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Commentary

Biomarkers for early diagnosis of diabetic kidney disease: still a long way to go

According to the International Diabetes Federation's Diabetes Atlas[1], the global burden of diabetes mellitus (DM) in 2021 was 537 million and prevalence is expected to increase by 46 per cent by the year 2045. It is alarming that three-fourth of the global burden of DM is in resource-constrained middle- and low-income countries. It would be no surprise that the resources required for the management of DM and its associated complications would fall woefully short of expected requirements. Therefore, the prevention and early diagnosis of DM or its complications are need of the hour. Diabetic kidney disease (DKD) is one of the dreaded complications in patients with DM. Approximately, 40 per cent of patients with type 2 DM will go on to develop DKD[2]. Conventionally, DKD is characterized by the appearance of albuminuria which is followed by progressive fall in estimated glomerular filtration rate (eGFR). However, it is also well known that up to one-third of patients with type 2 DM and DKD might have kidney involvement manifesting as fall in eGFR without any significant albuminuria[2]. Therefore, screening for DKD has relied on both measurement of albuminuria and estimation of GFR by creatinine-based eGFR equations.

Once established, DKD usually progresses to end-stage kidney failure requiring dialysis or kidney transplantation. The classical description of stages of diabetic nephropathy in patients with type 1 DM given by Mogensen[3] in 1983 identified a long period of hyperfiltration and structural changes in kidneys before the development of albuminuria. Identifying kidney involvement before the onset of albuminuria and fall in eGFR would offer an opportunity for earlier detection of DKD. With the availability of omics platforms and discovery of newer biomarkers of glomerular or tubulointerstitial injury, research to test the utility of these biomarkers in patients with DM is being done. It is important to note that early detection might become more meaningful when detection would offer an opportunity for early intervention to retard progression. Therefore, establishing such biomarkers could have both diagnostic and therapeutic potentials. In view of this, the study by Mahapatra *et al*[4] in this issue assumes significance. The authors have cross sectionally studied and classified patients with type 2 DM into clinical categories of hyperfiltration (HF), normoalbuminuria (NA), microalbuminuria (MA) or controls based on albuminuria and eGFR. The former three categories constituted the cases. Urinary angiotensinogen (ng/ml) and angiotensinogen to creatinine ratio (mg/g) were reported to be significantly different between controls and individual case groups (HF, NA or MA). In the multivariate logistic regression analysis, urinary angiotensinogen to creatinine ratio was independently associated with the classification of patients as cases or controls. The authors also measured urinary excretion of interleukin-18, neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C. However, these biomarkers failed to show any independent association with the classification of the study population as cases or controls[4].

Biomarkers in kidney disease can be related to structural or functional alterations in the kidney. These can be classified in various ways such as markers of glomerular or tubulointerstitial injury or markers of underlying processes such as inflammation, oxidative stress, fibrosis or repair[5]. In advanced stages of kidney disease due to any aetiology, almost all functional compartments would be affected, and hence, the specificity of biomarkers for one type of injury or process would be low. However, in the early phases of kidney disease due to a specific aetiology, it is likely that biomarkers related to specific, early mechanisms of injury may be altered before any overt clinical or biochemical manifestations. Although classically described as a glomerular disease, it is well known now that tubulointerstitial compartment may get simultaneously or independently affected during

early DKD. The fact that up to one-third of patients with type 2 DM with DKD may not have significant proteinuria attests to this fact. Furthermore, not all patients with DKD and those with mildly increased albuminuria progress to develop overt nephropathy. Therefore, the assessment of only albuminuria or proteinuria, especially when it is done only once, has its own share of drawbacks with respect to the diagnosis of DKD. Circulating cystatin C and kidney injury molecule-1, urinary NGAL, epidermal growth factor (EGF)/monocyte chemotactic protein-1 (MCP-1), α1 microglobulin and retinol-binding protein 4 are some of the tubular biomarkers that have been investigated in patients with DM for predicting the development or progression of DKD[5]. It is important to note that urinary EGF/MCP-1 has been inversely associated with the presence of DKD[6]. Urinary type 4 collagen, copeptin and CKD 273 (complex of 273 proteins identified on proteomics) are some of the other promising biomarkers that have been shown to be associated with the development of chronic kidney disease (CKD) in patients with DM[7].

Angiotensinogen in urine is an indirect marker of intra-renal renin-angiotensin aldosterone system (RAAS) activation which is one of the early mechanisms of kidney injury in patients with DM[8]. Specifically, increased urine angiotensinogen excretion implies increased generation of intra-renal angiotensin II[9]. Furthermore, intra-renal RAAS activation may occur independent of changes in systemic circulation. It is also important to note that in the presence of conditions that disrupt glomerular permeability barrier, *e.g*. podocyte injury, circulating angiotensinogen also appears in urine[9]. Therefore, it is not surprising to see the association of urinary angiotensinogen excretion with albuminuria or proteinuria. Increased urinary angiotensinogen excretion is not specific to DKD and can be seen in other causes of CKD[9]. It has also been shown to correlate with prognosis after acute kidney injury.

Urinary angiotensinogen excretion has been shown to increase in graded manner between healthy controls and progressively increasing clinically defined stages of DKD. In a comparison of urinary angiotensinogen to creatinine ratio between patients with type 1 DM without albuminuria and matched healthy controls, it was shown to be significantly higher in patients[10]. Importantly, circulating angiotensinogen levels did not differ between the groups[10]. In a study in normotensive patients with type 2 DM and almost similar design as the present study[4], the authors reported progressively increasing urinary angiotensinogen excretion with increasing urine albumin excretion starting from normoalbuminuric phase[11]. This study[11] included patients with eGFR between 30 and 60 ml/min/1.73 m^2 or presence of overt albuminuria (urine albumin excretion >300 mg/g of creatinine) unlike the present study. The present study, together with these studies, reinforces the graded association between urinary angiotensinogen excretion and varying degrees of kidney involvement in patients with DM. Associations have also been reported between urinary angiotensinogen excretion and cardiovascular complications in patients with DM and albuminuria[12]. However, at present, there is no evidence to support any impact of urinary angiotensinogen levels on therapeutic decision-making. Furthermore, its role in non-albuminuric DKD is still to be explored. Despite these limitations, strong associations with progression in DKD warrant more studies on this biomarker.

The ideal design to discover or validate biomarkers for the prediction or early diagnosis of complications in DM would be a well-phenotyped, prospective, long-term cohort study that enrols patients as soon as they are diagnosed with DM. Serial evaluation of biomarkers would allow the evaluation of association of change in biomarkers with clinical phenotype over time. However, these are not always possible as such studies would need enormous resources and time. Although urine albumin excretion and fall in eGFR are two criteria that are used to establish a clinical diagnosis of DKD in appropriate clinical circumstances, the gold standard for the diagnosis of DKD is kidney biopsy. There is increasing evidence that kidney involvement in patients with DM especially type 2 could be due to other causes as patients with type 2 DM often have other comorbidities such as obesity, hypertension, metabolic syndrome and infections[2]. Unfortunately, as of now, the kidney biopsy is very difficult to justify for establishing diagnosis of DKD in otherwise typical clinical picture of DKD. Kidney biopsy in a patient with DM and kidney involvement are only considered when the clinical course or investigations are atypical, *e.g*. rapid decline in kidney function, presence of massive proteinuria or active urinary sediment or hypocomplementemia, absence of proteinuria and extra-renal manifestations suggesting secondary kidney involvement. The study by Mahapatra *et al*[4] was a cross-sectional study that defined patient groups by their clinical course over 12 months in the absence

of kidney biopsy. Although clinically robust, these observations only suggest associations that would need to be tested and validated in properly designed studies.

***Conflicts of Interest*:** None.

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