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Editorial Comments

Urinary Protein Biomarkers in Chronic Kidney Disease

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Introduction - Chronic kidney disease

Chronic kidney disease (CKD) is increasingly recognized as an important national and worldwide public health problem because of its consequences on quality of life and high prevalence, existing in up to one-tenth of the adults in developed countries and 13% of the general population [1,2].
Currently used diagnostic and staging tools are mostly based on non-invasive analysis of serum creatinine and/ or urinary albumin and estimation of glomerular filtration rate (eGFR). These biomarkers although widely accepted, frequently fail to identify patients at higher risk of progression or death [3,4]. They are also not reliable parameters for early diagnosis, as rising of serum creatinine levels above normal is only evident after substantial loss of renal function and its level may be affected by additional factors, such as the loss of muscle mass [5]. On the other hand, urinary albumin levels are highly variable and lack of specificity, as patients with reduced eGFR can have normal urinary albumin levels [6,7]. Still, albuminuria has been suggested to be a better predictor of accelerated loss in renal function than eGFR [8]. This is also the case in patients with diabetes mellitus, where microalbuminuria is considered as a risk for development diabetic nephropathy (DN) [9]. Nevertheless, it is still challenging to predict which diabetic patients with normoalbuminuria will develop microalbuminuria and even more, to identify those in whom GFR will decline without ever developing overt albuminuria [3]. According to KDIGO guidelines, all individuals with an estimated GFR <60 mL/min/1.73m^2 for ≥3 months are classified as having CKD, irrespective of the presence or absence of kidney damage. Conversely, in patients with estimated glomerular filtration rate (eGFR) >60 mL/min/1.73m^2, additional evidence of kidney damage is required in order to diagnose them with CKD. This additional evidence may be provided by a renal biopsy or detected by abnormalities present in blood, urine or on kidney imaging tests [10].
Renal biopsy is the current standard for diagnosing patients with glomerular disorders and it is also used for directing and monitoring their therapy [11]. Renal histology parameters such as glomerulosclerosis, vascular sclerosis, interstitial inflammation and fibrosis are considered as valuable indicators of the disease severity [12], but as renal biopsy is invasive procedure, it is not feasible to be used for early diagnosis in patients at risk [13] or repeatedly performed to follow the progress of the disease.
There is an evident link between the kidney dysfunction and cardiovascular risk, where along with the disease progression CKD associated morbidity and mortality is increasing. Hence, it is important for the nephrologists, to be able to detect patients that are at risk for a disease progression. Additionally, there is a lack of understanding why some of the CKD patients progress to end-stage renal disease (ESRD) requiring renal replacement therapy (RRT), while others die prematurely due to cardiovascular diseases (CVD) instead of progressing to ESRD [3, 14-17].
Ultimately, it is important to identify additional noninvasive diagnostic biomarkers for early detection of renal diseases and possible timely therapeutical interventions and prognostics biomarkers as reliable predictors of progression towards ESRD and/or death outcomes [3,4,11,18-20].

Urinary biomarkers

Urine is one of the potential sources for biomarkers having many advantages. It can be collected non-invasively, repeatedly and in large quantities, which allows their use for repeated analysis [21]. Furthermore, the fact that approximately 70% of the proteins and peptides in urine originate from the kidney [22], makes it suitable source of biomarkers associated with kidney diseases and could be considered a "liquid biopsy" [13]. Those are the main reasons why the urine is widely used for proteomic biomarkers discovery [17,23,24].
Single-protein biomarkers are not effective and suitable to reflect complex diseases, such as CKD and therefore combination and simultaneous use of multiple biomarkers should improve the diagnostic performance [4,17,25]. Combination of multiple biomarkers in high-dimensional classifiers, substantially outperform linear combination of biomarkers [26].

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Electrophoresis coupled to mass spectrometry (CE-MS) appears to be an applicable method for urinary proteome analysis and has been extensively used in discovering and validating biomarkers for CKD [17,27].

CKD273 classifier

CKD273 classifier is a successful example of CKD-specific urinary biomarker model established by using this approach. The classifier is based on 273 sequenced peptides, combined by using support vector machines (SVM), which were identified that differed significantly between 230 patients with CKD of various etiologies and 379 controls in the initial cross-sectional study. In the first blinded validation, CKD 273 classifier significantly outperformed albuminuria, showing sensitivity of 86% and a specificity of 100% [28]. It was also validated in another cohort of CKD patients with different disease etiologies and healthy controls [29], and in diabetic patients with or without overt diabetic nephropathy [27,30]. Besides proving its capability to identify patients with established CKD in independent studies, CKD273 classifier was also able to predict progression of CKD. Overall, the classifier was able to predict development of micro-or macroalbuminuria and rapid eGFR decrease (i.e. >−5% decline per year), demonstrating its utility and advantage over the currently used clinical tools for predicting CKD progression [17,31-33].

Clinical implementation

CKD is a major challenge and financial burden for the public healthcare systems [34] which can be diminished with recent advances in urinary proteomic analyses, showing potential to improve the care of patients with renal diseases [11].

Since CKD is known to be asymptomatic at early stages, screening for the disease is one of the potential solutions to timely identify CKD patients, trying to reduce the risk of progression and developing further complications. If properly applied, screening tests should identify a large number of patients with minimum costs. In practice, population-based screening does not turn up to be cost-effective and instead, targeted screening is suggested to be more beneficial, especially in patients with high-risk factors such as hypertension, diabetes, obesity, and those from African American race [35-37].

Nowadays, it is evident that urinary proteome analyses are the most suitable approach for early detection, prediction and following the progression of CKD. Hopefully, proteomics could be able to replace kidney biopsies as an invasive procedure that neither can be applied for screening and early detection nor repeatedly performed for following the progression and response to treatment in the near future.

Although urinary proteome analysis is becoming a routine tool in research and a large number of proteomic biomarkers have been described, their transition towards clinical implementation is still hampered [3,13]. Their implementation should involve a wide variety of stakeholders (clinicians, statisticians, health economists, and representatives of patient groups, health insurance, pharmaceutical companies, biobanks, and regulatory agencies). Finally, besides investing efforts for clinical adoption and routine application, their cost-effectiveness has to be also evaluated, as the last point on road map towards clinical implementation [38].

Therefore, beside its utility, CKD273 classifier needs supporting evidence for its cost-effectiveness as compared with the costs of hospitalization, RRT (haemodialysis and/or renal transplantation) and patients' quality of life [31].

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