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]
In recent years, considerable attention has turned towards the disease (CKD) and end stage kidney disease (ESKD). 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).

Globally, diabetes is amongst the leading cause of chronic kidney disease (CKD) and end stage kidney disease (ESKD). 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). 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. 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.

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). 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).

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.9–12 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 m², 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.

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). 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. 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.

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).

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 m² 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

| Biomarker       | Biomarker       | Biomarker       |
|-----------------|-----------------|-----------------|
| 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

| Category       | 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

| Category       | Adipocytokines (Adiponectin, DPP-4, vaspin, omentin) | Vitamin C | Vitamin D |
|----------------|------------------------------------------------------|-----------|-----------|
|                |                                                     |           |           |

#### Endothelial/Vascular markers

| Category       | VEGF | Endocan | Selectin |
|----------------|------|---------|----------|
|                | Angiopoietin 2 | Fibrinogen |         |
|                | Endostatin     | LRG1      |          |

#### Fibrosis markers

| Category       | MMPs |
|----------------|------|
|                |      |

#### Oxidative stress markers

| Category       | Protein carbonylation | Ischaemia modified albumin | Heme oxygenase-1 |
|----------------|------------------------|-----------------------------|------------------|
|                |                        |                             |                  |

#### Others

| Category       | 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; AQPS, 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; L, 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, nephrilysin; 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; TNFa, tumour necrosis factor-a; 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.\textsuperscript{28–31} eGFR, estimated glomerular filtration rate; RAAS, renin angiotensin aldosterone system
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. 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. Studies have found that models comprising of such risk factors can accurately predict the development of renal events in diabetes and CKD. 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.

4.2 | Inflammatory biomarkers in DKD

Inflammation is recognised as a crucial player in the pathogenesis of DKD. 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. 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. 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. 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).
| Author and Year | Biomarkers | Sample size ± controls | Study characteristics (diabetes type, age, sex, region) | Population distribution | Exclusion criteria | Findings |
|-----------------|------------|------------------------|--------------------------------------------------------|-------------------------|-------------------|----------|
| Karimi et al. 2018 | 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 | 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 | 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 | VCAM-1, ICAM-1 | N = 1950 | T2D 57.5 ± 10.8 years 50.3% males Singapore (multiethnic 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, \( p = 0.002 \) while no significant association reported for ICAM-1 with eGFR, \( p = 0.506 \) and albuminuria, \( p = 0.061 \) |
| Pojskic et al. 2018 | CRP | N = 69 | T2D Mean age >60 years 34.8% males Bosnia and Herzegovina | Subjects divided into two groups: Normal albuminuria 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 normalalbuminuria \( p = 0.005 \) Raised hs-CRP associated with increased risk of microalbuminuria \( (OR=1.115 \ [1.014-1.225] ; p = 0.025) \) |
| Author and Year | Biomarkers | Sample size | Study characteristics (diabetes type, age, sex, region) | Population distribution | Exclusion criteria | Findings |
|-----------------|------------|-------------|--------------------------------------------------------|-------------------------|-------------------|----------|
| Bashir et al. 2014 | 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 | 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 | TNFR1 TNFR2 | N = 607 | T2D Mean age 61 years 66% males Sweden | 140 subjects had DKD defined as eGFR <60 ml/min/1.73 m² 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 | 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 |
| Author and Year | Biomarkers | Sample size ± controls | Study characteristics (diabetes type, age, sex, region) | Population distribution | Exclusion criteria | Findings |
|-----------------|------------|------------------------|--------------------------------------------------------|-------------------------|-------------------|----------|
| Doody et al. 2018 | 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 | 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-1α, 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 | 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 | IL-19      | $N = 200 + 50$ healthy age and sex matched controls | T2D, Mean age 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 | 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 [1.02–1.06]; $p = 0.03$) and IL-9 (OR 1.5 [1.05–2.14], $p = 0.03$) significant associated with DKD risk, after adjusting for age and gender |
| Author and Year          | Biomarkers | Sample size ± controls | Study characteristics (diabetes type, age, sex, region) | Population distribution | Exclusion criteria                                                                 | Findings                                                                                                                                                                                                 |
|-------------------------|------------|------------------------|--------------------------------------------------------|-------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sulaj, et al. 2017       | 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 correlates with CKD stages, p < 0.001 and eGFR, p < 0.05 |
| Shiju, et al. 2015       | 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          | 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          | 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        | 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) |
| Author and Year | Biomarkers | Sample size ± controls | Study characteristics (diabetes type, age, sex, region) | Population distribution | Exclusion criteria | Findings |
|----------------|------------|------------------------|--------------------------------------------------------|------------------------|-------------------|----------|
| Caner et al. 2014 | 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 (microalbuminuria) | - | 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 | 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-1β, interleukin-1-beta; IL-1α, 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, \( p = 0.061 \) \(^{[33]}\) (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\(^2\) \(^{[26]}\) (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, \( p = 0.023 \) \(^{[25]}\) (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 Yamamouchi 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
| Author and Year | Biomarkers | Sample Size ± controls | Study characteristics (diabetes type, age, sex, region) | Population distribution | Exclusion criteria | Findings |
|-----------------|------------|------------------------|-------------------------------------------------------|-------------------------|-------------------|----------|
| Gohda et al. 2018 | 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 | 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 | 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.
| Author and Year | Biomarkers | Study characteristics | Baseline eGFR and albuminuria$^b$ | Follow-up period | Renal outcomes | Findings |
|----------------|------------|-----------------------|----------------------------------|-----------------|---------------|----------|
| Niewczas et al. 2019$^3$ | 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$^4$ | TNFR2 | N = 349 T1D Median age 38 years 55% males USA—Joslin | CKD stage 1–3 Macrolalbuminuria | 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$^5$ | 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$^6$ | TNFR1 TNFR2 | 2 cohorts: 279 T1D Joslin: Median age 44 years, 48% males and USA 221 T2D Joslin: Median age 61 years, 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 >43 ng/ml with sensitivity of >70% Similar performance reported for TNFR2 |
| Forsblom et al. 2014$^7$ | 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)
| Author and Year | Biomarkers | Study characteristics | Baseline eGFR* and albuminuria | Follow-up period | Renal outcomes | Findings |
|----------------|------------|-----------------------|---------------------------------|-----------------|---------------|----------|
| Finland        |            |                       | Macroalbuminuria                |                 |               |          |
| Saulnier et al. 2014<sup>75</sup> | 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) \( p < 0.0001 \) | TNFR1 improved prediction of ESKD over clinical variables (eGFR, HbA1C and diabetes duration). C-index increased from 0.84 to 0.87 |
| Fernandez-Juarez et al. 2017<sup>76</sup> | TNFR1      | N = 101 T2D Mean age 69 years 76% males Spain | CKD stage 2 and 3 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<sup>77</sup> | 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 \( \geq \) 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 (1.4–12.8), \( p = 0.03 \) |          |
| Saulnier et al. 2017<sup>78</sup> | 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 \( \geq \)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 macroalbuminuria | Rapid renal function decline = decline in annual eGFR slope of \( \leq \)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<sup>79</sup> | CRP        | N = 1301 T2D Mean age 55 years 47% males Iran | CKD stage 2 and 3 Mean of 7.5 years | Development of DKD (microalbuminuria 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 |          |
| Author and Year | Biomarkers | Study characteristics | Baseline eGFR\(^a\) and albuminuria\(^b\) | Follow-up period | Renal outcomes | Findings |
|-----------------|------------|-----------------------|------------------------------------------|-----------------|----------------|---------|
| 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), \(p = 0.023\). AUROC of 0.87 for predicting albuminuria progression |
| Roy et al. 2015\(^30\) | 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  
Development of macroalbuminuria | Elevated plasma ICAM-1 predicted progression to macroalbuminuria, OR 4.72 (1.55-14.4), \(p = 0.006\)  
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 | 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\(^43\) | CRP  
TNF-\(\alpha\)  
IL-6 | N = 157  
T2D  
Mean age 52 years  
30% males  
Mexico | CKD stage 2  
(average eGFR >60)  
Nomo-, micro- and macro-albuminuria | 1 year | Progression of complication in T2D  
Serum TNF-\(\alpha\) 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) |
| Author and Year                  | Biomarkers          | Study characteristics | Baseline eGFR<sup>a</sup> and albuminuria<sup>b</sup> | Follow-up period | Renal outcomes                                                                 | Findings                                                                                                                                 |
|---------------------------------|---------------------|-----------------------|-----------------------------------------------------|------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| Peters et al. 2017<sup>4</sup>   | Promarker D: ApoA4 CDSL C1QB IBP3 | N = 345 T2D Mean age 67 years 52% males Australia | CKD stages 1–4 Normo- and microalbuminuria          | 4 years          | Rapidly declining eGFR trajectory Incident CKD (eGFR < 60 ml/min) eGFR decline ≥30% eGFR decline ≥5 ml/min/1.73 m<sup>2</sup>/yr | ApoA4, CDSL, 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<sup>5</sup>    | 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; CDSL, 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 superfamily-15; TNFRSF27, tumour necrosis factor receptor superfamily-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.

<sup>a</sup>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<sup>2</sup>, respectively.

<sup>b</sup>Albuminuria expressed in terms of stages, Normoalbuminuria (ACR < 30 mg/g), Microalbuminuria (30–300 mg/g) and Macroalbuminuria (>300 mg/g).
| Author and Year | Biomarkers | Study characteristics | Baseline eGFR and albuminuria | Follow-up period | Renal outcomes | Findings |
|----------------|------------|-----------------------|------------------------------|-----------------|---------------|---------|
| Colombo, et al. 2020 | 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 m² | 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, R² 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 | 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 m² NEPHRON-D: Decline in the eGFR ≥30 ml/min/1.73 m² 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 | 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 | eGFR decline defined as < −3 ml/min/1.73 m²/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 |
| Agarwal et al. 2014 | 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)
| 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      |            |                       |                                          |                 |                |          |
| **Kidney Injury** |            |                       |                                          |                 |                |          |
| Markers:        |            |                       |                                          |                 |                |          |
| KIM-1           |            |                       |                                          |                 |                |          |
| UMOD            |            |                       |                                          |                 |                |          |
| Cystatin C      |            |                       |                                          |                 |                |          |
| **Inflammatory** |            |                       |                                          |                 |                |          |
| Markers:        |            |                       |                                          |                 |                |          |
| TNFR1           |            |                       |                                          |                 |                |          |
| TNFR2           |            |                       |                                          |                 |                |          |
| MCP-1           |            |                       |                                          |                 |                |          |
| Tenascin C      |            |                       |                                          |                 |                |          |
| VCAM-1          |            |                       |                                          |                 |                |          |
| YKL-40          |            |                       |                                          |                 |                |          |
| CCL2            |            |                       |                                          |                 |                |          |
| **VEGF (marker of angiogenesis) associated with ESKD, OR 1.4, \(p < 0.05\)** | | | | | | |

Heinzl et al. 2018\(^90\)  
N = 481  
T2D  
Mean age 64 years  
53% males  
Austria, Hungary and Scotland  
CKD stage 1 and 2  
Normoalbuminuria  
Follow-up period: >2 years  
Renal outcomes: eGFR slope (subjects divided by rate of eGFR decline; stable or fast progressors)  
Findings: 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\(^71\)  
N = 35  
T1D and T2D  
Median age 50 years  
80% males  
Korea  
CKD stage 2 and 3  
Albuminuria not specified  
Follow-up period: Median follow-up of 242 months  
Renal outcomes: Annual decline in eGFR slope  
Findings: 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\(^72\)  
N = 1765  
T2D  
Mean age >55 years  
>50% males  
Korea  
Subjects divided according to eGFR (<60 and \(\geq 60 \text{ ml/min/1.73 m}^2\))  
Normo-, micro- and macro-albuminuria  
Follow-up period: 1–3 years  
Renal outcomes: Annual eGFR slope decline  
Findings: Studied biomarkers able to predict declining eGFR at eGFR <60 ml/min (MMP-2, 7, 13, TNFR1 and TIE2) and \(\geq 60 \text{ ml/min (MMP-2, 7, 8 and GH1)}, \ R^2 \) of 33.4% and 15.2% respectively. When combined with clinical variables, \(R^2\) improved to 64% and 35% respectively.

Satirapoj et al. 2018\(^73\)  
N = 83  
T2D  
Mean age 66 years  
64% males  
Thailand  
CKD stages 1–5  
Micro- and macro-albuminuria  
Follow-up period: 23 months  
Renal outcomes: GFR decline ≥25% per year from baseline  
Findings: 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, \(p < 0.005\).

Nadkarni et al. 2016\(^74\)  
N = 380  
T2D  
Mean age 62 years  
51% males  
USA and Canada  
CKD stage 1 and 2  
Normo- and microalbuminuria  
Follow-up period: 5 years  
Renal outcomes: eGFR decline ≥40% from baseline  
Findings: 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.
| 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 | CKD stage 2 and 3 T2D | Median age >65 years 48% males Sweden and UK | 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 | CKD stage 2 and 3 Normo-, micro- and macroalbuminuria | 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 | CKD stage 3 Normo-, micro- and macroalbuminuria | 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. |
| Kim et al. 2017\(^{98}\) | NAP KIM-1 NGAL L-FABP Angiotensinogen IL-18 YKL-40 | 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).
| Author and Year       | Biomarkers       | Sample Size ± controls | Study characteristics (diabetes type, age, sex, region) | Population distribution | Exclusion criteria                                                                 | Findings                                                                 |
|----------------------|------------------|------------------------|--------------------------------------------------------|-------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Siddiqi et al. 2017  | 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 | 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 | Plasma levels of: NGAL, B2M, OPN, UMOD | N = 66 + 73 non-diabetic controls | T1D - Canada                                           | Subjects divided into 2 groups: DKD and DKD resisters (eGFR > 60 ml/min and normo-albuminuria) | -                                                                                   | Plasma NGAL and B2M were significantly raised in DKD versus DKD resisters and controls, p < 0.05 UMOD lower in diabetes compared to controls (p < 0.05) |
| Author and Year | Biomarkers | Sample Size ± controls | Study characteristics (diabetes type, age, sex, region) | Population distribution | Exclusion criteria | Findings |
|-----------------|------------|------------------------|------------------------------------------------------|------------------------|-------------------|----------|
| Motawi et al. 2018<sup>108</sup> | 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 | 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) |
| Vijay et al. 2018<sup>109</sup> | 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 | Serum βTP and NGAL significantly raised in micro- versus normo-albuminuria and controls, p < 0.01. No difference between normalbuminuria and controls, p > 0.05 AUROC for NGAL in predicting microalbuminuria 0.96 versus 0.73 for βTP |
| Wu et al. 2014<sup>110</sup> | 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 | (Continues) |
| Author and Year    | Biomarkers       | Sample Size ± controls | Study characteristics (diabetes type, age, sex, region) | Population distribution | Exclusion criteria                                                                                                                                                                                                 | Findings                                                                                                                                                                                                 |
|-------------------|------------------|------------------------|--------------------------------------------------------|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kaul et al. 2018  | NGAL             | N = 144 + 54 controls  | T2D Median age >50 years ~61% males India               |                         | 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  | NGAL Clusterin   | N = 146 + 30 age and sex matched controls | T2D Mean age >55 years 57% males China                  |                         | 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 | NGAL             | N = 60 + 20 healthy controls | T2D Mean age 58 years ~66% males Egypt                 |                         | 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 |
|-----------------|------------|--------------------------|------------------------------------------------------|-----------------------|-------------------|----------|
| Zylka et al. 2018\(^1\) | Cystatin C, KIM-1, NGAL, Transferrin, IgG, UMOD | N = 80 T2D | Subjects divided into 2 groups: Normo- and micro-albuminuria | Poland | 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. AUROC of 0.99 for NGAL. |
| Bouvet et al. 2014\(^2\) | NAG | N = 36 T2D | Subjects divided into 2 groups: Normo- and micro-albuminuria | Argentina | 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 ($\gamma = 0.63$, $p < 0.0001$) and not eGFR. |
| Chen et al. 2017\(^3\) | DcR2, NAG | N = 311 and 139 T2D with biopsy confirmed DKD | Non-diabetic renal diseases, cancer, UTI, inflammation states, use of diuretics, Chinese medicines, or nephrotoxic drugs, severe hepatic or cardiac dysfunction | China | 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) |
| Author and Year | Biomarkers | Sample Size ± controls | Study characteristics (diabetes type, age, sex, region) | Population distribution | Exclusion criteria | Findings |
|-----------------|------------|------------------------|--------------------------------------------------------|------------------------|-------------------|----------|
| Qin et al. 2019 | 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, neoplasms, 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 | 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). |
| Author and Year | Biomarkers | Sample Size | Study characteristics (diabetes type, age, sex, region) | Population distribution | Exclusion criteria | Findings |
|----------------|------------|-------------|--------------------------------------------------------|------------------------|------------------|----------|
| Al-Malki, 2014 | 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 | 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 | 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 | 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 |
| Author and Year          | Biomarkers | Sample Size | Study characteristics (diabetes type, age, sex, region) | Population distribution | Exclusion criteria                                                                                                                                                                                                 | Findings                                                                                                                                                                                                 |
|--------------------------|------------|-------------|-----------------------------------------------------------|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| El Dawla et al. 2019     | E-cadherin | $N = 71 + 19$ 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 | 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 |
|                          | Periostin  |                          |                                                            |                          |                                                                                                                                                                                                                       | 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          | Cystatin C | $N = 200$     | 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 |
|                          | B2M        |                          |                                                            |                          |                                                                                                                                                                                                                       |                                                                                                                                  |
| Kim et al. 2016          | 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        | 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) |
| Author and Year | Biomarkers | Sample Size | Study characteristics (diabetes type, age, sex, region) | Population distribution | Exclusion criteria | Findings |
|-----------------|------------|-------------|----------------------------------------------------------|-------------------------|-------------------|----------|
| Jayakumar et al. 2014 | 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 | 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, hyperruricemia, 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 | 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 | 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, $p < 0.01$ |
| **Author and Year** | **Biomarkers** | **Sample Size ± controls** | **Study characteristics (diabetes type, age, sex, region)** | **Population distribution** | **Exclusion criteria** | **Findings** |
|--------------------|----------------|--------------------------|----------------------------------------------------------|----------------------------|----------------------|---------------|
| Chiu et al., 2018<sup>31</sup> | 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<sup>32</sup> | 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.
| Author and Year       | Biomarkers          | Study characteristics | Baseline eGFR and albuminuria | Follow-up period | Renal outcomes                                                                 | Findings                                                                                                                                                                                                 |
|-----------------------|---------------------|-----------------------|-------------------------------|------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bjornstad et al. 2018 | 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   | 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 0.8–12, $p > 0.05$ 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     | 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)
| Author and Year | Biomarkers | Study characteristics | Baseline eGFR and albuminuria<sup>a</sup> | Follow-up period | Renal outcomes | Findings |
|-----------------|------------|-----------------------|-------------------------------------------|------------------|----------------|---------|
| Mise et al. 2016<sup>137</sup> | 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) | Both NGAL and L-FABP significantly improved C-statistic from 0.828 (clinical model) to 0.833 and 0.832, \( p < 0.05 \) respectively |
| Foster et al. 2015<sup>138</sup> | 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, \( HR \ 1.14 \ (0.84–1.55) \) and \( 1.23 \ (0.94–1.62) \) respectively |
| Bjornstad et al. 2019<sup>139</sup> | 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<sup>2</sup> Development of albuminuria (UACR ≥30 mg/g) Rapid GFR decline (>3 ml/min/1.73 m<sup>2</sup>/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 |
| Author and Year | Biomarkers | Study characteristics | Baseline eGFR and albuminuria<sup>a</sup> | Follow-up period | Renal outcomes | Findings |
|-----------------|------------|-----------------------|-----------------------------------------|-----------------|---------------|----------|
| Devetzis et al. 2015<sup>40</sup> | 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<sup>2</sup>, OR 4.15, p = 0.031 CAF strongly correlated with progression to ESKD, r = 0.34, p = 0.004 |
| Gordin et al 2014<sup>41</sup> | 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<sup>14</sup> | Cystatin C KIM-1 NGAL Transferrin IgG UMOD Longitudinal component | 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<sup>30</sup> | Glypican-5 Longitudinal component | 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<sup>31</sup> | Cyclophilin A | 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.

<sup>a</sup>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<sup>2</sup>, respectively.

<sup>b</sup>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 m² over 5 years in T1D86 (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 < 0.000178 (Table 4). TNFR-1 and 2 were also found to predict eGFR decline ≥30 ml/min/1.73 m² if baseline eGFR > 60 or ≥50% decline if baseline eGFR < 60, improving C-statistic from 0.68 to >0.7, p < 0.0587 (Table 5). In contrast, studies utilising eGFR slope trajectories have generally reported poor predictive performances of TNFRs88–91 (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, R² < 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 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 m² compared to when eGFR < 60 ml/min/1.73 m². 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, angiotensin-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 < 0.05105–114 (Table 6). The cumulative AUROC reported for NGAL was >0.80 for predicting microalbuminuria across several studies105,108,109,111,112 (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), peristin and transferrin (Tables 3 and 6). Increased levels of these biomarkers have been found to associate with microalbuminuria in diabetes.53,64,105–107,109,112,114–123

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 participants116,117 (Table 6). Similarly, B2M had moderate to low AUROC of 0.79, 0.65 and 0.58 in three separate studies involving T2D subjects117,118,124 (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 > 0.0564,107,119 (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, respectively64,105,109,112 (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 another64,117 (Tables 3 and 6). The other biomarkers namely, transferrin, peristin and VDBP have shown high AUROC of
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.\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{84,95,96} reporting superior performance of KIM-1 in predicting eGFR decline \( \geq 20\% \), progression to eGFR \( <30 \text{ ml/min} /1.73 \text{ m}^2 \) 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 \( \geq 30 \text{ ml/min} /1.73 \text{ m}^2 \) or \( \geq 50\% \) from baseline\textsuperscript{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\textsuperscript{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 \( <60 \text{ ml/min} /\text{year} \) and microalbuminuria, \( p > 0.05 \)\textsuperscript{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, \( p > 0.05 \)\textsuperscript{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, \( p = 0.725 \)\textsuperscript{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.\textsuperscript{95,118} In the study by Bjornstad et al.\textsuperscript{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 \( <60 \text{ ml/min} /1.73 \text{ m}^2 \) (Table 7). In Colombo et al.\textsuperscript{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 \( \geq 20\% \) (Table 5). B2M is also part of a collection of kidney injury proteins that makes up non-albumin proteinuria (NAP).\textsuperscript{98,132} NAP was found to predict annual eGFR decline and eGFR \( <60 \text{ ml/min} /1.73 \text{ m}^2 \) with the highest C-statistic of 0.83 compared to KIM-1 and NGAL which had C-statistic of \( <0.7 \).\textsuperscript{98}

However, like KIM-1, studies have also reported conflicting results for B2M. For instance, no association of B2M was reported with \( \geq 50\% \) decline in eGFR or ESKD over 2 years, HR 1.23 (0.94–1.62)\textsuperscript{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)\textsuperscript{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.\textsuperscript{65,67,100,101} However, the use of surrogate endpoints requires careful consideration primarily because of the inherent inaccuracies surrounding eGFR.\textsuperscript{67} For instance, eGFR decline \( <30 \text{ ml/ min} /1.73 \text{ m}^2 \) may not be a reliable endpoint given that eGFR can differ from mGFR by up to 30\%.\textsuperscript{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\textsuperscript{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.\textsuperscript{29} Few studies have attempted to elucidate the temporal association of biomarkers with declining kidney function. In the study by Baker et al.,\textsuperscript{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 \( <60 \text{ ml/min} /28 \text{ years} \) 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 \( >3.5 \text{ ml/min} /1.73 \text{ m}^2 /\text{year} \) with final eGFR of \( <60 \text{ ml/min} /1.73 \text{ m}^2 \).\textsuperscript{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., 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 m² 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., 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. However, the use of albuminuria is contentious given that progression in the albuminuric stage is not a necessary prerequisite for the development of DKD. 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. 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.

In the 2019 study by Niewczas et al., 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. Few cross-sectional studies have distributed subjects based on eGFR, while few have used both eGFR and albuminuria. This emphasises the need for more biomarker studies to investigate the association with both eGFR and albuminuria. Care must still be taken when interpreting eGFR which lacks accuracy and is prone to misclassification.

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. and Bjornstad et al. (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. Thus, the choice of endpoints can potentially be a confounding factor with biomarkers favouring certain endpoints.

Another consideration involves duration of studies. Baker et al. 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. 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.

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. 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. Another study reported improved prediction of multiple biomarkers for the outcome of declining eGFR slope at various levels of eGFR, R² of >15%. In this study, most single biomarkers made only the modest contribution, R² < 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. 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. However, there is an issue of cost, access and availability which are crucial determinants to consider for clinical application at present. In fact, a simple, reliable, cheap and accurate biomarker is highly desirable and more likely to be accepted for clinical use. The study by Colombo et al. 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., Roy et al. and another recent publication by Colombo et al. (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. 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., 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. 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. identified five miRNAs to be associated with DKD from 53 miRNA studies selected for analysis. More recently, Fayed et al. 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., single nucleotide polymorphisms in the gene which encodes for the enzyme protein 11-beta hydroxysteroid dehydrogenase 1 was found to be associated 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. With regards to ion markers, in 2017, Bherwani et al. found hypomagnesaemia to be associated with increased DKD prevalence. Araki et al. 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.

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 drafting 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.
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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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