and EGF/MCP-1 ratio was independently associated with the outcome, $p < 0.05$
Nadkarni et al. 2016[94]	MCP-1 IL-18 KIM-1 YKL-40	$N = 380$ T2D Mean age 62 years ~51% males USA and Canada	CKD stage 1 and 2 Normo- and micro-albuminuria	5 years	eGFR decline ≥40% from baseline eGFR ≤45 ml/min/1.73 m^2	Only MCP-1 associated with risk of eGFR decline ≥40%, OR 2.27 (1.44–3.58) and with greatest improvement in C-statistic from 0.70 to 0.74

TABLE 5 (Continued)

Author and Year	Biomarkers	Study characteristics	Baseline eGFR[a] and albuminuria[b]	Follow-up period	Renal outcomes	Findings
Colombo et al. 2019[95]	42 biomarkers	*N* = 657 + 183 controls T2D Median age >65 years 48% males Sweden and UK	CKD stage 2 and 3 Normo-, micro- and macro-albuminuria	Median 7 years	eGFR decline of >20% from baseline during follow-up	From 42 biomarkers, the addition of 2 kidney injury markers serum KIM-1 and B2M to model of clinical variables improved AUROC by 0.079, 0.073 and 0.239 in the 3 cohorts, respectively B2M had the strongest association with eGFR decline with cumulative OR >1.5, $p < 0.001$ across the cohorts studied
Colombo et al. 2019[96]	30 protein circulating biomarkers	*N* = 1174 T1D Median age >45 years ~50% males Scotland and Finland	CKD stage 2 and 3 Normo-, micro- and macro-albuminuria	Median of 5.2 and 8.8 years for two respective cohorts	Rapid eGFR progression (> 3 ml/min/1.73 m^2/year) Final eGFR	A sparse panel of CD27 and KIM-1 contains most of the predictive information for eGFR progression, combined OR >1.6, $p < 0.001$ and accounts for 75% of R^2 CD27 and KIM-1 part of the panel with greatest improvement in AUROC, 0.51–0.65 (*Scottish cohort*) and 0.70–0.74 (*Finnish cohort*)
Looker et al. 2015[97]	207 serum biomarkers	*N* = 307 T2D Median age ~73 years ~40% males Scotland	CKD stage 3 Normo-, micro- and macroalbuminuria	3.5 years	eGFR decline ≥40% from baseline	*14 biomarkers*: SDMA/ADMA, creatinine, **B2M**, α1-antitrypsin, **KIM-1**, uracil, NT-proBNP, C16-acylcarnitine, hydroxyproline, FGF-21, creatine, adrenomedullin, H-FABP demonstrated enhanced predictive ability over clinical covariates, AUROC 0.71–0.87
Kim et al. 2017[98]	NAP KIM-1 NGAL L-FABP Angiotensinogen IL-18 YKL-40	*N* = 73 T2D Mean age 55 years 42% males Korea	CKD stage 1 and 2 Normo- and micro-albuminuria	Median of 50 months	Annual eGFR decline and development of eGFR <60 ml/min/1.73 m^2	NAP found to be better and more practical predictor of endpoints than other urinary biomarkers in early stage DKD in T2D, C-statistic of 0.83

Biomarkers abbreviations: AUROC, area under receiver operating characteristic; B2M, beta-2-microglobulin; CD27, cluster of differentiation-27; CKD, chronic kidney disease; CCL2, chemokine ligand-2; DKD, diabetic kidney disease; EGF, epidermal growth factor; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; FGF-21, fibroblast growth factor-21; FGF-23, fibroblast growth factor-23; GH1, growth hormone-1; H-FABP, heart-type fatty acid binding protein; HGF, hepatocyte growth factor; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid-binding protein; MCP-1, monocyte chemoattractant protein-1; MMP-#, matrix metalloproteinase-#; NAP, non-albumin proteinuria; NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, N-terminal prohormone b-type natriuretic peptide; SDMA/ADMA, symmetric dimethylarginine/asymmetric dimethylarginine; TEK, tyrosine kinase; TNFR1, tumour necrosis factor receptor-1; TNFR2, tumour necrosis factor receptor-2; YKL-40, chitinase 3-like protein 1.

Other abbreviations: OR, odds ratio; T1D, type-1 diabetes; T2D, type-2 diabetes; UACR, urine albumin–creatinine ratio; UK, United Kingdom; UMOD, uromodulin; USA, United States of America; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

[a]eGFR expressed in terms of CKD stages, 1, 2, 3, 4 and 5 which corresponds with ≥90, 60–89, 30–59, 15–29 and <15 ml/min/1.73 m^2, respectively.

[b]Albuminuria expressed in terms of stages, Normoalbuminuria (ACR <30 mg/g), Microalbuminuria (30–300 mg/g) and Macroalbuminuria (>300 mg/g).

TABLE 6 Cross-sectional studies of kidney injury biomarkers in diabetic kidney disease, January 2014 to February 2020

Author and Year	Biomarkers	Sample Size ± controls	Study characteristics (diabetes type, age, sex, region)	Population distribution	Exclusion criteria	Findings
Siddiqi et al. 2017[105]	NGAL Cystatin C	*N* = 180	T2D Mean age >40 years ~55% males India	Subjects divided into 2 groups: Normo-albuminuria (*controls*) and micro-albuminuria (*cases*)	HTN, cancer, infections, inflammatory states, cardiovascular, pulmonary or other endocrine diseases, severe renal impairment (eGFR <30 ml/min)	Serum and urine NGAL and serum cystatin C significantly raised in microalbuminuric versus normoalbuminuric patients, $p < 0.05$ Biomarkers displayed strong performance for detecting microalbuminuria AUROC of 1 for urinary NGAL, 0.8 for serum NGAL and 1 for serum Cystatin C
de Carvalho et al. 2016[106]	KIM-1 NGAL	*N* = 117	T2D Mean age >55 years ~37% males Brazil	Subjects divided into 3 groups based on levels of UACR: <10 mg/g (*normoalbuminuria*), 10–30 mg/g (*normoalbuminuria*) and >30 mg/g (*micro- and macro-albuminuria*)	Urinary tract diseases, kidney disease other than DKD, neoplastic disorders, uncontrolled thyroid disorders, infectious and liver diseases, active or chronic persistent infection or inflammatory disorders, pregnancy, kidney transplant, use of nephrotoxic drugs	Urine KIM-1 and NGAL significantly raised progressively with increasing albuminuria groups, $p < 0.001$ Significant positive correlation with UACR, $p < 0.001$ Both biomarkers were independently associated with DKD. *OR 1.056 (1.024–1.079, $p < 0.001$)* for KIM-1 and OR *1.241 (1.117–1.380, $p < 0.001$)* for NGAL
Bjornstad et al. 2019[107]	Plasma levels of: NGAL B2M OPN UMOD	*N* = 66 + 73 non-diabetic controls	T1D - - Canada	Subjects divided into 2 groups: DKD and DKD resistors (*eGFR* > 60 ml/*min and normo-albuminuria*)	-	Plasma NGAL and B2M were significantly raised in DKD versus DKD resistors and controls, $p < 0.05$ UMOD lower in diabetes compared to controls ($p < 0.05$)

TABLE 6 (Continued)

Author and Year	Biomarkers	Sample Size ± controls	Study characteristics (diabetes type, age, sex, region)	Population distribution	Exclusion criteria	Findings
						but no significance between DKD and DKD resistors ($p = 0.83$) OPN levels not significant across all groups, $p > 0.05$. Only NGAL correlated with GFR in diabetic subjects ($r = -0.33$; $p = 0.006$)
Motawi et al. 2018[108]	NGAL βTP	$N = 50 + 25$ healthy controls	T2D Mean age >45 years 80% males Egypt	Subjects divided into 2 groups: Normo- and micro-albuminuria	CVD, stroke or peripheral artery disease, HTN, endocrine diseases, pregnancy, acute infections, tumours, glucocorticoid use, chronic inflammatory disease	Serum βTP and NGAL significantly raised in micro- versus normo-albuminuria and controls, $p < 0.01$. No difference between normoalbuminuria and controls, $p > 0.05$ AUROC for NGAL in predicting microalbuminuria 0.96 versus 0.73 for βTP
Vijay et al. 2018[109]	NGAL Cystatin C	$N = 126 + 30$ non-diabetic controls	T2D Mean age >45 years 54% males India	Subjects divided into 2 groups: With and without micro-albuminuria	Presence of thyroid disease, use of steroids, nephrotoxic drugs, ACE inhibitors or ARBs, systemic arterial hypertension, macroalbuminuria, or elevated serum creatinine values	Urinary NGAL and cystatin-C levels were significantly elevated in patients with micro-albuminuria versus without albuminuria and controls, $p < 0.001$. Both biomarkers positively correlated with micro-albuminuria ($r > 0.75$) Urine NGAL AUROC of 0.86. urine cystatin-C AUROC of 0.78
Wu et al. 2014[110]	NGAL	$N = 462 + 160$ controls	T2D Mean age >50 years	Subjects divided into 3 groups:	Hepatic diseases, other kidney diseases,	Levels of serum NGAL elevated

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TABLE 6 (Continued)

Author and Year	Biomarkers	Sample Size ± controls	Study characteristics (diabetes type, age, sex, region)	Population distribution	Exclusion criteria	Findings
			46.3% males China	Normo-, micro- and macro-albuminuria	cardiac diseases, rheumatic diseases, neoplastic diseases, infectious or other endocrine diseases (except diabetes)	with higher albuminuria stage compared to controls $p < 0.001$ No difference observed between micro- and macro-albuminuria groups, $p > 0.05$
Kaul et al. 2018[111]	NGAL	$N = 144 + 54$ controls	T2D Median age >50 years ~61% males India	Subjects divided into 3 groups: Normo-, micro- and macro-albuminuria	Use of RAAS inhibitors, age <18 years, infection, inflammatory disorders, uncontrolled HTN, NSAID use, nephrotoxic medications, immune-suppressant, non-DKD, CAD, stroke, malignancy, pregnancy, liver dysfunction, thyroid disorders	NGAL higher with progressive albuminuria and when compared to controls, $p < 0.05$ Positively correlate with albuminuria, $p < 0.05$ AUROC >0.99 for detection of micro/macro-albuminuria
Zeng et al. 2017[112]	NGAL Clusterin Cystatin C	$N = 146 + 30$ age and sex matched controls	T2D Mean age >55 years 57% males China	Subjects divided into 2 groups: Non-DKD group and DKD group (*eGFR < 60 and/or presence of albuminuria*)	Chronic infections, malignancy, immunologic disorders, HTN or use of anti-hypertension medications, severe liver dysfunction, recent history of AMI or stroke, UTI, primary glomerulonephritis, hypertensive nephropathy, lupus nephritis, interstitial nephritis or prior kidney transplantation	Urinary NGAL, clusterin and cystatin C were significantly raised in DKD compared to non-DKD T2D and controls, $p < 0.001$ For detection of DKD: NGAL AUROC 0.82 Clusterin AUROC 0.78 Cystatin C AUROC 0.80
Hosny et al. 2018[113]	NGAL	$N = 60 + 20$ healthy controls	T2D Mean age 58 years ~66% males Egypt	Subjects divided into 3 groups: Normo-, micro- and macro-albuminuria	T1D, UTI, glomerulonephritis and other cause of proteinuria, renal or hepatic diseases, drugs causing proteinuria such as amlodipine,	NGAL higher in diabetes group versus controls, $p < 0.001$ No difference between albuminuria in diabetes groups, $p > 0.05$

TABLE 6 (Continued)

Author and Year	Biomarkers	Sample Size ± controls	Study characteristics (diabetes type, age, sex, region)	Population distribution	Exclusion criteria	Findings
					amoxicillin and azithromycin and pregnancy	AUROC of 0.99 for NGAL
Zylka et al. 2018[114]	Cystatin C KIM-1 NGAL Transferrin IgG UMOD	$N = 80$	T2D Mean age >55 years ~50% males Poland	Subjects divided into 2 groups: Normo- and micro-albuminuria	Anaemia, neoplasm, connective tissue disease, infection, allergy, nephrotoxic drugs, kidney disease other than DKD, uncontrolled HTN, heart failure, UTI, increased physical activity, women during menstruation and pregnant women	All biomarkers significantly higher in microalbuminuria group except for UMOD which was lower, $p < 0.05$ Only NGAL, KIM-1, IgG and Transferrin associated with risk of microalbuminuria significant OR, $p < 0.05$ with urine IgG and KIM-1 having highest OR at 59 and 7.12, respectively High AUROC reported for KIM-1 and IgG of >0.8
Bouvet et al. 2014[115]	NAG	$N = 36$	T2D Mean age >60 years 58.3% males Argentina	Subjects divided into 2 groups: Normo- and micro-albuminuria	BMI ≥30, other endocrinopathies, HTN, UTI, urinary stones, proteinuria and abnormal urinary sediment, renal failure (eGFR <60 ml/min)	Urine NAG significantly increased in microalbuminuria group versus normoalbuminuria, $p < 0.001$ NAG correlated with albuminuria ($r = 0.63$, $p < 0.0001$) and not eGFR
Chen et al. 2017[116]	DcR2 NAG	$N = 311$ and 139 T2D with biopsy confirmed DKD	T2D Mean age >55 years ~50% males China	311 subjects divided into 3 groups: Normo-, micro- and macro-albuminuria 139 subjects divided into groups based on TII score	Non-diabetic renal diseases, cancer, UTI, inflammation states, use of diuretics, Chinese medicines, or nephrotoxic drugs, severe hepatic or cardiac dysfunction	Urine DcR2 and NAG levels significantly elevated with progressively worsening albuminuria, $p < 0.05$ and correlated with eGFR and albuminuria, $p < 0.05$ Urine DcR2 had an AUROC of 0.91 for assessing

(Continues)

TABLE 6 (Continued)

Author and Year	Biomarkers	Sample Size ± controls	Study characteristics (diabetes type, age, sex, region)	Population distribution	Exclusion criteria	Findings
						TII in DKD while NAG was 0.78
Qin et al. 2019[117]	Transferrin IgG RBP B2M GAL NAG	*N* = 1053	T2D Mean age >53 years 62.4% males China	Subjects divided into 2 groups: 1) normo-albuminuria and eGFR>60 and 2) micro-/macro-albuminuria and eGFR>60 (*DKD group*)	Anaemia, neoplasm, severe cardiovascular, cerebrovascular and liver diseases, chronic glomerulonephritis, known kidney diseases other than DKD, infection, autoimmune diseases, acute diabetic complications such as ketoacidosis, HTN, fever, vigorous physical activity, UTI, pregnancy, and those on their menstrual period	DKD group had higher levels of all 6 biomarkers, $p < 0.05$ All biomarkers except for B2M and GAL were associated with increased risk of DKD, OR 1.2 for transferrin, 1.2 for IgG, 2.3 for RBP and 1.04 for NAG, $p < 0.001$ GAL, NAG and B2M have weak prognostic ability combined AUROC <0.61 versus transferrin, RBP and IgG, combined AUROC >0.83
Kim et al. 2014[118]	B2M	*N* = 366	T2D Mean age 56 years 44.5% males South Korea	-	T1D or secondary diabetes history, systemic infection, use of corticosteroids, pregnancy, history of myocardial, stroke or peripheral vascular disease, acute infection, malignancy, tuberculosis, chronic inflammatory disease or liver disease	Serum B2M associated with microalbuminuria, $p < 0.05$ High serum B2M an independent risk factor for DKD *OR 2.29 (1.11-4.72)* Poor predictive performance of B2M, AUROC of 0.65 for DKD (*defined as presence of albuminuria, UACR ≥ 30 mg/g*)

TABLE 6 (Continued)

Author and Year	Biomarkers	Sample Size ± controls	Study characteristics (diabetes type, age, sex, region)	Population distribution	Exclusion criteria	Findings
Al-Malki, 2014[119]	Osteopontin IgM Podocytes	*N* = 60 + 20 age and sex matched healthy controls with eGFR ≥90	Not stated Mean age 37 years 66.7% males Saudi Arabia	Subjects divided into 3 groups: 20 normo-, 20 micro- and 20 non-diabetic nephrotic syndrome	-	Urine osteopontin, podocyte and IgM significantly raised in microalbuminuria group versus normoalbuminuria, $p < 0.001$ IgM and podocyte have the highest AUROC of 0.9 and 0.92, respectively, while osteopontin is 0.73
Petrica et al. 2014[120]	KIM-1 Alpha1-microglobulin Nephrin VEGF	*N* = 70 + 21 healthy controls	T2D Median age >55 years *Not stated* Romania	Subjects divided into 2 groups: Normo- and micro-albuminuria	-	All biomarker levels higher in micro- versus normo-albuminuria, $p < 0.05$
Fawzy et al. 2018[121]	VDBP	*N* = 120 + 40 healthy controls	T2D Mean age >45 years <20% males Saudi Arabia	Subjects divided into 3 groups: Normo-, micro- and macro-albuminuria	UTI, kidney disease other than DKD, neoplastic disorders, severe liver disease, active or chronic infection or inflammatory disorders, haematological diseases, pregnancy or a recent history of AMI, stroke, or occlusive peripheral vascular disease	Urine VDBP higher in microalbuminuria group versus normoalbuminuria and controls and macroalbuminuria group higher than microalbuminuria, $p < 0.001$ AUROC 0.97 for detection of microalbuminuria from controls. Cut-off at 216 ng/mg
Satirapoj et al. 2015[122]	Periostin	*N* = 328 + 30 healthy controls	T2D Mean age >60 years 50.3% males Thailand	T2D subjects divided into 3 groups based on albuminuria: Normo-, micro- and macro-albuminuria	Active urinary tract infection, renal disease other than DKD, cancer, liver disease, active or chronic infection or	Urine periostin significantly raised with progressing stages of albuminuria compared with controls, $p < 0.001$

(Continues)

TABLE 6 (Continued)

Author and Year	Biomarkers	Sample Size ± controls	Study characteristics (diabetes type, age, sex, region)	Population distribution	Exclusion criteria	Findings
					inflammatory disorders, pregnancy, history of myocardial, stroke or peripheral vascular disease	Periostin independently associated with albuminuria, $p < 0.001$ and declining eGFR, $p = 0.002$ Periostin exhibited strong potential as diagnostic marker for all 3 albuminuria stages 0.78, 0.99 and 0.95 respectively
El Dawla et al. 2019[123]	E-cadherin Periostin	$N = 71 + 19$ healthy controls	T2D Age 45–55 years ~60% males Egypt	Subjects divided into 3 groups: Normo-, micro- and macro-albuminuria	T1D, pregnancy, UTI, neoplastic disorders, severe liver disease, infection (acute or chronic), autoimmune conditions, CHF, ischaemic heart disease, kidney disease other than DKD	E-cadherin significantly lower with progressive albuminuria, $p < 0.05$ Periostin levels significantly higher with progressive albuminuria stage, $p < 0.05$ AUROC for detection of microalbuminuria: E-cadherin 0.99 and Periostin 0.83
Chen et al 2017[124]	Cystatin C B2M	$N = 200$	T2D China	Subjects divided into 3 groups: Normo-, micro- and macro-albuminuria	-	AUROC of 0.87 (sensitivity 92%) for cystatin C and 0.79 (sensitivity 80%) for B2M for micro-albuminuria
Kim et al. 2016[125]	NAG	$N = 592$ (*29 prediabetes and 563 diabetes*)	T2D Median age >55 years 62.5% males Korea	-	<20 years of age, T1D, use of sodium–glucose cotransporter 2 inhibitor, pregnancy	Urine NAG positively correlated with UACR, $p < 0.001$ and negatively correlated with eGFR measured via CKD-EPI equation, $p < 0.001$ and not significantly correlated for MDRD equation, $p = 0.10$
Akour et al. 2019[126]	Megalin	$N = 209$	T2D Mean age 55.6 years *Not stated* Jordan	Subjects divided based on levels of urinary megalin: High versus low	Pregnancy, UTI or other glomerulopathies, refused consent, systemic diseases involving the kidneys	Urine megalin negatively correlated with eGFR and associated with progression factors of DKD (*urine albumin*, *SBP*, *HbA1c*, *triglycerides*, *Vitamin D3*)

TABLE 6 (Continued)

Author and Year	Biomarkers	Sample Size ± controls	Study characteristics (diabetes type, age, sex, region)	Population distribution	Exclusion criteria	Findings
Jayakumar et al. 2014[127]	Netrin-1	*N* = 87 + 42 non-diabetic controls	T1D and T2D Mean age >50 years 71.3% males Netherlands	Subjects divided into 3 groups: Normo-, micro- and macro-albuminuria	Cancer, infections, or inflammatory conditions, renal disease other than diabetic nephropathy, use of nephrotoxic drugs, kidney transplant, pregnant	Urine netrin-1 significantly higher in diabetes group versus controls, $p < 0.05$, but no significant difference between albuminuria Significant association with eGFR, $p = 0.004$ and albuminuria, $p = 0.0002$, after adjustment for age and sex
Tsai et al. 2015[128]	Cyclophilin A	*N* = 100 + 20 healthy controls	T2D Mean age >40 years 55% males Taiwan	Subjects divided into stages of CKD[1–5]: 20 in each stage	Age <20 years, infectious disease, inflammatory disease, liver disease, smokers, malignancy, use of medications for conditions other than HTN, diabetes, hyperlipidaemia, hyperuricemia, and CVD	Cyclophilin A increased with worsening CKD stage, $p < 0.001$ Cyclophilin A had an AUROC of 0.85 for diagnosing CKD stage 2 with sensitivity of 90%
Gao et al. 2018[129]	MIOX	*N* = 90 + 30 age, sex matched healthy controls	T2D Mean age >45 years 54.4% males China	Subjects divided into 3 groups: Normo-, micro- and macro-albuminuria	Use of adrenal cortical hormones, immune-suppression drugs or RAAS inhibitors, urinary tract infections, or with inflammatory, neoplastic, cardiovascular, hepatic, renal, lung or neuro-endocrine disease	Serum and urine MIOX were significantly increased progressively with worsening albuminuria and compared to controls, $p < 0.05$ Serum and urine MIOX found to have high AUROC of 0.98 in predicting diabetes from controls
Li et al. 2019[130]	Glypican-5	*N* = 57 + 20 healthy controls	T2D Mean age >55 years 54.4% males China	Subjects divided into 2 groups: Normo- and macro-albuminuria	T1D, bilateral renal-artery stenosis, coronary heart disease, cardiomyopathy, serious arrhythmia, cerebrovascular disease, UTI, or acute or severe chronic liver disease	Glypican-5 higher in macroalbuminuria group versus normoalbuminuria, $p = 0.004$ and controls, $p < 0.01$

(Continues)

TABLE 6 (Continued)

Author and Year	Biomarkers	Sample Size ± controls	Study characteristics (diabetes type, age, sex, region)	Population distribution	Exclusion criteria	Findings
Chiu et al. 2018[131]	Cyclophilin A CD147	*N* = 131	T2D Mean age >69 years ~40% males Taiwan	Subjects divided based on level of biomarker	Active infection, pregnancy, recent admission to a hospital, malignancy, severe liver cirrhosis and autoimmune disease	High cyclophilin A and CD147 associated with higher albuminuria, $p = 0.009$ and $p = 0.029$, respectively
Kim et al. 2014[132]	NAP	*N* = 118	T2D Mean age 56.8 years 43.2% males Korea	Subjects divided based on levels of urinary NAP	Active UTI, renal disease other than DKD, neoplastic disorder, thyroid disorder, severe liver dysfunction, active or chronic infection and inflammation, pregnancy, recent AMI, stroke or PVD	The urinary NAP to creatinine ratio was significantly correlated with UACR, KIM-1 NGAL and L-FABP, $p < 0.001$. No correlation with eGFR, $p = 0.160$

Biomarkers abbreviations: B2M, beta-2-microglobulin; CD147, cluster of differentiation-147; DcR2, decoy receptor 2; GAL, beta-galactosidase; IgG, immunoglobulin G; IgM, immunoglobulin M; KIM-1, kidney injury molecule-1; L-FABP, L-type fatty acid binding protein; MIOX, myo-inositol oxygenase; NAG, N-acetyl beta-glucosaminidase; NAP, non-albumin proteinuria; NGAL, neutrophil gelatinase-associated lipocalin; OPN, osteopontin; UMOD, uromodulin; βTP, beta trace protein; RBP, retinol binding protein; VEGF, vascular endothelial growth factor; VDBP, vitamin-D binding protein.

Other abbreviations: ACE, angiotensin converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin II receptor blockers; AUROC, area under receiver operating characteristic; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, chronic kidney disease epidemiology collaboration; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HTN, hypertension; MDRD, modification of diet in renal disease; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio; PVD, peripheral vascular disease; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; TII, tubulointerstitial injury; T2D, type-2 diabetes; T1D, type-1 diabetes; UACR, urine albumin–creatinine ratio; UTI, urinary tract infection.

TABLE 7 Longitudinal studies of kidney injury biomarkers in diabetic kidney disease, January 2014 to February 2020

Author and Year	Biomarkers	Study characteristics	Baseline eGFR[a] and albuminuria[b]	Follow-up period	Renal outcomes	Findings
Bjornstad et al. 2018[134]	13 plasma kidney injury biomarkers	*N* = 527 T1D Mean age 39 years 47% males USA	CKD stage 1 and 2 Normoalbuminuria	Mean of 12 years	Development of eGFR <60 ml/min/1.73 m^2 Development of albuminuria (UACR ≥30 mg/g)	Biomarkers KIM-1, Cystatin C and UMOD significantly associated with development of eGFR <60, $p < 0.05$ while Osteoactivin and UMOD associated with development of albuminuria (UACR ≥30 mg/g), $p < 0.05$ after adjusting for clinical variables The group consisting of biomarkers B2M, Cystatin C, NGAL and OPN improved C-statistic from 0.89 to 0.92, $p = 0.049$ for eGFR <60 outcome. No significant improvement noted for the other renal outcome
Panduru et al. 2015[135]	KIM-1	*N* = 1573 T1D Mean age ~40 years ~50% males Finland	CKD stage 1–3 Normo-, micro- and macro-albuminuria	6 years	Progression to higher stage of albuminuria towards ESKD	Urinary KIM-1 found not to be an independent predictor of albuminuria progression, HR 0.8–1.2, $p > 0.05$ KIM-1 (AUROC 0.73) did not outperform eGFR (AUROC 0.86) and AER (AUROC 0.79) and when combined there was no significant improvement to AUROC, $p > 0.05$
Fufaa et al. 2015[136]	KIM-1, L-FABP NAG NGAL	*N* = 260 T2D Mean age 42 years 31% males USA—Pima Indians	CKD stage 1 and 2 Normo-, micro- and macro-albuminuria	Median 14 years	ESKD	NGAL and L-FABP associated with ESKD, HR 1.59 (1.20–2.11) and 0.40 (0.19–0.83) respectively. This was not the case for KIM-1 and NAG

(Continues)

TABLE 7 (Continued)

Author and Year	Biomarkers	Study characteristics	Baseline eGFR[a] and albuminuria[b]	Follow-up period	Renal outcomes	Findings
						Both NGAL and L-FABP significantly improved C-statistic from 0.828 (clinical model) to 0.833 and 0.832, $p < 0.05$ respectively
Mise et al. 2016[137]	NAG B2M	$N = 149$ T2D Mean age 58 years 79% males Japan	CKD stage 3 Normo-, micro- and macro-albuminuria (*the majority*)	Median of 2.3 years	Decline in eGFR ≥50% from baseline or needing dialysis (*ESKD indicator*)	Urine NAG and B2M did not demonstrate improved predictive ability after adjusting for clinical and biochemical predictors in advanced DKD, HR 1.14 (0.84–1.55) and 1.23 (0.94–1.62) respectively
Foster et al. 2015[138]	BTP B2M	$N = 250$ T2D Mean age 42 years 31% males USA—Pima Indians	CKD stage 1 and 2 Normo-, micro- and macro-albuminuria	Median 14 years	ESKD	BTP but not B2M significantly associated with ESKD, HR 1.53, $p < 0.05$ and 1.54, $p > 0.05$ respectively Both BTP and B2M did not significantly improve C-statistic, $p = 0.4$ from baseline model of clinical variables
Bjornstad et al. 2019[139]	UMOD	$N = 527$ T1D Mean age 39 years 47% males USA	CKD stage 1 and 2 Normoalbuminuria	12 years	Development of eGFR <60 ml/min/1.73 m^2 Development of albuminuria (UACR ≥30 mg/g) Rapid GFR decline (>3 ml/min/1.73 m^2/year)	Higher UMOD associated with lower risk of developing eGFR <60, OR 0.44, $p = 0.01$ and microalbuminuria or worse, OR 0.37, $p = 0.02$ and rapid GFR decline, OR 0.56, $p = 0.02$ UMOD significantly improved C-statistic for developing eGFR <60 by 0.08, $p = 0.01$ but did not significantly improve C-statistic for the other 2 renal outcomes

TABLE 7 (Continued)

Author and Year	Biomarkers	Study characteristics	Baseline eGFR[a] and albuminuria[b]	Follow-up period	Renal outcomes	Findings
Devetzis et al. 2015[140]	CAF	*N* = 71 T2D Mean age 70 years ~50% males Greece	CKD stage 3 Micro- and macro-albuminuria	12 months	eGFR decline Onset of ESKD, dialysis or transplant	CAF significantly associated with eGFR decline >1 ml/min/1,73 m^2, OR 4.15, $p = 0.031$ CAF strongly correlated with progression to ESKD, $r = 0.34$, $p = 0.004$
Gordin et al 2014[141]	OPN	*N* = 2145 T1D Mean age 37 years ~50% males Finland	CKD stage 1 and 2 Normo-, micro- and macro-albuminuria	Median of 10.5 years	Progression to higher stages of albuminuria towards ESKD	OPN associated with progression to higher stages of albuminuria towards ESKD, HR 1.01–1.03, $p < 0.05$
Zylka et al. 2018[114] *Longitudinal component*	Cystatin C KIM-1 NGAL Transferrin IgG UMOD	*N* = 29 T2D Mean age ~64 years ~60% males Poland	CKD stage 1 and 2 Normoalbuminuria	>1 year	eGFR decline and increase in UACR/trajectory	Urine NGAL significantly associated with eGFR decline, $p < 0.05$ while urine NGAL, KIM-1 and IgG significantly associated with increase in UACR $p < 0.05$
Li et al. 2019[130] *Longitudinal component*	Glypican-5	*N* = 37 T2D Mean age ~55 years ~50% males China	CKD stage 2 and 3 Macroalbuminuria	52 weeks	eGFR decline/trajectory	Urinary glypican associated with significant increase in albuminuria and decline in eGFR, $p < 0.001$
Chiu et al. 2018[131] *Longitudinal component*	Cyclophilin A CD147	*N* = 131 T2D Mean age 70 years ~40% males Taiwan	CKD stage 2 and 3 Micro- and macro-albuminuria	Mean of 11.2 years	eGFR decline/trajectory	Baseline plasma cyclophilin A correlated with rapid declining eGFR, $p = 0.016$ Cut-off value for cyclophilin A of >93.6 ng/ml associated with worse eGFR decline compared to group with <93.6 ng/ml, $p = 0.001$

Biomarkers abbreviations: B2M, beta-2-microglobulin; BTP, beta trace protein; CAF, C-terminal fragment of agrin; CD146, cluster of differentiation 147; IgG, immunoglobulin G; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid-binding protein; NAG, N-acetyl beta-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; OPN, osteopontin; UMOD, uromodulin.

Other abbreviations: AUROC, area under receiver operating characteristic; CKD, chronic kidney disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; HR, hazard ratio; OR, odds ratio; T1D, type-1 diabetes; T2D, type-2 diabetes; UACR, urine albumin–creatinine ratio; USA, United States of America.

[a]eGFR expressed in terms of CKD stages, 1, 2, 3, 4 and 5 which corresponds with ≥90, 60–89, 30–59, 15–29 and < 15 ml/min/1.73 m^2, respectively.

[b]Albuminuria expressed in terms of stages, Normoalbuminuria (ACR <30 mg/g), Microalbuminuria (30–300 mg/g) and Macroalbuminuria (>300 mg/g).

sizes and/or shorter follow-up periods as well as those assessing early stages of DKD, often tend to use surrogate endpoints.[65,67,100,101]

Unlike ESKD, studies employing surrogate endpoints have reported conflicting results for TNFRs. A panel of serum biomarkers comprising TNFR-1 improved the C-statistic from 0.88 to 0.95 for the outcome of eGFR <30 ml/min/1.73 m^2 over 5 years in T1D[86] (Table 5). A separate study in T2D found TNFR-1 to associate with increased risk of eGFR decline ≥40%, HR 1.8, $p < 0.0001$ and rapid decline in eGFR slope, OR 2.3, $p < 0.0001$[78] (Table 4). TNFR-1 and 2 were also found to predict eGFR decline ≥30 ml/min/1.73 m^2 if baseline eGFR > 60 or ≥50% decline if baseline eGFR < 60, improving C-statistic from 0.68 to >0.7, $p < 0.05$[87] (Table 5). In contrast, studies utilising eGFR slope trajectories have generally reported poor predictive performances of TNFRs[88–91] (Table 5). One study reported no significant improvement to the C-statistic for the model comprising of TNFR-1, $p = 0.262$.[88] Another study found no association between TNFRs and eGFR slope progression over 2–6 years, $p > 0.05$.[89] A validation study involving 481 subjects with T2D also found negligible contribution made by individual biomarkers, including TNFR1, in predicting declining eGFR slope trajectory, $R^2 < 1\%$.[90] The lack of association observed in these studies may be attributed to the reliability of eGFR slope as a surrogate endpoint. The use of eGFR slopes or trajectories assumes that eGFR follows a linear decline pattern.[70,102] However, that is not always the case and in fact fluctuations in eGFR are more commonly observed in people with diabetes.[102] Despite the limitation, its use has been validated for early stages of CKD and in shorter duration studies.[67] Given that studies utilising surrogate endpoints have generally involved participants with preserved kidney function (Tables 4 and 5), it may be reasonable to assume that TNFRs are not reliable predictors at early stages of DKD. This is further supported by Mayer et al.[92] who found TNFR-1 to not be a significant predictor of eGFR slope when baseline eGFR ≥ 60 ml/min/1.73 m^2 compared to when eGFR < 60 ml/min/1.73 m^2. TNFRs therefore have potential as biomarkers for DKD in more advanced stages of kidney injury.

Apart from TNFRs, other inflammatory biomarkers have also demonstrated an association with ESKD and/or various surrogate outcomes in longitudinal studies. These are: CRP, angiopoetin-like protein 2 (ANGPTL2), ICAM-1, eotaxin, vascular adhesion protein-1 (VAP-1), growth differentiation factor-15 (GDF-15), MCP-1, TNF-alpha and some complement proteins as part of the Promarker D panel[58,79–84,93,94] (Tables 4 and 5). However, when compared to the number of studies conducted on TNFRs, these biomarkers fall short, indicating the potential need for more extensive research to validate their association with DKD.

4.3 | Kidney injury biomarkers in DKD

Biomarkers of kidney injury can be divided into two categories, glomerular and tubular markers.[103] Glomerular biomarkers encompass markers originating from the glomerulus from structures such as podocytes, endothelium, basement membrane and mesangial matrix.[30,103] Examples include, transferrin, immunoglobulin G (IgG) and laminin.[103] Tubular biomarkers contrastingly represent those originating from the renal tubules.[103,104] Reports suggest that kidney injury markers are present early on in DKD and precede the onset of albuminuria.[103] Majority of studies have involved primarily markers of tubular injury such as, kidney injury molecule-1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), neutrophil gelatinase-associated lipocalin (NGAL) and beta-2-microglobulin (B2M).[104]

4.3.1 | Cross-sectional studies

Several cross-sectional studies involving participants with diabetes from diverse backgrounds and clinical characteristics have reported significantly higher levels of NGAL in microalbuminuria compared to those with normoalbuminuria and/or controls, $p < 0.05$[105–114] (Table 6). The cumulative AUROC reported for NGAL was >0.80 for predicting microalbuminuria across several studies[105,108,109,111,112] (Table 6). However, majority of these studies have utilised a relatively small population of <200 participants. Moreover, only Bjornstad et al.[107] reported associations in T1D while the remaining studies were all conducted in population with T2D, indicating lack of validation in T1D. Studies have also predominantly assessed for association with albuminuria and not eGFR. Hence for NGAL to be considered for clinical use as biomarker for DKD, further evaluation in T1D population and the relationship with eGFR needs to be exemplified.

Aside from NGAL, several other biomarkers of kidney injury have also been frequently studied in cross-sectional studies. These include, NAG, B2M, KIM-1, osteopontin (OPN), Cystatin C, retinol binding protein (RBP), vitamin D binding protein (VDBP), periostin and transferrin (Tables 3 and 6). Increased levels of these biomarkers have been found to associate with microalbuminuria in diabetes.[63,64,105–107,109,112,114–123]

Unlike NGAL, studies of NAG, B2M and OPN have generally reported weaker ability to detect DKD. NAG for instance exhibited modest predictive ability with AUROC of 0.61 and 0.78 in two large studies involving >300 participants[116,117] (Table 6). Similarly, B2M had moderate to low AUROC of 0.79, 0.65 and 0.58 in three separate studies involving T2D subjects[117,118,124] (Table 6). OPN which is a protein mainly expressed in bone as well as glomerular basement membrane and endothelial cells, also displayed poor performance with AUROC of 0.69 and 0.73 and did not associate with stages of albuminuria, $p > 0.05$[64,107,119] (Tables 3 and 6). On the other hand, studies evaluating the performance of cystatin C and RBP have reported conflicting diagnostic performances. Two studies reported moderate to low AUROC of <0.8 for cystatin C in detecting micro- and macro-albuminuria, while two other studies reported high AUROC of 1 and 0.80 for detection of microalbuminuria and eGFR <60 ml/min, respectively[64,105,109,112] (Tables 3 and 6). Similarly, RBP was found to have low AUROC of 0.57 in one study and high AUROC of 0.89 in another[64,117] (Tables 3 and 6). The other biomarkers namely, transferrin, periostin and VDBP have shown high AUROC of

>0.8 in separate studies while KIM-1 had a high AUROC of 0.84 in one study[63,64,114,117,121–123] (Tables 3 and 6).

Overall, like NGAL, these studies have primarily investigated for an association with albuminuria and involved people with T2D. There appears to be lack of studies assessing association with eGFR and T1D subjects. Furthermore, studies have also generally involved small number of participants. Interestingly, for studies which have investigated the association with eGFR, the choice of eGFR equation appears to influence on the study outcome. For instance, in a study by Kim et al.[125] significant correlation of NAG was reported with chronic kidney disease epidemiology collaboration (CKD-EPI) eGFR equation, $p < 0.001$ but not with modification of diet in renal disease (MDRD) eGFR equation, $p = 0.10$. This emphasises the inaccuracies that exist with eGFR as a marker of kidney function.[133]

Other kidney injury biomarkers that were investigated in cross-sectional studies but infrequently cited include, urine megalin, uromodulin, immunoglobulins, netrin-1, cyclophilin-A, myo-inositol oxygenase and glypican-5[107,114,119,126–131] (Table 6). Further research would assist with validation of these markers.

4.3.2 | Longitudinal cohort studies

Several longitudinal studies have reported the tubular injury marker KIM-1 as a potential candidate in predicting the development and progression of DKD. Of note are three recent publications by Colombo et al.[86,95,96] reporting superior performance of KIM-1 in predicting eGFR decline ≥20%, progression to eGFR <30 ml/min/1.73 m^2 and rapid eGFR slope progression (Table 5). Another study reported the highest increase in AUROC from 0.68 to 0.74 after the addition of KIM-1 in predicting declining eGFR ≥30 ml/min/1.73 m^2 or ≥50% from baseline[87] (Table 5). Furthermore, KIM-1 and B2M were the two shortlisted kidney injury biomarkers that were associated with increased risk of rapid eGFR slope progression, OR 1.93 and 3.19, respectively[97] (Table 5). KIM-1 is therefore an attractive biomarker with strong potential in DKD. Note that these studies have predominantly utilised surrogate endpoints.

Despite KIM-1 demonstrating significant predictive potential, several studies have argued otherwise. In a study involving 527 T1D subjects, KIM-1 was part of a panel found to exhibit no significant improvement in AUROC for predicting progression to eGFR <60 ml/min/1.73 m^2 and microalbuminuria, $p > 0.05$[134] (Table 7). Moreover, KIM-1 did not predict progression to higher stages of albuminuria and ESKD over 6 years in T1D, HR 0.8–1.2, $p > 0.05$[135] (Table 7). KIM-1 was also not associated with increased risk of developing ESKD over 14 years in T2D, HR 0.95 (0.71–1.28), and did not significantly improve the C-statistic, $p = 0.725$[136] (Table 7). Note that in this case, two of the studies reporting poor performance of KIM-1 have utilised ESKD as the renal outcome. Therefore, although KIM-1 is a biomarker with potential, questions remain on its association with kidney function decline in people with diabetes.

B2M is another biomarker reported to have strong potential in DKD across several longitudinal studies. It is expressed by all nucleated cells as a component of the major histocompatibility class 1 molecule that is filtered by the glomerulus and reabsorbed by proximal tubules of the kidney.[95,118] In the study by Bjornstad et al.[134] the biomarker panel consisting of B2M, cystatin C, NGAL and OPN significantly improved AUROC by 0.02, $p = 0.049$ for predicting progression to eGFR <60 ml/min/1.73 m^2 (Table 7). In Colombo et al.[95] B2M had a cumulative OR >1.5, $p < 0.001$ across three separate cohorts and together with KIM-1 displayed robust ability to predict eGFR decline of ≥20% (Table 5). B2M is also part of a collection of kidney injury proteins that makes up non-albumin proteinuria (NAP).[98,132] NAP was found to predict annual eGFR decline and eGFR <60 ml/min/1.73 m^2 with the highest *C*-statistic of 0.83 compared to KIM-1 and NGAL which had *C*-statistic of <0.7.[98]

However, like KIM-1, studies have also reported conflicting results for B2M. For instance, no association of B2M was reported with ≥50% decline in eGFR or ESKD over 2 years, HR 1.23 (0.94–1.62)[137] (Table 7). Similarly, no association with ESKD was noted after adjustment for mGFR and clinical variables, HR of 1.54 (0.98–2.42)[138] (Table 7). Note that studies involving surrogate endpoints tended to show promising results for both KIM-1 and B2M, unlike those involving ESKD. This could indicate the need for further validation with ESKD or alternatively, could suggest enhanced performances of KIM-1 and B2M at early stages of DKD since surrogate endpoints tend to involve participants with preserved kidney function at baseline.[65,67,100,101] However, the use of surrogate endpoints requires careful consideration primarily because of the inherent inaccuracies surrounding eGFR.[67] For instance, eGFR decline <30 ml/min/1.73 m^2 may not be a reliable endpoint given that eGFR can differ from mGFR by up to 30%.[32]

Other biomarkers to have undergone longitudinal analysis namely glypican-5, cyclophilin A, uromodulin (UMOD), C-terminal fragment of agrin (CAF), beta-trace protein (BTP) and OPN have also demonstrated significant associations with kidney outcomes[130,131,138–141] (Table 7). However, these biomarkers have not been frequently studied compared to the above-mentioned biomarkers and hence require further validation.

4.4 | Biomarkers and progression of DKD

The relationship of biomarkers with respect to progression and pathogenesis of DKD is yet to be fully characterised and represents an area of active research.[28] Few studies have attempted to elucidate the temporal association of biomarkers with declining kidney function. In the study by Baker et al.,[85] levels of inflammatory biomarkers including TNFR-1 were observed to increase over time with rising age, as well as, in those who developed renal outcomes of eGFR <60 ml/min and macroalbuminuria. Similarly, we have demonstrated an increase in the concentration of TNFR-1 in parallel with declining eGFR over 8 years amongst participants with eGFR decline of >3.5 ml/min/1.73 m^2/year with final eGFR of <60 ml/min/1.73 m^2.[142] This increase in biomarker levels with time have been reported to precede changes in albuminuria and lends itself to use at early stages

of DKD. For instance, in a recent study by Colombo et al,[86] serum biomarkers including TNFR-1 and KIM-1 were found to be elevated in participants with normal baseline eGFR prior to an increase in albuminuria amongst those who subsequently progressed to eGFR <30 ml/min/1.73 m^2 during follow-up. Hence, there appears to be a potential role for biomarkers in detecting kidney function decline before the onset of albuminuria. Furthermore, there is limited understanding of whether high levels of serum biomarkers observed in DKD are a consequence of increased production or reduced renal clearance from compromised kidney function. In the recent publication by Niewczas et al.[70] increased urine excretion of KRIS proteins was noted amongst those at risk of ESKD, highlighting that raised levels of these markers were unlikely a result of poor kidney function, but rather of excess production. This could prove useful in the detection of kidney function decline in people with diabetes.

Findings from this review also appear to indicate a potential temporal relationship of biomarkers with declining kidney function. For instance, TNFRs demonstrated stronger association with ESKD and inconsistent association with surrogate endpoints, while KIM-1 and B2M demonstrated more robust association with surrogate endpoints than with ESKD. This could suggest potential upregulation of TNFRs at later stages of kidney injury and their role as late markers of disease progression. KIM-1 and B2M alternatively may be better suited as markers of early decline in kidney function.

4.5 | Potential biomarkers of inflammation and kidney injury in DKD

In determining biomarkers with most potential in DKD, several factors require consideration, one involves the way participants are categorised within cross-sectional studies. Most studies have stratified participants into stages of albuminuria as markers of DKD, namely, microalbuminuria and/or macroalbuminuria.[40–42,44,51–57,59,63,64,105,106,108–111,113–116,119–124,127,129,130] However, the use of albuminuria is contentious given that progression in the albuminuric stage is not a necessary prerequisite for the development of DKD.[4,14] Hence, biomarkers associated with albuminuria do not capture progressive DKD without albuminuria. In addition, albuminuria is not a specific marker of DKD and can be caused by other conditions for instance hypertension, heart failure, infections of urinary tract and diet rich in protein.[32] This has ramifications on studies with poorly defined exclusion criteria. Additionally, microalbuminuria being prone to fluctuate also means that biomarkers associated with this outcome may not be reliable.[14,17] In the 2019 study by Niewczas et al.,[70] albuminuria was not considered a risk factor but rather an intermediate phase in the disease process highlighting the gradual shift from using it as an endpoint. Nonetheless, a recent meta-analysis involving observational studies reported consistent association of changes in albuminuria with risk of ESKD, supporting its utility in clinical trials.[69]

Few cross-sectional studies have distributed subjects based on eGFR,[48,50,60,62] while few have used both eGFR and albuminuria.[46,107,112,117,128] This emphasises the need for more biomarker studies to investigate the association with both eGFR and albuminuria.[143] Care must still be taken when interpreting eGFR which lacks accuracy and is prone to misclassification.[18,32]

Another important factor is the choice of endpoints used in studies. For instance, biomarkers associated with progressive albuminuria may differ from those with declining eGFR, as in the study by Roy et al.[80] and Bjornstad et al.[134] (Tables 4 and 7). Furthermore, differing associations of biomarkers with eGFR slope and ESKD were observed, for instance in the study by Agarwal et al.[89] (Table 5). Thus, the choice of endpoints can potentially be a confounding factor with biomarkers favouring certain endpoints.[89]

Another consideration involves duration of studies. Baker et al.[85] assessed biomarkers at two timepoints, 3-years and 10-years. No association of biomarkers was noted at 3-years for developing macroalbuminuria, however, at 10-years, TNFR2, E-selectin and plasminogen activator inhibitor-1(PAI-1) were significantly associated, cumulative HR > 1.15, $p < 0.05$.[85] This implies that follow-up time can influence on study outcomes. The reliability of *C*-statistic/AUROC is another limiting factor. An improvement or a high *C*-statistic may not always translate to clinical usefulness and what constitutes an acceptable *C*-statistic is still unclear.[99]

Overall, the association of TNFRs with DKD have been validated across multiple studies involving both types of diabetes and diverse population backgrounds. Studies of TNFRs have also involved adequate sample sizes and utilised variety of endpoints. Hence, when accounting for the following factors: renal endpoints, validation, sample size, follow-up time and C-statistic, TNFRs emerge as the strongest inflammatory biomarker candidate. In terms of kidney injury biomarkers, research appears to target biomarkers of tubular injury, particularly, KIM-1, B2M and NGAL. However, as evident in discussion, findings have largely been conflicting, highlighting the need for further validation especially with clinical endpoints and in people with T1D.

4.6 | Single or multiple biomarkers?

There are opposing views in literature with regards to the utility of single biomarker or panel of biomarkers in predicting DKD. Pena et al.[88] reported enhanced predictive ability of multiple biomarkers representing distinct pathways of DKD pathogenesis in a cohort of T2D. This was despite individual markers displaying no significant association with kidney function decline implying potential for synergy between groups of markers.[88] Another study reported improved prediction of multiple biomarkers for the outcome of declining eGFR slope at various levels of eGFR, R^2 of >15%.[92] In this study, most single biomarkers made only the modest contribution, R^2 < 5%. Hence, the utility and performance of multiple biomarkers seem promising and appear to be the direction of future research, especially given the advancement in proteomics and metabolomics which yield large datasets.[21] Additionally, given the complex and multifactorial nature of DKD, multiple biomarkers

representing different aspects of the disease process may come close to capturing the biological blueprint of an individual, enabling enhanced predictive ability.[24] However, there is an issue of cost, access and availability which are crucial determinants to consider for clinical application at present.[6,95] In fact, a simple, reliable, cheap and accurate biomarker is highly desirable and more likely to be accepted for clinical use.[6] The study by Colombo et al.[95] revealed no difference between a larger panel of biomarkers when compared with just two serum biomarkers namely KIM-1 and B2M in predicting renal outcomes in diabetes. Moreover, studies that have investigated multiple biomarkers have also reported significant association with only a few biomarkers, for instance, studies of Agarwal et al.[89] Roy et al.[80] and another recent publication by Colombo et al.[96] (Tables 4 and 5). Hence, even though multiple biomarkers may provide a more accurate prediction of DKD, single biomarkers may be more practical for use clinically.

4.7 | Other biomarkers

Biomarker research is rapidly growing and numerous other markers relating to downstream consequences of inflammatory response such as reactive oxygen species (ROS), inflammatory cell infiltrates, inflammasome activation, intracellular cell components/factors such as genetic, ions and lipid markers have also been implicated in DKD.[144–150] Discussion of these markers and their association with DKD is beyond the scope of this review.

In recent years, studies have emerged highlighting the increasing significance of these markers in the development of kidney injury in diabetes. In a 2016 study by Yuan et al.[144] increase in the expression of NLRC4-inflammasome as well as macrophages and intracellular signalling pathways of MAP Kinase and NF-kappaB was found in DKD. Additionally, oxidative changes to proteins have been demonstrated in the 2019 study by Almogbel et al.[148] which looked at protein carbonylation in DKD. Oxidative stress is a well-known downstream mechanism in the pathogenesis of DKD.

With respect to nucleic acid markers, a 2018 meta-analysis by Gholaminejad et al[149] identified five miRNAs to be associated with DKD from 53 miRNA studies selected for analysis. More recently, Fayed et al.[151] found urinary mRNA levels of podocyte injury proteins (Nephrin, Podocin and Podocalyxin) to correlate with albuminuria and serum creatinine. In the study by Mori et al.[152] single nucleotide polymorphisms in the gene which encodes for the enzyme protein 11-beta hydroxysteroid dehydrogenase 1 was found to associate with increased risk of DKD in T1D cohort.The increasing relevance of lipid markers has led to the emergence of lipidomic, a branch of metabolomics that focussed on study of lipids and their derivatives.[147] With regards to ion markers, in 2017, Bherwani et al.[150] found hypomagnesaemia to be associated with increased DKD prevalence. Araki et al.[153] found raised urine K+ excretion to be associated with slow decline in kidney function in T2D. More recently, studies on the progression of chronic kidney disease have found low NaCl as a consequence of metabolic acidosis, to be a predictor of kidney decline over 4 years.[154]

In summary, the abundance of markers that currently exist and those to be discovered in the future reflects the ever-changing complexity of DKD and illustrates the challenge of identifying a reliable biomarker.

4.8 | Conclusion

In conclusion, after accounting for factors such as sample size, validation and endpoints, of the inflammatory biomarkers, TNFRs demonstrated greatest potential as markers of DKD. With respect to kidney injury biomarkers, potential candidates are KIM-1, B2M and NGAL, although further studies are needed to validate their performance. Future cross-sectional studies should aim to consider the use of both eGFR and albuminuria as predefined outcomes when enrolling participants as there seems to be lack of studies utilising them. Finally, when deciding on clinical utility, at present, single rather than a panel of multiple biomarkers may be preferred as they can be just as reliable, cost effective, easier to access, collect and potentially simpler to interpret. Biomarkers outside the scope of this review (RNAs, ROS, lipids, ions and metabolites) also warrant consideration for utility as markers in DKD.

AUTHOR CONTRIBUTIONS

Authors Vuthi Khanijou, Neda Zafari, Melinda T. Coughlan, Richard J. MacIsaac, Elif I. Ekinci worked collaboratively in the production of this review article. Vuthi Khanijou, Neda Zafari and Elif I. Ekinci were involved in screening articles for inclusion in the review. Vuthi Khanijou and Neda Zafari contributed to draughting of the manuscript, figures, and tables. Melinda T. Coughlan, Richard J. MacIsaac and Elif I. Ekinci contributed to the evaluation, analysis and professional critique of the review. All authors have read and approve of the final manuscript.

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CONFLICT OF INTEREST

No conflict of interest to be disclosed.

DATA AVAILABILITY STATEMENT

No datasets were generated or analysed in this review; hence data sharing is not applicable. Supplementary material can be accessed via the link in bibliography. File uploaded to Figshare Data Repository.

ETHICS STATEMENT

No ethics statement.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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