===== REVIEW =====

Biomarkers of the End-Stage Renal Disease Progression: Beyond the GFR

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Abstract—Chronic kidney disease can progress to the end-stage renal disease (ESRD) characterized by a high risk of morbidity and mortality. ESRD requires immediate therapy or even dialysis or kidney transplantation, therefore, its timely diagnostics is critical for many patients. ESRD is associated with pathological changes, such as inflammation, fibrosis, endocrine disorders, and epigenetic changes in various cells, which could serve as ESRD markers. The review summarizes information on conventional and new ESRD biomarkers that can be assessed in kidney tissue, blood, and urine. Some biomarkers are specific to a particular pathology, while others are more universal. Here, we suggest several universal inflammatory, fibrotic, hormonal, and epigenetic markers indicative of severe deterioration of renal function and ESRD progression for improvement of ESRD diagnostics.

INTRODUCTION

Chronic kidney disease (CKD) is characterized by a gradual loss of kidney function and involves a series of local and systemic pathological processes, from decrease in glomerular filtration rate (GFR) to the development of end-stage renal disease (ESRD) [1-3]. CKD and particularly ESRD are important factors in the deterioration of patients' quality of life and mortality. The mortality rate in ESRD patients is significantly higher than in patients with CKD only (in the absence of ESRD) and varies from 20 to 50% over 24 months even when modern hemodialysis techniques are used [4]. The late CKD stages require renal replacement therapy, such as peritoneal dialysis, hemodialysis, or kidney transplantation. However, allograft transplantation is available only for 10% patients

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Abbreviations: AGT, angiotensinogen; α-SMA, α-smooth muscle actin; BNP, brain natriuretic peptide; BMP-7, bone morphogenetic protein 7; CKD, chronic kidney disease; CNP, C-type natriuretic peptide; CTGF, connective tissue growth factor; CXCL16, C-X-C motif chemokine ligand 16; DcR2, decoy receptor 2; ECM, extracellular matrix; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HE4, human epididymal secretory protein E4; MCP-1, monocyte chemoattractant protein 1; miRs, microRNAs; MTHFR, methylenetetrahydrofolate reductase; RAAS, renin-angiotensin-aldosterone system; TGFβ1, transforming growth factor beta 1; UUO, unilateral ureteral obstruction; PRO-C6, fragment reflecting collagen VI formation; C1M, fragment of collagen I hydrolysis with MMP; C3M, fragment reflecting collagen III degradation; PRO-C3, fragment reflecting collagen III formation; PINP, procollagen type I N-terminal propeptide; PIIINP, procollagen type III N-terminal propeptide.

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needing new organs [5]. By the end of 2018, the number of people with ESRD exceeded 785,000 in the United States [6] and the number of patients diagnosed with this pathology has been steadily increasing [4].

At present, assessment of CKD stage and diagnostics of ESRD are based on morphological and functional symptoms of kidney damage. The definition and classification of CKD was proposed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) in 2002 and approved by the Kidney Disease: Improving Global Outcomes organization (KDIGO) in 2004 [7]. According to KDIGO 2012 clinical practice guideline [8], CKD classification is based on the estimated GFR (eGFR) (Fig. 1): stage 1 — normal eGFR (above 90 ml/min/1.73 m^2) with microalbuminuria; stage 2 — eGFR, 60-89 ml/min/1.73 m^2 with microalbuminuria; stage 3 — eGFR, 30-59 ml/min/1.73 m^2; stage 4 — eGFR, 15-29 ml/min/1.73 m^2; stage 5/ESRD — eGFR, below 15 ml/min/1.73 m^2. Stages 3-5 are defined as CKD.

Clinical practice uses several approaches to the GFR assessment, including those based on measuring the clearance of endogenous creatinine and cystatin C (eGFR) or clearance of exogenous substances, such as radiopharmaceuticals, e.g., ^{99m}Tc-labeled diethylenetriamine pentaacetate (measured GFR, mGFR) [9, 10]. mGFR is a more accurate parameter for GFR assessment, but its evaluation requires special equipment and permission to work with radiopharmaceuticals, which significantly limits the use of this method.

Recently, using eGFR as a single parameter in the diagnostics of CKD has been criticized and found insufficient, as it has the following limitations: (i) kidney is a multifunctional organ, while GFR reflects only one of its functions; (ii) various non-renal factors can influence GFR measurements; (iii) GFR has intrinsic variability and depends on food and fluid intake, cardiovascular status, and blood pressure, especially in the case of impaired autoregulation or use of medications; (iv) GFR changes with age in a unique nonlinear pattern; (v) eGFR may not correlate with GFR under certain conditions and in certain diseases. Therefore, eGFR can be used as an initial screening tool, but should not be applied to the diagnostics of CKD without careful assessment of the entire clinical profile [11]. Therefore, there is still a need for biomarkers that can be employed for the diagnostics of CKD and, especially, ESRD.

Renal fibrosis is a typical outcome of inflammation that occurs in almost all nephropathies [12, 13]. Fibrosis can affect all kidney compartments, ultimately causing destruction of the renal parenchyma and ESRD development. Therefore, markers of kidney fibrosis can also be used as universal markers in the diagnostics of CKD and ESRD. Renal failure is also accompanied by endocrine disorders and epigenetic changes in various cells, which can serve as ESRD biomarkers as well. In this review,
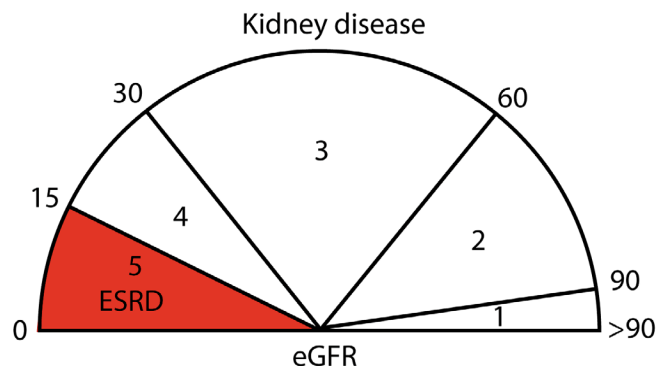

Fig. 1. Classification of CKD based on eGFR (numbers outside the semicircle indicate eGFR; numbers inside the semicircle correspond to the stages of renal failure. ESRD is highlighted in red).

we summarize information on currently known biomarkers of inflammation, kidney fibrosis, hormonal changes, and epigenetic changes and discusses their application in the diagnostics of CKD-to-ESRD progression.

ESRD PROGRESSION

The most common cause of CKD and ESRD is diabetes mellitus [14]. Other causes [4, 15] are hypertension, renal vascular disease, primary or secondary glomerulonephritis, cystic kidney disease, tubulointerstitial nephritis, obstruction or dysfunction of the urinary tract, recurrent kidney stone disease, congenital kidney or bladder defects, acute kidney injury, autoimmune diseases, nephrotoxins, obesity, and certain medications, including nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, and antiretroviral drugs.

All these diseases are characterized by changes in renal function, reflecting the contribution of individual nephrons to the total GFR [4]. A decline in the renal function can be initially asymptomatic and cause hyperfiltration in nephrons. Together with the compensatory nephron hypertrophy, hyperfiltration allows kidneys to maintain the GFR. As a result, a patient with mild renal dysfunction can have normal creatinine levels, so that the disease can remain undetected for some time [16]. Sooner or later, this adaptive mechanism exhausts itself, which eventually results in the damage of glomeruli of remaining nephrons [4]. An increased glomerular capillary pressure damages the capillaries, leading to focal and segmental glomerulosclerosis and then to global glomerulosclerosis. Pathomorphological alterations characteristic of ESRD are shown in Fig. 2.

One of the most important factors in the development of renal pathology is inflammation [15, 17, 18]. ESRD can also accompany glomerulosclerosis, tubulointerstitial fibrosis, and atrophy [15, 19]. Finally, ESRD is associated with endocrine disorders and epigenetic changes.
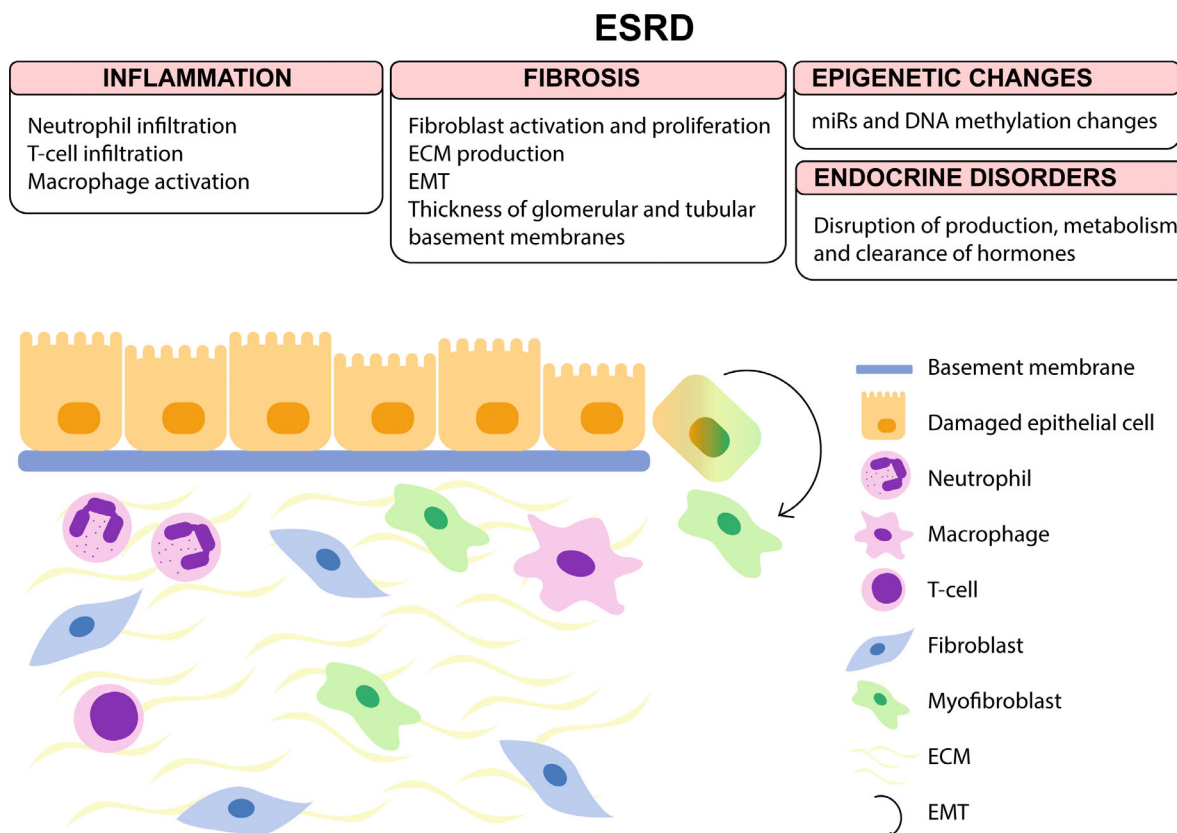
ESRD

INFLAMMATION	FIBROSIS	EPIGENETIC CHANGES
Neutrophil infiltration T-cell infiltration Macrophage activation	Fibroblast activation and proliferation ECM production EMT Thickness of glomerular and tubular basement membranes	miRs and DNA methylation changes
		ENDOCRINE DISORDERS
		Disruption of production, metabolism and clearance of hormones

Legend:
- Basement membrane
- Damaged epithelial cell
- Neutrophil
- Macrophage
- T-cell
- Fibroblast
- Myofibroblast
- ECM
- EMT

Fig. 2. Pathological mechanisms of CKD-to-ESRD progression.

INFLAMMATORY MARKERS

Chronic inflammation plays an important role in the development of renal diseases and can be used as a prognostic factor in the all-cause and cardiovascular mortality in hemodialysis patients [20]. Inflammatory response involves multiple molecules, including pro-inflammatory cytokines, chemokines, cell adhesion molecules, and various growth and nuclear factors [21].

There have been a number of studies on the efficacy of inflammatory markers in the detection of deteriorating kidney function. It was found that when used in combination with the evaluation of creatinine content, inflammatory and prothrombotic markers can serve as predictors of changes in the renal function in elderly patients without direct measurements of GFR [22]. At the same time, no associations between nine inflammatory and procoagulant markers [C-reactive protein, interleukin-6 (IL-6), intercellular adhesion molecule 1, white blood cell count, fibrinogen, factor VII, factor VIII, D-dimer, plasmin−antiplasmin complex) and rapid decline in the renal function has been revealed [23]. The only parameter consistently associated with eGFR (estimated with cystatin C) was a decrease in the baseline level of serum albumin [23].

It was shown that CKD (in particular, CKD stage 5) is accompanied by the elevation of plasma IL-6, which could be used for the prediction of the all-cause and cardiovascular mortality in pre-dialysis patients with CKD stages 2-5 [20]. Moreover, IL-6 plasma levels as predictors of mortality ensured more precise results than the other three major inflammatory biomarkers, namely, C-reactive protein, TNF-α, and serum albumin [20]. The data on the association of C-reactive protein (common inflammatory biomarker) with eGFR and its use for the prediction of eGFR decline are contradictory [24-26]. It was also found that the concentration of IL-18 negatively correlates with the creatinine clearance, which was masked by continuous ambulatory peritoneal dialysis [27].

Analysis of potential inflammatory biomarkers and kidney injury biomarkers in diabetic kidney disease highlighted the controversial results in cohort studies of the predictive ability of tumor necrosis factor receptors (TNFRs) for ESRD in diabetes [28]. In IgA nephropathy, circulating TNFRs reflected histological changes and clinical severity of the disease and negatively correlated with eGFR. Moreover, elevated serum concentrations of TNFRs during the disease onset served as early biomarkers of subsequent renal progression in IgA nephropathy patients [29]. Seventeen circulating inflammatory proteins, many of the belonging to the TNFR superfamily, were proposed as predictors of a 10-year risk of ESRD in type 1 and type 2 diabetes [30].

The following biomarkers of systemic inflammatory response identified in blood were found to be closely associated with CKD progression [18]:

- proinflammatory cytokines: TNF-α, IL-6, and IL-18;
- chemokines: IL-8 (CXCL8), IL-34, stromal cell-derived factor 1α (SDF1α/CXCL12), monocyte chemoattractant protein-1 (MCP-1/CCL2), and macrophage inflammatory protein 1β (MIP-1β/CCL4);
- growth factors: GM-CSF (granulocyte-macrophage colony-stimulating factor), fibroblast growth factor (FGF) 23, and HGF (hepatocyte growth factor);
- soluble forms of receptors: sTNFR1 and sTNFR2, soluble CD40 ligand (sCD40L), and sCD163 (SR-I3);
- cyclophilin A.

Unfortunately, there is a limited information on the relationship between inflammatory markers, GFR levels, and ESRD development at different CKD stages, including patients on dialysis. Recently, it was shown that the circulating adhesion molecule VCAM-1 is inversely associated with eGFR and can predict eGFR decline in a general population [26]. Another inflammatory marker measured in CKD was activity of serum adenosine deaminase [31] which negatively correlated with eGFR [31], although the authors noted that using only one parameter of renal function would be insufficient for ESRD evaluation.

Soluble molecules are not the only inflammatory biomarkers. Thus, *in situ* inflammatory status and lymphocyte immune phenotype [32, 33] can be used for distinguishing ESRD patients from the control group. Reduction in the number of regulatory T cells (Tregs) can contribute to the ESRD development in systemic lupus erythematosus. Also, ESRD patients with a low Treg count have shown a shift in the cytokine profile from the anti-inflammatory toward proinflammatory cytokines, as well as higher concentration of antibodies against human leukocyte antigen in peripheral blood [32]. Confocal microscopy of biopsies from patients with lupus nephritis showed that the high count of B cells correlated with the resistance to ESRD development, while high amounts of CD8$^+$, γδ, and other CD4$^-$CD8$^-$ T cells were associated with acute renal failure and ESRD progression [33]. The differences in the phenotypic patterns of the T- and B-cell populations were observed between ESRD patients and healthy controls. ESRD patients demonstrated reduction in the number of naïve CD4 subpopulations, CD19$^+$IgD$^+$CD27$^+$ cells, and CD8$^+$PD1$^+$ cells, along with the increase in the content of senescent cell subpopulations [34].

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) can also have a diagnostic significance in the assessment of inflammation in ESRD patients. NLR was found to be associated with inflammation in ESRD patients, including both hemodialysis and peritoneal dialysis patients [35-37], and with the estimated survival of hemodialysis patients [38, 39].

It was demonstrated that PLR is also associated with inflammation and can be used to predict mortality in hemodialysis patients [37, 38]. A 7-year cohort study of non-dialysis ESRD patients revealed that both NLR and PLR were related to inflammation, as demonstrated by their association with C-reactive protein [40].

Since ESRD development is a unique process observed in different pathologies, the use of inflammatory markers in renal failure seems contradictory and has to be combined with other diagnostic approaches.

FIBROSIS MARKERS

Healthy tissues are characterized by a balance between the synthesis and proteolysis of extracellular matrix (ECM) proteins (collagen, fibronectin, laminin, etc.). Disturbances of this balance can induce uncontrolled deposition of ECM components, ultimately impairing organ morphology and/or function and leading to fibrosis development [12]. This process can occur in all organs and causes almost 45% deaths in developed countries [41]. Since 1990s, the prevalence of CKD, which is accompanied by renal fibrosis, has increased and reached 1.2 million deaths worldwide in 2017 [42].

Excessive deposition of ECM in renal fibrosis results in the damage and replacement of functional parenchyma, leading to kidney failure [13]. This pathological process can affect three different renal compartments: glomeruli (causing glomerulosclerosis), tubulointerstitium (interstitial fibrosis), and vasculature (arteriosclerosis and perivascular fibrosis) [43]. Regardless of the cause and origin of fibrosis, its histological pattern in different kidney diseases is essentially the same. Hence, kidney fibrosis markers can be considered as universal molecules for the diagnostics of CKD and ESRD.

Collagens. Collagens are the most common markers of fibrosis. Renal interstitium contains collagens I, II, III, IV, VI, VII, and XV [44]. Type I collagen is the main component of fibrous tissues in all organs [44, 45]. Collagens II and III are believed to accumulate at the early stages of kidney fibrosis development [46]. An increase in the content of collagens IV and VI in kidney fibrous tissue has also been demonstrated [47, 48]. Type IV collagen is a component of the basement membrane and is used as a marker of glomerulosclerosis and interstitial fibrosis [49, 50].

The most common method for fibrosis identification in clinical and experimental studies is staining the biopsies with Masson's trichrome or Picrosirius Red. However, despite the widespread use of Masson's staining, it has poor specificity to collagen itself and reflects interstitial volume rather than fibrosis *per se* [51]. Picrosirius Red is more suitable for fibrillar collagen staining, but it also has its limitations, in particular, the lack of specificity to collagen IV, which prevents the use

of this stain in the analysis of tubular basement membrane thickening or diagnostics of glomerulosclerosis [51]. Immunohistochemical assays lack the above-mentioned limitations and can directly reveal the content and tissue location of collagens, allowing evaluation of the degree of kidney fibrosis by morphometric measurements [52, 53].

Beside histological and immunohistochemical methods, the content of collagen can be evaluated by the biochemical analysis of hydroxyproline [51], because collagen is one of the few proteins containing this amino acid. The percentage of hydroxyproline in the amino acid composition of collagen is constant in most mammalian organs [54, 55].

The most available biological samples in clinical and experimental studies are serum and urine, which can be assayed for the presence of collagen fragments (Table 1). Hence, collagen or its fragments can be assessed in the urine or blood samples as biomarkers of renal failure and, in particular, ESRD, using noninvasive methods. This approach can be employed to investigate the dynamics of renal failure development. For instance, the study on the relation between the GFR and levels of collagen III fragments reflecting its active formation (PRO-C3) and degradation (C3M) has shown that the C3M/creatinine ratio in urine increased with CKD development [56]. The PRO-C3/creatinine ratio in urine and serum increases only at stages 4 and 5 [56]. And vice versa, low C3M/creatinine ratio in the urine and increased serum content of PRO-C3 were associated with an increased risk of developing ESRD and death [56]. However, no association between the urine and serum levels of C3M and mortality in the diabetic kidney disease was found [57].

Comparison of healthy people and patients with CKD based on the data of the Human Urinary Proteome Database has shown that collagen Ia1 fragments can be used for the diagnostics of kidney failure. Sixty-three out of 707 urinary collagen Ia1 fragments positively associated with the GFR; 6 fragments negatively associated with the GFR [58].

Analysis of collagens and collagen fragments by immunoassay methods is even more useful for the clinical diagnostics of renal failure. Thus, the content of collagen IV in the urine of young patients with type 1 diabetes correlated with a decreased GFR, although no association with ESRD has been found [59]. The same results were obtained for patients with type 2 diabetes [60]. An increase in the serum level of PRO-C6 (fragment reflecting collagen VI active formation) showed association with the GFR decline, ESRD development, and mortality in patients with type 1 diabetes, while higher urinary levels of PRO-C6, on the contrary, correlated with a reduced risk of GFR reduction [61]. Serum and urine levels of endotrophin (collagen VI fragment) can be used for prediction of ESRD development in CKD patients [62, 63] and were chosen as indicators (instead of eGFR) in the multivariable model of CKD-related mortality due to their higher predictive power [62]. Urinary endotrophin/creatinine ratio was found to be associated with one-year CKD progression, independently of traditional risk factors, such as eGFR, age, sex, and urinary albumin/creatinine excretion ratio [63].

It has been shown that using a combination of biomarkers (sLG1M, sPRO-C3, sPRO-C6, uPRO-C3/creatinine ratio, uPRO-C6/creatinine ratio, uC3M/creatinine ratio) can improve prediction of renal outcome (sensitivity 50.0%; specificity 77.8%; Area under the curve (AUC) 0.806) compared to the clinical parameters, such as eGFR and proteinuria (sensitivity 45.2%; specificity 87.3%; AUC 0.751) [64]. Therefore, a combination of GFR and ECM components as fibrosis biomarkers may improve prediction of CKD progression and renal outcome.

ECM and intermediate filament as biomarkers. Beside collagen, ECM contains fibronectin and thrombospondin 1 (TSP-1). Intermediate filament proteins (vimentin, nestin) are associated with kidney fibrosis (Table 2). Some of them can be used for the diagnostics of renal failure, as their levels correlate with the GFR. Thus, the content of fibronectin in the urine of patients with the Bardet−Biedl syndrome correlates with eGFR [74]. Detection of vimentin mRNA in urine can also be useful in the diagnostics of renal failure because of its negative correlation with GFR in patients with CKD [75].

Other kidney fibrosis markers. Non-ECM proteins can also be used in the diagnostics of kidney fibrosis (Table 3), as some of them are associated with the GFR and can be helpful in ESRD prognosis in renal diseases and after kidney transplantation.

High TGF-β1/BMP7 ratio can indicate ESRD development in patients with type 2 diabetes [89]. Another potential biomarker of kidney failure is galectin 3 due to its correlation with the GFR in patients with diabetic kidney disease [117]. In the same patients, identification of C-X-C motif chemokine ligand 16 (CXCL16) in urine indicates fibrosis development [72], while the plasma levels of this cytokine reflect GFR and CKD transition to ESRD [118, 119]. The content of CXCL16 in CKD patients with type 2 diabetes mellitus is higher than in CKD patients with no diabetes [118]; therefore, the serum and/or urine levels of CXCL16 can serve as prognostic/diagnostic markers for the severity of CKD and its progression to ESRD. Similarly, the content of endostatin in the plasma is negatively associated with the GFR [120, 121] and reflects CKD development; it can also predict mortality in patients with type 2 diabetes [122, 123] or kidney transplant damage [122].

The plasma content of monocyte chemoattractant protein 1 (MCP-1) can reflect the development of fibrosis, GFR decline, and mortality, in CKD [124].

Table 1. Collagen and its fragments assessed in patients' urine and serum in the diagnostics of renal damage and kidney fibrosis

Collagen type/fragment	Urine/serum	Detection method	Diagnostic value	References
PIIINP (procollagen III N-terminal propeptide); collagen IV	urine, serum	ELISA (collagen IV); radioimmun-odetection (PIIINP)	strong positive correlation between circulating and urinary PIIINP and severity of kidney interstitial fibrosis in samples from patients with nephropathy; no correlation for collagen IV	[65]
PIIINP	urine, serum	radioimmun-odetection	increased urinary levels of PIIINP and urinary PIIINP/creatinine ratio correlate with severity of kidney fibrosis; however, no association between serum PIIINP and PIIINP excretion in urine or interstitium fibrosis stage	[66]
PIIINP	urine	radioimmun-odetection	possible diagnostic significance of urinary PIIINP/creatinine ratio in kidney fibrosis	[67]
PIIINP	urine	ELISA	correlation between the levels of urinary PIIINP and severity of renal fibrosis in patients with cystic fibrosis after lung transplantation	[68]
PIIINP; PINP (procollagen I N-terminal propeptide)	urine	radioimmun-odetection	PIIINP and PINP as markers of kidney fibrosis	[69]
PIIINP; C1M (fragment of collagen I hydrolysis with MMP); C3M	urine, serum	ELISA	serum levels of C1M and C3M increase 2-3 times in rats with 5/6 nephrectomy and adenine-induced nephropathy, but not with chronic anti-Thy1.1 nephritis. At the same time, urinary levels of C1M and C3M increase 9 to 100 times in all three pathologies, whereas PIIINP is highly increased only in the urine of rats with 5/6 nephrectomy	[70]
PRO-C3; PRO-C6; C3M	urine, serum	ELISA	serum PRO-C6 and urinary C3M correlate with histological markers of interstitial fibrosis in patients with lupus nephritis	[71]
Endostatin (20-kDa C-terminal fragment of collagen XVIII)	urine, serum	ELISA	increase (5 to 6-fold) in endostatin renal expression and its serum levels accompanies progressive tubulointerstitial fibrosis in two mouse strains; the content of endostatin in urine during interstitial fibrosis and kidney tubular atrophy increases in patients with diabetic kidney disease	[72, 73]
Endotrophin (C-terminal fragment of collagen VI)	urine, serum	ELISA	urinary endotrophin/creatinine ratio is associated with CKD progression to ESRD within 1 year; endotrophin serum level is independently associated with mortality in CKD patients and can predict ESRD development	[62, 63]

Table 2. ECM proteins as kidney fibrosis markers

Biomarker	Location	Association with kidney fibrosis
Fibronectin	kidney	fibronectin accumulation in kidneys is one of the earliest symptoms of fibrosis [76]
Nestin	kidney	nestin is detected in tubular epithelial and interstitial cells in unilateral ureteral obstruction (UUO) [77]; the level of nestin expression in tubular interstitial cells positively correlates with tubulointerstitial fibrosis in patients with glomerulonephritis [77]
TSP-1	kidney	increase in the expression and content of TSP-1 in glomerulonephritis is associated with interstitial fibrosis and accompanies fibrosis development [78]
Vimentin	kidney	increase in vimentin expression is observed in in UUO mice with kidney fibrosis [79]

Table 3. Kidney fibrosis markers

Marker	Source	Association with kidney fibrosis
α-Smooth muscle actin (α-SMA)	kidney	α-SMA is a marker of fibrogenic activity of myofibroblasts [80-84]; it is widely used in different models of kidney injury [85-87]; however, only few collagen-producing renal cells have been shown to express α-SMA [83]
Bone morphogenetic protein 7 (BMP7)	serum	low levels of BMP7 indicate an increased risk of developing ESRD and correlate with the increased TGFβ content [88]; increased total TGFβ1/BMP7 ratio can be used in the diagnostics of ESRD [89]
Connective tissue growth factor (CTGF/CCN2)	kidney, serum	increased number of cells expressing CTGF mRNA is detected in chronic tubulointerstitial damage [90, 91]; serum levels of CTGF in patients with 1 type of diabetes correlate with ESRD development and all-cause mortality [92]
C-X-C motif chemokine ligand 16 (CXCL16)	urine	urine content of CXCL16 increases during development of interstitial fibrosis and kidney tubular atrophy in patients with diabetic kidney disease [72]
Decoy receptor 2 (DcR2) and urinary DcR2/creatinine ratio	urine	urine levels of DcR2 and uDcR2/creatinine ratio correlate with the development of tubulointerstitial fibrosis in patients with IgA nephropathy [93]
Epidermal growth factor (EGF) and uEGF/creatinine ratio	urine	decreased amount of EGF mRNA in kidneys and urine content of EGF correlates with the development of interstitial fibrosis [94, 95]; uEGF/creatinine ratio is associated with CKD stage [94, 96]
Galectin 1	kidney	galectin 1 is involved in the late stages of CKD associated with fibrosis [97]
Galectin 3	urine, serum	increased plasma or serum levels of galectin 3 levels are associated with an increased risk of developing CKD and rapid decline of kidney functions [98-100]; increased galectin 3 plasma levels are associated with more severe renal fibrosis [101]; a combination of galectin 3 measurements in urine and plasma has a higher predictive power [102]
Human epididymal secretory protein E4 (HE4/Wfdc2)	kidney	increased HE4 expression in kidneys is observed during fibrosis development in the UUO model [103]; the amount of HE4 increases in kidneys in CKD [104], which can be associated with its elevated expression by myofibroblasts [103]
Monocyte chemoattractant protein 1 (MCP-1)	urine	MCP-1 expression leads to interstitial and mesangial fibrosis [105-107]; the content of MCP-1 in urine can be measured for CKD diagnostics in clinical practice [108]
Matrix metalloproteinase-7 (MMP-7)	urine, serum	MMP-7 in content correlates with the development of kidney fibrosis in patients with 2 type diabetes [109]; the level of MMP-7 in urine is associated with development of kidney fibrosis in CKD patients [110]
Retinol-binding proteins (RBP)	urine	urinary levels of RBP and RBP/creatinine ratio are positively associated with development of kidney fibrosis in CKD patients [111]
TGFβ1	urine, serum	analysis of biopsies from 127 patients showed a correlation between the development of fibrosis and increase in the urinary TGFβ1 content [112-114]; detection of TGFβ in the serum of patients after kidney transplantation can have a prognostic value in the diagnostics of allograft nephropathy [115]; TGFβ1 in the blood can predict persistent development of nephropathy in type 2 diabetes patients [89]
Uromodulin	serum	evaluation of uromodulin in serum can be used for detection of early stages of fibrosis after transplantation [116]

Other fibrosis markers associated with the development of renal failure and GFR in CKD include retinol-binding proteins (RBP) in urine [125], connective tissue growth factor (CTGF) in plasma [126], and human epididymal secretory protein 4 (HE4) in serum [127]. The content of RBP and the DcR2/creatinine ratio in urine can be used for the diagnostics of IgA nephropathy [93, 128]. The plasma level of CTGF and upregulated expression of its mRNA in kidneys reflect the stages of CKD in patients with lupus nephritis [129]. Serum FGF-2 negatively correlates with the GFR and proteinuria in patients with glomerulonephritis.

The risk of ESRD development in elderly patients can be predicted by measuring the serum level of uromodulin [130], whereas blood levels of uromodulin reflect the development of renal failure after kidney transplantation [116]. The EGF/creatinine ratio in the urine of patients after transplantation correlates with a GFR decline [116]. Identification of interstitial fibrosis with Masson's trichrome staining together with the levels of α-smooth muscle actin (α-SMA) in biopsies, can accurately predict the development of renal allograft chronic dysfunction [131].

Some of the above-described fibrosis biomarkers have more predictive power in the case of CKD progression and loss of renal function than the GFR. For example, urinary MCP-1/creatinine levels have been used to diagnose inflammatory activity in kidneys in male patients, even when the eGFR values were normal. MCP-1 measurements can reveal renal inflammation early in the development of the Alport syndrome [132]. In IgA nephropathy, urinary MMP-7 levels can serve as an independent and powerful predictor of disease progression, even in the early-stage patients with eGFR of ⩾60 ml/min/1.73 m² [133]. Thus, the use of urinary MMP-7 content together with other parameters, such as eGFR, mean arterial blood pressure, proteinuria, and histological score, has significantly improved prediction of a 3-year risk of IgA nephropathy progression [133]. Hence, kidney fibrosis biomarkers can reflect the severity of CKD and its progression to ESRD, as well as to predict kidney transplant rejection and even mortality.

EPIGENETIC MARKERS

Involvement of epigenetic processes in the development of renal fibrosis has been repeatedly demonstrated in cell cultures, animal models, and patients with diabetic nephropathy, ischemia, lupus nephritis, and other pathologies [134-137]. Epigenetic changes can directly mediate transition from acute injury to chronic kidney disease [138-141]. It was suggested that epigenetic markers could predict the severity of CKD, distinguish between different CKD stages, and evaluate the risk of ESRD. The most promising epigenetic markers of re-

nal fibrosis are microRNAs (miRs) and DNA methylation; they are commonly analyzed in blood cells or urine and used as prognostic factors of CKD and ESRD development.

miRs. miRs are small non-coding RNAs encoded in gene introns or transcribed independently. The primary transcripts are processed into mature miRs that suppress the activity of various genes through RNA interference. At the same time, the effect of individual miRs can be very broad, as almost every miR has more than 100 targets, and depends on the type and state of affected cells. miRs have been widely studied in various models of renal pathologies, and many miRs involved in the development of renal fibrosis have been identified [142]. For instance, miR-21, miR-92, and miR-122 can be used for evaluating the stages of CKD and risks of ESRD development. The main effects of miR-21 involve the shift of cellular metabolism to glycolysis. miR-21 increases cell viability during acute stress by downregulating many genes, such as its direct targets peroxisome proliferator-activated receptor α (PPARα), acyl-coenzyme A oxidase 1 (ACOX1), coenzyme A synthase, pyruvate dehydrogenase, and pyruvate carboxylase. miR-21 also represses the genes of Mpv17-like proteins that regulate redox metabolic pathways [143-150]. There are other miRs associated with renal pathologies, but their diagnostic value in the case of ESRD still has to be established. The data of miRs potentially involved in CKD and ESRD are presented in Table 4.

DNA methylation. Due to the revealed correlation between the DNA methylation level and kidney pathologies, DNA methylation can serve as a biomarker for CKD or ESRD severity and risk of their development. One of the markers of DNA methylation is 5-methyl-2'-deoxycytidine (5-Me-dC), whose content is increased in the urine of patients with late-stage CKD. When accompanied by macroalbuminuria or appearance of α1-microglobulin (α1m) in urine, this marker predicts the end-stage CKD [161].

Methylation of the p66Shc promoter in blood is another ESRD biomarker. p66Shc is a stress response protein involved in the oxidative stress and atherosclerosis development. Decreased methylation of the p66Shc promoter in peripheral blood mononuclear cells in patients with ESRD was found to correlate with an increased risk of cardiovascular death [162]. It is assumed that the decrease in the p66Shc promoter methylation can be a result of hyperhomocysteinemia, which often accompanies kidney diseases.

Multiple genomic sites have has been discovered whose methylation levels are associated with ESRD [163-166]. However, there were almost no overlaps between the results of these studies, although three of them used the same technology (Infinium HumanMethylation450 Beadchip) to assess DNA methylation, suggesting the need for comprehensive investigation of these sites

Table 4. miRs associated with CKD and ESRD

miR	CKD regulation	Application in CKD diagnostics	References
miR-21	↑	+	[143-150]
miR-92	↑	+	[151, 152]
miR-93-5p	↓	+ correlates with GFR; expression before and after transplantation differs	[153]
miR-95-3p	↓	+ low level can serve as a marker of ESRD development	[154]
miR-122	↓	+	[155]
miR-125b	↓	−	[156]
miR-126	↓	+	[157]
miR-145	↓	−	[156]
miR-155	↓	+	[156, 157]
miR-192	↑	+	[158]
miR-223-3p	↓	+ correlates with GFR; expression before and after transplantation differs	[153]
miR-342	↓	−	[159]
miR-499	−	+	[158, 160]
miR-631	↑	+ high level can serve as a marker of ESRD development	[154]

in order to identify individual features of their regulation under different conditions.

Some of these regions have been studied in more detail, e.g., the methylenetetrahydrofolate reductase (MTHFR) gene. MTHFR regulates metabolism of methyl groups and homocysteine. Methylation of the MTHFR gene is significantly upregulated in patients with ESRD, which correlates with lower GFR, glycated hemoglobin (HbA1C) content, glycemia, and total and low-density-lipoprotein cholesterol content [165, 167]. Methylation of the MTHFR gene is also associated with hyperhomocysteinemia, which can lead to further glomerular damage and GFR reduction [168].

CKD can cause premature aging of renal tissue, so the use of epigenetic clocks in the assessment of kidney health may be of some scientific interest. The correlation between epigenetic age and biomarkers of renal failure has been shown by several methods [169, 170]. It was found that GFR is associated with the Horvath, Hannum, and Pheno accelerated age scores, MS (mortality risk score based on 10 prominent mortality-related CpG sites), and extrinsic epigenetic age acceleration age/lifespan predictors that can be evaluated by analysis of DNA methylation.

CHANGES IN THE ENDOCRINE SYSTEM AS CKD AND ESRD BIOMARKERS

Hormones play an important role at the endocrine and paracrine levels in the functioning of kidneys as osmoregulatory and detoxifying organs. Normally, kidneys are involved in the excretion of hormones, such as cortisol, aldosterone, sex steroids, thyroid hormones, and catecholamines, and in biodegradation of peptide hormones (e.g., parathyroid hormone, calcitonin, and insulin) [171]. In the course of CKD progression (stages 3-5) [172-174], production, metabolism, and clearance of hormones are disrupted, which causes their accumulation in the blood and more active excretion in the urine. Almost all endocrine axes (from hypothalamus to specific endocrine glands) undergo significant changes during CKD [171, 175].

Changes in the hormone levels in physiological fluids and renal tissue can suggest kidney fibrosis and serve as an indication for changes in the therapeutic strategy in the CKD treatment. Below, we discuss if the hormones controlling the water-salt balance and blood pressure can be used as markers of CKD and ESRD (Table 5).

Renin−angiotensin−aldosterone system. Angiotensin II (AngII) is the principal components of renin−angiotensin−aldosterone system (RAAS) involved in the regulation of vascular tone, blood pressure, and sodium homeostasis [176, 177]. This hormone is a powerful aggravating factor of kidney fibrosis. AngII directly and indirectly stimulates transforming growth factor beta 1 (TGFβ1)-mediated signaling and ECM accumulation upon activation of the profibrotic signaling pathway initiated by activation of AT1 receptors [176, 178, 179]. RAAS includes both circulatory and local components, with intrarenal RAAS being the most developed one, since the kidney has all necessary substrates and enzymes for its functioning.

Intrarenal RAAS plays a special role in the CKD-to-ESRD transition, and its activation is critically important in the renal pathophysiology in CKD patients. Increased renal expression of angiotensinogen (AGT), chymase, and AT1 receptors promotes intrarenal RAAS

Table 5. miRs being associated with CKD and ESRD

Marker	Detection source	Association with CKD and ESRD
AGT (intrarenal RAAS)	urine	high urinary AGT levels are associated with more than 50% decrease in eGFR and with ESRD occurrence in non-dialysis CKD patients [187]; urinary AGT level can serve as an early biomarker of renal function deterioration in patients with CKD (stages 3-4) [226]
AGT (intrarenal RAAS)	kidney	increased renal expression of AGT, chymase, and AT1 receptors promotes intrarenal RAAS activation and is associated with kidney damage even after the start of dialysis [182]
ANP, BNP	serum	plasma levels of ANP and BNP or their N-terminal fragments are increased in CKD patients [189-192]
CNP	urine	urinary CNP is significantly decreased in the rat UUO model (decrease occurring before albuminuria development); creatinine and blood urea nitrogen levels are upregulated [199]
Erythropoietin	serum, kidney	significant decrease in the blood concentration and biosynthesis of erythropoietin in the kidneys in CKD and ESRD [209, 210]
Guanylin	serum	increased guanylin plasma level in patients with CKD [203], glomerulonephritis, and nephrotic syndrome [204]
Kinin/kallikrein system	serum	positive correlation between the urinary kallikrein/creatinine ratio and decreased eGFR in patients with CKD [223]
Prolactin	serum	significantly elevated (up to 70%) serum prolactin in CKD patients on hemodialysis is associated with the impaired clearance of this hormone [218, 219]
Uroguanylin	serum	plasma concentration of uroguanylin is increased in patients with CKD and glomerulonephritis [205]

activation and is associated with kidney damage even after the start of dialysis [180]. Activation of the intrarenal RAAS also occurs in kidney donors without pre-existing kidney damage, which increases the risk of developing ESRD by the donor; however, it does not correlate with changes in the blood pressure, eGFR, plasma AngII levels, and albuminuria [181].

Urinary AGT is used as a biomarker of intrarenal RAAS activation in patients with CKD [182, 183], although some researchers believe that the urinary AGT/creatinine ratio is a more informative parameter than the AGT content alone [184, 185]. High urinary AGT levels are associated with a more than 50% decrease in the eGFR in non-dialysis CKD patients, as shown by the Korean Cohort Study for Outcomes in Patients with Chronic Kidney Disease (KNOW-CKD) [185]. Similar results on the association of urinary AGT with an adverse renal outcome have been obtained in the studies of patients with autosomal dominant polycystic kidney disease [184] and type 2 diabetes mellitus [184, 186].

Natriuretic peptides. Natriuretic peptides act as RAAS antagonists in the regulation of vascular tone and blood pressure. They protect against hypertension and related pathologies, including kidney damage [187].

Natriuretic peptide family includes atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), guanylin, and uroguanylin.

Measurements of the plasma concentrations of ANP and BNP can be useful for the risk stratification of patients with ESRD [188, 189]. The plasma levels of ANP and BNP and their N-terminal fragments are increased in patients with CKD, and therefore, have been suggested as prognostic markers of the CKD-to-ESRD transition and fibrosis [189-192]. The main causes for the increased serum concentration of these hormones are hypervolemia, arterial hypertension, and concomitant heart disease, as well as a sharp decrease in or complete absence of renal clearance [188, 193]. High mortality in patients with ESRD is due to a significant risk of developing heart failure associated with a high incidence of left ventricular hypertrophy, various cardiomyopathies, and coronary heart disease [194].

CNP plays an important role in preventing kidney tissue remodeling [195, 196]. Hypoxia and increased release of cytokines and profibrotic growth factors accompanying remodeling stimulate CNP production and secretion [197]. Among all natriuretic peptides, CNP is the first to be degraded by neutral endopeptidase [198],

which hinders its detection in physiological fluids. Since the serum content of CNP is very low, it is believed that CNP and products of its degradation should be analyzed in urine rather than in blood [197]. A number of authors consider urinary CNP as an early marker of tubulointerstitial fibrosis. A significant decrease in the urinary CNP was found in the rat UUO model; moreover, this decrease was detected before the emergence of albuminuria and proteinuria and increase in the blood content of creatinine and urea nitrogen [199].

Guanylin is a low-molecular-weight natriuretic peptide produced mainly by intestinal mucosal cells and kidneys [200-202]. Guanylin is associated with various kidney diseases; for example, increased guanylin plasma levels have been observed in patients with CKD [203], glomerulonephritis, and nephrotic syndrome [204]. Uroguanylin, which is similar in structure to guanylin, has been poorly studied in the context of renal pathologies, but its plasma concentration is known to increase in patients with CKD and glomerulonephritis [205]. There are data on the elevated plasma levels of uroguanylin in hemodialysis patients. An increase in the serum concentration of uroguanylin is strongly contributed by the reduced GFR in such patients [206] and amount of table salt consumed by the patients with food [207].

Erythropoietin. Erythropoietin is a glycoprotein synthesized in the kidney. One of its main functions is stimulation of erythropoiesis [208]. Since CKD and ESRD lead to significant disturbances in the erythropoietin synthesis, patients with varying degrees of kidney damage develop anemia [209, 210]. According to the World Health Organization, anemia is defined as a decrease in hemoglobin level to less than 13 g/dl in males and 12 g/dl in females before the menopause. The majority of patients (90%) with the GFR of 25 ml/min are diagnosed with anemia since their hemoglobin level is less than 10 g/dl [211]. Administration of exogenous erythropoietin slows down CKD development, reduces cardiovascular mortality, and increases exercise tolerance [212, 213].

Prolactin. Prolactin is involved in regulation of lactation, reproduction, immunomodulation, and natriuresis [207, 214-217]. A significant elevation of the prolactin blood content is observed in CKD patients and in up to 70% patients on hemodialysis due to the reduced clearance of this hormone [218, 219]. Increasing the frequency of dialysis procedure does not reduce the serum concentration of prolactin [220], unlike with other hormones (for example, dialysis resolves the problem of hyperinsulinemia in patients with CKD-associated insulin resistance [171]). In diagnostics, urine and serum are typically assayed for the so-called macroprolactin, which is a complex of prolactin with IgG with a molecular weight of >100 kDa [221, 222]. According to the published data, hyperprolactinemia in ESRD is an indirect indication for the kidney transplantation.

Kallikrein−kinin system. The kallikrein−kinin system includes polyfunctional blood proteins acting at the endo- and paracrine levels and responsible for the regulation of blood pressure and vasodilation mediated by the nitric oxide release. The most important proteins of this system are kallikrein and bradykinin. A positive correlation between the urinary kallikrein/creatinine ratio and decrease in the eGFR in CKD patients, as well as the urinary content of the inflammatory marker MCP-1, has been found, which makes kallikrein a potential biomarker for assessing the functional state of kidneys [223]. Similar data have been obtained for patients with type 1 diabetes. In these patients, decreased activity of plasma kallikrein was associated with the progression of diabetic nephropathy, the lowest activity of this serine protease being found in patients on hemodialysis. It was suggested that preventing the loss of kallikrein in diabetic nephropathy could preserve the functional activity of kidneys [224]. The promoter of the kallikrein gene *KLK1* is characterized by polymorphism, which complicates the identification of gene alleles. However, one of the alleles was found to be more common in ESRD patients than in the control group [225].

PROSPECTS OF ESRD DIAGNOSTICS

Integration of the above biomarkers into everyday diagnostics will allow to attain personalized approach to patients in order to better predict the disease outcome and to select the treatment. The clinical picture can change during the course of CKD depending on the disease itself and personal characteristics of a patient. Hence, we can observe accumulation of different biomarkers in different diseases (Fig. 3).

Some biomarkers have been identified in a particular disease only and therefore, can be used for selective diagnostics of this disease, while other have been detected in two, three, or more major renal disorders (e.g., C3M and MMP-7 were found in all mentioned pathologies). It seems also helpful to use a combination of several biomarkers n for disease diagnostics. For example, C3M and MMP-7 (with eGFR) are the major diagnostic parameters in the assessment of ESRD development. The use of other markers (TNFRs, BMP-7, DcR2, PRO-C6, PRO-C3, CTGF, MCP-1, CXCL16) can narrow the spectrum of diagnosed diseases. Thus, endotrophin and TGF-β are specific for IgA nephropathy, whereas galectin 3 is specific for diabetic nephropathy only. Hormone markers (kallikrein, AGT, guanylin, and uroguanylin) predict ESRD only in patients with diabetic nephropathy or glomerulonephritis.

Epigenetic markers, such as miR-21, miR-93-5p, and miR-92, are not unique for ESRD: miR-146a is specific for IgA nephropathy and glomerulonephritis.
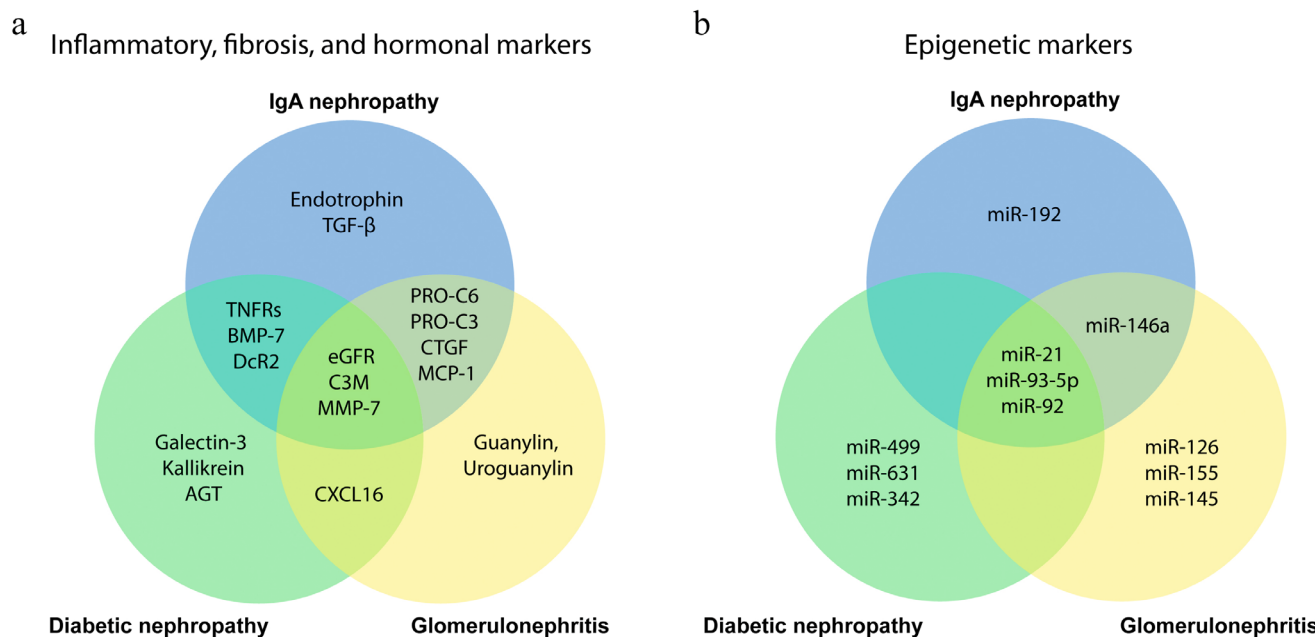
a
Inflammatory, fibrosis, and hormonal markers

b
Epigenetic markers

Fig. 3. Venn diagrams of biomarkers associated with major CKD-related pathologies. a) Inflammatory, fibrosis, and hormonal markers; b) prospective epigenetic markers.

The other markers shown in the diagram are also specific for particular diseases. There are some limitations for the application of miRs in clinical practice. For example, there are insufficient data on the correlation between miRs and particular diseases. Inclusion of miRs in the diagram in Fig. 3 is based on currently available scientific data, so in the future, it may turn out that all these miRs should be in the middle of the circles. It might give an impression that all known miRs are only weakly specific for the disorders leading to the CKD development and that the use of miRs alone as biomarkers is insufficient to determine the patient's condition and to omit eGFR as a diagnostic factor. However, different miRs have their specific characteristics, and their combination could be a powerful diagnostic tool (for example, in a form of test strips used for rapid simultaneous detection of multiple miRs).

CONCLUSION

At present, there are multiple biomarkers associated with CKD transition into ESRD that have been identified in clinical studies and animal models. Some of them are specific to a particular pathology, while others are more versatile. Here, we reported putative inflammatory, fibrosis, hormonal, and epigenetic markers indicative of severe deterioration of renal function and ESRD progression. Their application together with conventional renal failure indicators, such as eGFR, can improve the prognosis of ESRD for immediate initiation of therapy or recommendation for transplantation.

Ethics declarations. The authors declare no conflict of interest. This article does not contain description of studies involving human participants or animals performed by any of the authors.

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