Urinary biomarkers to predict CKD: the future is in multi-marker panels?

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Running title: multimarker panels to predict CKD

Keywords: biomarker, proteomics, urine, CKD, HIV

Chronic kidney disease (CKD) is characterized by gradual decrease in renal function and affects more than 10% of the general population. CKD has the potential to lead to end stage renal disease but it is already associated with cardiovascular complications at earlier stages of the disease process. Diabetes and hypertension are among the main causes of CKD [1,2], with age, smoking and obesity being important pathophysiological co-factors. A further independent risk factor for CKD and acute kidney injury (AKI) is HIV infection [3-5]. The United States Renal Data System database reported a risk of ESRD by 50-fold higher in HIV-infected than in non-HIV infected [6].

In general there is no cure for CKD. Once CKD is established the pragmatic therapeutic goal in clinical practice is prevention of further progression. It is clear, however, that a primary preventative approach with treatment before the onset of CKD would be much more attractive. Approaches to apply primary preventative intervention to all patients at presumed risk, e.g. by treating all patients with diabetes and normoalbuminuria, are hampered by an unfavourable balance between a possible preventative effect on CKD and adverse events related to the medication [7]. A targeted preventative approach in those at highest risk of developing CKD has the potential to overcome these problems.

Such personalised primary prevention requires the availability of precise biomarkers of CKD. Decreased glomerular filtration rate and presence of albuminuria are established markers of CKD. However, these markers occur relatively late in the disease process are not directly associated with the underlying molecular pathophysiology but rather a result of the compromised kidney function. More recently, urinary biomarkers emerged as a valid approach to detect CKD, and to predict development and progression of CKD [8-10]. Urine is considered an excellent source of biomarkers for CKD as products from the kidney are directly “deposited” in urine. However, it appears that single biomarkers cannot fully describe changes in renal function related to the complex pathophysiology of CKD. As a consequence, the concept of a multi-marker approach has been advocated for CKD [11].

The recent report by Scherzer et al. [12] adds to the number of studies investigating early urinary biomarkers for incident CKD and again highlights the benefit of multiple urinary biomarkers to predict CKD progression. The authors measured 8 urine biomarkers previously associated with incidence of CKD in 902 HIV-infected women as part of the Women’s Interagency HIV study [13-15]. NAG, KIM-1, alpha-1

microglobulin (α1m), IL-18, NGAL, ACR, L-FABP, and AAG were selected as candidate biomarkers. Among these biomarkers NAG, KIM-1, alpha-1 microglobulin displayed the highest combined predictive value and divided the cohort into three clusters, with cluster 1 being the lowest and cluster 3 being the highest risk group for CKD after multivariate adjustment for traditional kidney and HIV risk factors. Main results were:

a) In the highest risk cluster women were older, often African American and hypertensive.
b) After multivariate adjustment for traditional kidney and HIV risk factors, clusters 2 and 3 displayed the higher risk of CKD, compared to the cluster 1.
c) Cluster 3 was associated with a more than 2-fold greater risk of mortality compared to cluster 1.
d) The addition of three selected biomarkers (NAG, KIM-1, alpha-1 microglobulin) to the model based on traditional kidney and HIV risk factors identified an additional 15% of patients at high risk, however 7.9% of patients were inappropriately reclassified as lower risk patients.
e) Each biomarker was individually associated with an increased risk of CKD and mortality, after adjustment for traditional and HIV-related risk factors.

Participants classified as high risk had more comorbidities and worse HIV-related characteristics at baseline. Relative to those who were in the low risk category, this high risk cluster had 4-fold higher rates of incident CKD (50% vs. 13%) and all-cause mortality (41% vs. 10%). Although the new cluster variable only moderately improved model discrimination for CKD risk compared with a model containing traditional risk factors, the cluster was independently associated with each study outcome. The authors acknowledge that the data have not yet been validated in an external cohort, but envision that clinicians will ultimately be able to use a biomarker panel to determine the level of risk (low, moderate, or high) for CKD and mortality of an individual HIV-infected patient.

While the report highlights the potential of such an approach, it leaves several questions open that are to be answered in future studies. Among them is the question if three biomarkers suffice to describe, assess and predict the outcome of a heterogeneous disease such as CKD, and HIV-related CKD is in no way a uniform and homogenous condition. While in the data presented the tested additional

biomarkers did not add significant value, this may also be due to limited power. If strength is in numbers, the addition of further biomarkers may improve the stability of the classifier, and increase the possibility to better define a disease [16]. Even though multiple biomarkers have been employed by Scherzer et al., their value needs to be assessed in an independent set. Only such validation will ensure that the biomarkers meet the patients' needs. Given the fairly large dataset, the study may also provide an opportunity to investigate performance of different algorithms to be employed when combining multiple biomarkers. The choice by the authors was a very successful one, but others like e.g. artificial neural networks or support vector machines may provide even more power [17].

As also outlined by the authors, only markers of proximal tubular injury and function, with the exception of ACR (glomerular injury) and NGAL (maybe distal or mixed proximal/distal), were assessed in this study. Incorporation of markers that identify other aspects of nephron function and injury will probably allow even better assessment of risk.

The study included only women, and little is known about associations of urine biomarkers with kidney outcomes in HIV-infected men. Furthermore, racial differences in CKD incidence and progression to ESRD in HIV-infected individuals are well known [18]. Indeed, HIV-associated nephropathy (HIVAN) appears to progress more aggressively to ESRD in those of African descent [19] [20]. Also in the present study, Scherzer at al. confirmed the higher risk of African American Women. Racial differences are highly relevant for the assessment of such complex disease and must be taken into account to overcome possible bias in the results.

An important conclusion to be drawn from the present study is that a combination of urinary biomarkers is of value in the assessment of renal diseases in HIV-infected individuals. The use of a large set of patients allowed a better stratification of different level of risk groups. It is, however, equally important to stress that certain aspects (e.g. appropriate control groups, adjustment for variance and confirmation in validation test) need to be assessed before translation of such biomarkers into clinical practice.

The study adds significant additional evidence supporting the hypothesis that multiple urinary biomarkers, in combination, enable early detection/prognosis of

onset and progression of CKD. The findings, in combination with the current knowledge, raise several highly relevant questions:

1) Which biomarkers should be used, and how should they be combined? A comparative study assessing the performance of the different biomarkers and algorithms seems urgently required. This was already proposed and also implemented for other clinical areas[21,22], and it appears high time that similar efforts are undertaken in CKD.

2) What are the consequences of early detection? While interference with the RAAS may be a valid option in diabetic nephropathy, this may not necessarily apply to HIV-associated CKD.

3) How to evaluate success of such a strategy? If the current dogma of many regulators, that success can only be demonstrated based on economic benefit or significant impact on hard endpoints, then these potentially highly beneficial developments will never be implemented to benefit patients. An answer to this question can likely only be found on a political level.

Collectively, the demonstration of the value of urinary protein biomarker in the early detection/prognosis of progression of CKD by Scherzer et al. in this issue of NDT [12], the recent indication by EMA to accept disease prevention as a relevant endpoint in a study in CKD [23], and the recent attempts to utilize molecular data to identify potential additional specific novel therapeutic targets in CKD [24] give rise to the enthusiastic hope that CKD can in fact be successfully addressed in the near future. A first approach in this direction appears to be the PRIORITY trial [25], where urinary biomarkers are employed for the early detection of diabetic nephropathy, and only those at highest risk for development of clinically overt CKD will be randomised to active preventative therapy.

Conflicts of interest

H. Mischak is the founder and co-owner of Mosaiques Diagnostics, who developed the CE-MS technology for clinical application. Claudia Pontillo is employed by Mosaiques Diagnostics.

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