New Insights Into the Use of Biomarkers of Diabetic Nephropathy

Jay C. Jha, Karin A. M. Jandeleit-Dahm, and Mark E. Cooper

Diabetic nephropathy (DN) is a major microvascular complication of diabetes characterized by increasing albuminuria and progressive loss of kidney function. Increased excretion of albumin into the urine is a key feature of DN, and its assessment is considered to be an early marker predicting the onset and progression of DN. However, albuminuria has certain limitations; therefore, the quest for more reliable renal biomarkers with higher sensitivity and specificity are needed for early prediction of the onset and monitoring of the progression of DN. Furthermore, such biomarkers may also provide a better insight into identifying the complex pathophysiological processes responsible for DN. This article aims to provide a comprehensive and critical review of the current literature on relevant biomarkers of kidney injury, including markers of renal fibrosis, inflammation, and oxidative stress, as well as addressing contemporary proteomic approaches.

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Introduction

Diabetes mellitus represents a global threat for premature morbidity and mortality, and it is likely to be the 5th leading cause of death worldwide.[1] According to the recently updated International Diabetes Federation's *Diabetes Atlas Report*, more than 371 million people have diabetes, and this figure is increasing globally at an alarming rate. Diabetic nephropathy (DN) is a major chronic microvascular complication of diabetes, and it is the leading cause of ESRD worldwide, often requiring dialysis and/or transplantation.[2] DN is characterized by a progressive increase in albuminuria and a decline in glomerular filtration rate (GFR), which often occur in association with an increase in blood pressure, ultimately leading to end-stage kidney failure.[3] Proteinuria is considered a hallmark of DN, and it has generally been considered to primarily reflect glomerular injury and increased glomerular permeability to macromolecules.[4] In addition, renal functional changes are associated with structural abnormalities, including glomerular basement membrane (GBM) thickening and mesangial expansion as a result of the accumulation of extracellular matrix (ECM), which leads to glomerulosclerosis and tubulointerstitial fibrosis.

Mechanisms underlying nephropathy in diabetes include a range of hemodynamic and metabolic factors, such as hyperglycemia, dyslipidemia, systemic and intraglomerular hypertension, activation of the renin-angiotensin system, impaired insulin signaling, infiltration by inflammatory cells, increased growth factors and proinflammatory mediators, and activation of key intracellular signaling pathways and transcription factors leading to the development and progression of diabetes-associated kidney disease.[5,6] Several mechanisms have been proposed to explain the detrimental effects of hyperglycemia-induced tissue damage, including flux through the polyol pathway, advanced glycation end product (AGE) formation, hexosamine pathway flux and activation of protein kinase C, angiotensin II, and nicotinamide adenine dinucleotide phosphate oxidase.[3,6-8] A growing number of studies support that the generation of reactive oxygen species as a common downstream pathway of most of these mechanisms ultimately leads to inflammation and fibrosis[7-9] (Fig 1). However, the exact pathogenesis of DN is complex and poorly understood. The early assessment of the nature, severity, and rate of progression of DN could assist in successful therapeutic intervention and in the development of more effective treatment strategies for diabetic patients. Therefore, sensitive and specific biomarkers need to be carefully considered and their usefulness validated. Furthermore, such biomarkers will help to elucidate the pathophysiology of DN and direct investigators toward the use of new therapeutic agents.

Biomarkers of DN

In general, a biomarker is a biological substance that may reflect the pathophysiological processes or pharmacological responses to a therapeutic intervention. The ideal renal biomarker should be easy to measure and noninvasive; it should be accurate and highly reproducible; and it should demonstrate high sensitivity, and high specificity, cost-effectiveness in its ability to predict the presence of disease, prognosis of the disorder, and progression of the condition. Advanced technologies have resulted in the identification of several potential biomarkers in the serum, urine, and

From JDRF Danielle Alberti Memorial Centre for Diabetic Complications, Diabetic Complications Division, Baker IDI Heart & Diabetes Institute, Department of Medicine, Monash University, Melbourne, Australia.

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Address correspondence to Mark E. Cooper, MBBS, PhD, Diabetic Complications, Baker IDI Heart & Diabetes Research Institute, PO Box 6492 St. Kilda Road, Melbourne, Victoria 8008, Australia. E-mail: Mark.Cooper@bakeridi.edu.au

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kidney tissues of patients with diabetic kidney disease, and they are often initially explored in animal models. However, many of these biomarkers require further validation. These biomarkers have been categorized based on their ability to detect glomerular and tubular injuries as well as inflammation or oxidative stress (Fig 1). Furthermore, recent proteomic approaches have provided further information about a range of potential renal biomarkers.

Biomarkers of Kidney Injury in DN

Albuminuria

Proteinuria is a hallmark of DN, and its presence is a strong prognostic indicator of the likelihood of kidney disease progression. It primarily reflects glomerular injury and increased glomerular permeability to macromolecules, including in particular a low-molecular-weight protein, albumin (65 kDa).[4] The glomerular portion of the nephron participates in filtration of albumin followed by tubular reabsorption. Alteration in structure and function of these 2 compartments results in excretion of excessive albumin into the urine and is considered to represent an early clinical manifestation of DN.[10] The severity and progression of DN is categorized into at least 3 stages by the rate of urinary albumin excretion: microalbuminuria (30-300 mg/day), macroalbuminuria (300 mg to 3 g/day), and nephrotic-range albuminuria (>3 g/day). Another approach is to classify the degree of albuminuria by calculating the urine albumin-to-creatinine ratio (ACR). This ratio is unaffected by variations in urine concentration and avoids the requirement for timed specimens.[11] Microalbuminuria has been considered to be a predictor of the progression of kidney disease in type 1 and type 2 diabetic patients.[12,13] Furthermore, the measurement of urinary albumin levels in diabetic patients provides an important prognostic indicator of cardiovascular outcomes.[14] However, not all patients with proteinuria will undergo progressive kidney dysfunction, and not all diabetic patients with progressive kidney impairment will develop proteinuria. Therefore, it has been argued that the assessment of microalbuminuria/proteinuria has limitations with respect to its specificity for DN and prognostic value for kidney outcomes.[15] Indeed, it is likely that some normoalbuminuric subjects will have a significant decline in GFR, and as yet we do not have appropriate biomarkers in the urine of such subjects to predict subsequent decline in GFR.[16]

CLINICAL SUMMARY

- Albuminuria is a key feature of DN and is considered an early marker of predicting the onset and progression of DN.
- A range of potential biomarkers have been identified but to date, albuminuria remains the gold-standard for diagnosing and categorizing DN.
- Proteomics-based approaches may lead to identification of new biomarkers for prognosis and prediction of treatment response in patients with DN.

Transferrin

Transferrin is a glycoprotein with a molecular weight of 76.5 kDa, which is slightly greater than that of albumin. However, it is more readily filtered through the glomerular barrier than albumin because it is less anionic.[10] Therefore, urinary transferrin has been considered to be a more sensitive early marker for glomerular damage, with transferrinuria occurring before the onset of microalbuminuria in diabetic patients. Indeed, microtransferrinuria has been shown in some type 2 diabetic patients with diffuse glomerular lesions in the context of normoalbuminuria.[17] Furthermore, many of the early studies in DN involved the use of transferrin rather than albumin in assessing the progression of DN.[18,19] A direct correlation between the urinary excretion of transferrin and other kidney biomarkers, such as albumin, α1-microglobulin, or *N*-acetyl-β-D-glucosaminidase (NAG), has been observed in type 2 diabetic patients.[15,17] Transferrinuria also correlated with the degree of interstitial fibrosis, tubular atrophy, and interstitial inflammatory cell infiltration in patients with DN.[17] These findings indicate that urinary transferrin may be useful in detecting DN at an early stage even before the onset of microalbuminuria. However, urinary transferrin excretion is also elevated in primary glomerulonephritis and other kidney diseases, and it is not specific for DN.[20] The identification of albumin as another protein marker in urine that could be used to monitor kidney disease progression led most researchers to choose albumin rather than transferrin as a preferred marker of proteinuria.

Markers of Glomerular Injury

Adiponectin

Adiponectin is a 30-kDa adipocyte-derived vasoactive peptide hormone. High concentrations of adiponectin have been reported in the urine and serum samples of patients with diabetic kidney disease.[21,22] It has been suggested that adiponectin levels in urine are as reliable as the albumin excretion rate in predicting the progression from macroalbuminuria to ESRD in type 1 diabetic patients.[21] A recent study in type 2 diabetic patients with microalbuminuria has suggested that quantification of urinary adiponectin excretion appeared to be an independent indicator of vascular damage potentially

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