Review Article

The role of prognostic assessment with biomarkers in chronic kidney disease: a narrative review

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Abstract: Chronic kidney disease (CKD) is associated with high morbidity and mortality. In the past, residual kidney function in CKD patients was assessed by serum creatinine-based equations. However, due to low accuracy of those calculations there is a need for alternative biomarkers. As cardiovascular disease is a major cause of increased mortality in patients with CKD novel biomarkers to estimate risk of cardiovascular death are vital. We reviewed articles approaching beta-trace protein, beta-2 microglobulin (B2MG) and cystatin C as alternative biomarkers to estimate glomerular filtration rate (GFR) in CKD patients. Furthermore, we included recent publications showing the role of high sensitive troponin and sFlt-1 in assessment of progressing cardiovascular disease in patients with renal failure as well as the role of inflammatory biomarkers in those patients. Lastly, we present basic research regarding the role of *APOL1* gene variants, suPAR and αvβ3 integrin on decline of renal function. Measuring GFR with serum creatinine and cystatin C seems to be more accurate than equations based on beta-trace protein and B2MG. Beta-trace protein however, seems to be a predictive marker to assess risk of end-stage renal disease. A recent study showed that serum sFlt-1 levels after heparin injection could predict cardiovascular mortality in patients with chronic renal failure. High sensitive troponin is a recently introduced biomarker measuring myocardial damage in acute myocardial infarction (MI) and can predict short-term all cause death in patients with reduced GFR. Progression of renal disease is attributed to increased inflammation levels and can be predicted by measuring proinflammatory biomarkers such as TNF-receptor 1, TNF-receptor 2 and KIM-1. We gave an updated review of novel biomarkers in CKD. While some have proven useful in certain situations it is unclear whether one single biomarker for assessing renal function or predicting mortality in patients with renal failure can be found.

Keywords: Chronic kidney disease (CKD); cardiovascular disorders; low-molecular weight proteins; biomarker

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Introduction

Assessment of kidney function is clinical routine and part of every laboratory screening irrespective of medical discipline.

Kidney function in chronic kidney disease (CKD) correlates tightly with morbidity and mortality and has a great impact on quality of life (1,2). In addition, patients with CKD are predisposed to severe threats, especially cardiovascular disorders like atherosclerosis and myocardial infarction (MI) (3).

For decades, the assessment of kidney function has mainly been based on determination of serum creatinine and creatinine-based equations to assess GFR. However, it

is increasingly recognized that this marker is neither perfect nor accurate (4). This highlights the clinical necessity for new biomarkers and equations based on other cost-effective biomarkers, especially for a longitudinal monitoring of kidney function in patients with CKD.

With respect to the great variety of pathological entities leading to CKD identification of a single biomarker, which provides a specific and reliable non-invasive measurement with minimal confounders might appear utopian.

This review therefore gives an updated overview about new and conventional filtration markers and introduces new biomarkers with special attention to cardiovascular disorders in patients with CKD.

Assessment of kidney function based on new and conventional filtration markers

Over the past years, several endogenous markers of kidney function have been introduced. Of those, the most intensively investigated biomarkers are beta-trace protein (BTP), cystatin C and beta-2 microglobulin (B2MG) (5-8).

They are low-molecular-weight proteins (BTP, 23–29 kDa; cystatin C, 13.3 kDa; B2MG, 11.8 kDa) which accumulate in serum if renal function declines. Compared to creatinine, they have been shown to be influenced less by age, sex, race and muscle mass (9).

BTP has a minimal non-renal elimination (10). However, this study was published in 1973 and included only four patients. In contrast, cystatin C shows a considerable non-renal clearance of 22.3 mL/min/1.73 m^2 and thus greatly overestimates renal clearance in advanced renal failure (11,12). B2MG is filtered by the kidney, but is also increased in acute and chronic inflammation, malnutrition and malignancy (13).

Albeit these biomarkers appear to be at least partially superior to creatinine, all of them have serious confounders or are poorly investigated, which limit their ability to predict kidney function in clinical routine. In summary, determination of a single biomarker certainly does not fit every pathology. Since invasive measurement of GFR is not feasible, it has to be estimated based on endogenous biomarkers. Several investigations addressed this issue recently.

Routinely estimated GFR (eGFR) is still based solely on serum creatinine, although it has been reported that the addition of cystatin C improves the accuracy of GFR estimation compared to equations based on single biomarkers (14,15). Furthermore, equations based on cystatin C combined with creatinine seem to fortify the association between a declining eGFR and cardiovascular diseases (16).

Also, equations based on BTP and B2MG have been introduced, however best assessed in specific populations, e.g. kidney transplant recipients (13) and children (17,18).

To close this gap, a recent study by Inker *et al.* developed GFR equations based on serum BTP and B2MG in a cohort derived from three study populations with CKD (9). Even though these equations might not be superior for determination of kidney function at a time, predictive assessment based on filtration markers at multiple time points may improve the prediction of clinical outcomes over a single measurement (19). An observational analysis of two trials tested the predictive value of the change in eGFR either creatinine-based or using BTP, B2MG and cystatin C along with invasive measurement of GFR for end-stage renal disease (ESRD) and mortality in a 12- and 24-month follow-up. A decline in eGFR (BTP) was associated more strongly with the risk for ESRD than invasively measured GFR. This leads to the assumption, that BTP potentially shows a predictive value for ESRD and might be a valuable tool for repeated assessment of kidney function.

Two recently published equations based on B2MG have been suggested for assessment of residual kidney function in hemodialysis patients (11,20). The first claims an equation combining serum B2MG and BTP for estimation of residual kidney function in patients undergoing hemodialysis, the latter provides an equation based solely on B2MG.

Biomarkers in CKD related diseases

The leading cause of death in patients suffering from CKD is cardiovascular disease (3). As eGFR declines, overall mortality and the risk of cardiovascular events and hospitalization rise (21).

Soluble fms-like tyrosine kinase (sFlt-1)

Primarily, the sFlt-1 was found to be a biomarker for preeclampsia in pregnant women (22,23). sFlt-1 is a soluble isoform of the Flt-1 receptor which plays an important role in the development of atherosclerotic disease. After binding with placental growth factor (PlGF) on the epithelial cell Flt-1 promotes atherosclerotic processes by mediating intramural angiogenesis and release of proinflammatory cytokines (24,25). sFlt-1, a product of splicing Flt-1 mRNA binds to PlGF inhibiting the Flt-1/PlGF-pathway

and therefore inducing an antiangiogenic state (26). Elevated levels of sFlt-1 in CKD patients were associated with endothelial dysfunction and subsequently with cardiovascular mortality (27-29). This even seems to be apparent in patients undergoing haemodialysis (HD) (30). Matsui *et al.* showed that plasma sFlt-1 levels are higher in patients with CKD. Surprisingly, this changed after intravenous heparin injection. While sFlt-1 serum levels rose in all 343 subjects, peak concentrations were significantly lower in the 291 CKD patients (eGFR below 60 mL/min per 1.73 m^2 and/or continuous proteinuria over 3 months) compared to patients in the control group. Furthermore, higher postheparin PlGF/sFlt-1 ratio was associated with significantly higher incidence of cardiovascular events during a roughly 6 months median follow-up period. However, this was not the case for PlGF/sFlt-1 ratio before heparin injection (31). As mentioned above, previous studies have shown high sFlt-1 plasma levels being associated with increased mortality in renal failure suggesting an increased production in endothelial cells (32,33). In an experimental mouse model sFlt-1 mRNA expression was reduced in nephrectomized mice compared to wild-type mice. sFlt-1 was stored on endothelial cells and was released following heparin treatment. *In vitro* experiments with cultured human endothelial cells support these findings and reveal that sFlt-1 is reduced in presence of endothelial damage markers. Therefore, sFlt-1 production seems to decline with a reduction in eGFR, while sFlt-1 plasma levels rise (31). The release of sFlt-1 by heparin replacing it from its binding site from heparan sulfate proteoglycans was previously shown (34). However, Matsui *et al.* showed that the postheparin sFlt-1 levels reflect its overall production and thus could be a biomarker to estimate cardiovascular mortality (31,35).

High sensitive troponin (hsTn)

As descried above patients with renal impairment are in greater risk of dying from MI. Even in early-stage CKD risk of long-term cardiovascular death after acute MI is higher compared to patients with preserved renal function (36). In recent years, hsTn has shown to have diagnostic and prognostic utility in acute MI (37,38). However, patients with CKD were often excluded in those studies. Elevated levels of cardiac troponin in those patients can occur not only in MI but also in other cardiac diseases as well as noncardiac diseases (39). Ballocca *et al.* analysed data from seven different centres over a 2-year period. Overall 647 patients with an eGFR below 60 mL/min/m^2 were admitted into the emergency room with suspected acute MI. hsTnI or hsTnT levels were assessed before coronary angiography as well as 3 and 6 hours after admission. Seventy-eight percent of the patients were treated with percutaneous transluminal angioplasty. Both hsTnI and hsTnT peak levels were predictive for short-term all cause death with hsTnI being more accurate than hsTnT in detecting coronary disease (40). Those findings are in contrast to previous studies that showed hsTnT as a poor marker for detecting acute MI in patients with renal failure (41).

Profiling of inflammatory biomarkers

Increased mortality in patients with CKD is attributed to inflammation. This is reflected by investigations suggesting cytokines and chemokines as new biomarkers. In the Chronic Renal Insufficiency Cohort (CRIC) study in 2012, kidney function was inversely associated with serum levels of proinflammatory biomarkers (IL-1β, IL-1 receptor antagonist, IL-6, TNF-α, CRP, and fibrinogen) and positively with albuminuria (42). This association is even highlighted by a recently published study in a cohort of diabetics with kidney disease (43). Here, TNF-receptor 1 and TNF-receptor 2 as well as kidney injury molecule-1 (KIM-1) were independently associated with higher risk of decline in eGFR. Importantly, these results were validated in a cohort of incident diabetic kidney disease and a cohort of patients with progressive diabetic kidney disease implying that these biomarkers might serve as good predictors for the progression of CKD, at least in patients suffering from diabetes.

With regard to the association of CKD and cardiovascular disorders, evidence suggests an influence of uremic toxins on cardiovascular morbidity and mortality by activation of leukocytes and enhancement of monocyte-endothelial interactions, which has been reviewed elsewhere (44).

Addressing this issue, a recently published study on 14 individuals of a CKD cohort investigated arterial wall inflammation in aorta and carotid arteries by PET/CT imaging. The CKD cohort displayed an increase in arterial wall inflammation, chemokine receptor expression and transepithelial migration capacity compared to the control cohort (45). Since severe confounders like body mass index (BMI), blood pressure and plasma cholesterols were comparable between the CKD and control cohort, the data is convincing. However, no definite conclusions of the contribution of CKD on arterial wall inflammation can be drawn so far.

Table 1 Summarizing table of reviewed biomarkers for a prognostic assessment in CKD

Biomarker	Site of expression	Known functions	Biomarker property rationale
Beta-trace protein	Several organs	Prostaglandin-D-synthase	23–29 kDa (low-molecular weight protein)
Beta-2-microglobulin	Nucleated cells	Soluble subunit of MHC I	11.8 kDa (low-molecular weight protein)
Cystatin C	Nucleated cells	Cysteine protease inhibitor	13.3 kDa (low-molecular weight protein)
sFlt-1	Endothelial cells	Binding site for PlGF	Intramural angiogenesis; proinflammatory
hsTnT/hsTnI	Cardiac myocytes	Contraction of striated muscle	Marker for MI
Proinflammatory cytokines (IL-1β, IL-6, TNFα, IL-18)	Monocytes/macrophages/dendritic cells	Inflammation; immunomodulator	Attribution of CKD to inflammation
APOL1 risk variants	Soluble; podocytes; proximal tubules	Minor apoprotein component of HDL	Inflammatory-mediated podocyte death
suPAR	Soluble	Membrane bound receptor for urokinase	Marker for immune activation

PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase; hsTn, high sensitive troponin; APOL1, apolipoprotein L1; MI, myocardial infarction; CKD, chronic kidney disease; HDL, high-density lipoprotein; suPAR, soluble urokinase plasminogen activator receptor.

Soluble urokinase plasminogen activator receptor (suPAR)

Recently published data shed light on the association of gene variants of apolipoprotein L1 (APOL1), suPAR (a member of a signaling protein family and a marker for immune activation) (46-48) and $\alpha_v\beta_3$ integrin (49).

Gene variants in the *APOL1* gene of individuals of African ancestry (50-54) have been described to be associated with distinct forms of CKD. Irrespective of this, measurement of plasma levels of suPAR (55) identified a tight association between elevated level of suPAR and incident CKD as well as an accelerated decline of eGFR. Podocytes express $\alpha_v\beta_3$ integrin, which has been suggested as a suPAR binding molecule regulating the glomerular filtration barrier (56-60). This study investigated a putative pathophysiological link between podocyte dysfunction, suPAR levels and *APOL1* gene variants.

They demonstrated higher levels of suPAR modifying the association between *APOL1* genotype and eGFR decline in two cohorts of African American individuals. Further, individuals with *APOL1* risk genotype revealed an even steeper decline in eGFR. This effect was suggested to be mediated by protein-protein binding of APOL1 and suPAR as well as between APOL1 and $\alpha_v\beta_3$ integrin on podocytes. This tripartite complex leads to activation of the $\alpha_v\beta_3$ integrin pathway on podocytes resulting in dysregulation of the cytoskeleton and cell detachment. Importantly, only risk variants of *APOL1* synergize with suPAR allowing complex formation with $\alpha_v\beta_3$ integrin on podocytes. These results are underlined by data generated in mice models where expression of *APOL1* risk alleles is causal for altered podocyte function and glomerular disease *in vivo*. Expression of the risk-variant *APOL1* alleles led to inflammatory-mediated podocyte death and glomerular scarring (61).

Conclusions and perspectives

We have presented an update on biomarkers for the assessment of kidney function with focus on cardiovascular diseases. Due to the great variety, only a small excerpt of available biomarkers could be reviewed here (*Table 1*). We pointed out, that until now no biomarker appears to be particularly suitable in clinical routine. The biggest challenge might be to identify biomarkers and equations, which are cost-effective, reliable and beneficial for the assessment of kidney function. Insights in pathophysiological mechanisms will allow more accurate choices of biomarkers for specific populations.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.

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