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Proteinuria in diabetic kidney disease: A mechanistic viewpoint

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Proteinuria is the hallmark of diabetic kidney disease (DKD) and is an independent risk factor for both renal disease progression, and cardiovascular disease. Although the characteristic pathological changes in DKD include thickening of the glomerular basement membrane and mesangial expansion, these changes *per se* do not readily explain how patients develop proteinuria. Recent advances in podocyte and glomerular endothelial cell biology have shifted our focus to also include these cells of the glomerular filtration barrier in the development of proteinuria in DKD. This review describes the pathophysiological mechanisms at a cellular level which explain why patients with DKD develop proteinuria.

Kidney International (2008) **74,** 22–36; doi:10.1038/ki.2008.128; published online 16 April 2008

KEYWORDS: podocyte; mesangial cell; glomerular endothelial cell; diabetic nephropathy; albuminuria; proteinuria

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Received 9 July 2007; revised 6 December 2007; accepted 22 January 2008; published online 16 April 2008

Diabetic kidney disease (DKD) is the leading cause of chronic and end-stage kidney disease, and is epidemic worldwide. The clinical signature of DKD is proteinuria, which is a marker of disease severity and is used clinically to guide our therapies. It is also an independent risk factor for cardiovascular disease.[1,2] Proteinuria is considered to play a central role in the pathogenesis of progressive renal dysfunction. Mechanisms may include enhanced tubular cell uptake of protein leading to complement activation and tubulointerstitial inflammation and increased filtration of pro-oxidant heme proteins, fibrogenic growth factors, and inflammatory cytokines (reviewed in Abbate *et al.*).[3] However, it should be recognized that progressive renal impairment has recently been described in patients with diabetes in the absence of proteinuria, despite having the classic histological features of DKD.[4] Additionally, studies have detected a linear decline in renal function prior to the development of overt proteinuria, questioning whether the loss of glomerular filtration rate (GFR) is etiologically linked to proteinuria or whether the two may occur in parallel.[5]

There has been an exciting increase in our understanding of the mechanisms underlying proteinuria at a molecular and cellular level. Although the exact chronological sequence of events leading to the functional and histological characteristics of DKD is not well defined, our review is based on a model in which proteinuria is a double-edged sword: it serves as a clinical indicator/marker of injury to the kidney, yet also plays an integral role in the pathogenesis of DKD (see Figure 1). In this review, we will not discuss the clinical significance of proteinuria, the risk factors leading to DKD, nor the treatment of proteinuria and disease progression, as these have been keenly discussed in excellent reviews elsewhere.[3,6,7] For the most part, we will also not discuss the pathobiology leading to the individual cellular changes, which are highlighted in Table 1 and reviewed elsewhere.[8,9] The intent of this review is to rather focus comprehensively on the underlying mechanisms of proteinuria in DKD and to highlight the major advances in this area.

Proteinuria and albuminuria, not microalbuminuria

Although approximately 20% (180 l) of renal plasma flow is filtered at the glomerulus daily, only small amounts of protein are detected in normal urine (40–80 mg day^{-1}). Transient increases in proteinuria may occur with fever,

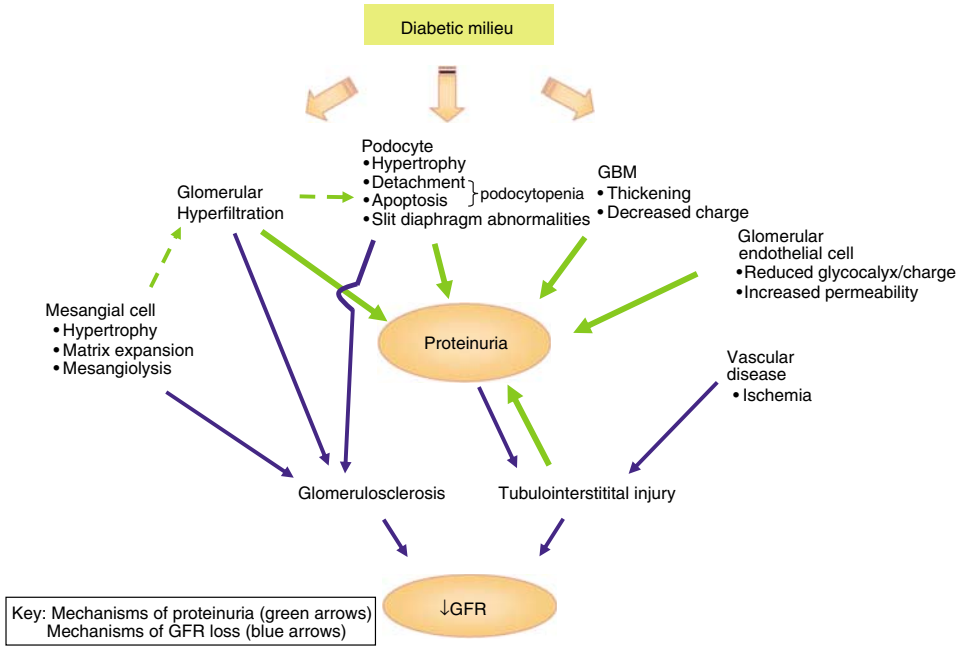

Figure 1 | Proposed schema unifying the mechanisms of proteinuria and decrease in GFR in DKD. This schema summarizes events leading to albuminuria/proteinuria (represented by the green arrows) and reduced GFR (represented by the purple arrows) in patients with DKD. The diabetic milieu has effects on all cell types within the kidney (represented by the thick arrows) and these contribute either primarily or secondarily to the development of albuminuria/proteinuria and reduced GFR. At the level of the glomerulus, both hemodynamic effects and injury to the individual components of the glomerular filtration barrier (podocyte, GBM, and glomerular endothelial cell) primarily lead to proteinuria (green arrows). In addition, tubulointerstitial injury may diminish tubular protein reuptake. Mesangial cell injury likely contributes secondarily to proteinuria by (i) mesangial expansion causing a loss of glomerular filtration surface area leading to glomerular hyperfiltration (dashed green arrows) or (ii) by mesangiolysis leading to structural changes in the capillary loops. Proteinuria itself may result in a decrease in GFR by causing tubulointerstitial injury.

Table 1 | Mechanisms of proteinuria in DKD

Site of injury	Effect	Underlying mechanisms
Glomerular hemodynamics	Glomerular hyperfiltration	Afferent arteriole vasodilatation
		Efferent arteriole vasoconstriction
		↑glomerular capillary pressure
Glomerular endothelial cell	Endothelial cell injury	Hyperglycemia, AGE, ROS
	Diminished endothelial glycocalyx	Endothelial cell injury or enzymatic cleavage
	Altered VEGF signaling	Podocyte injury or loss
GBM	Irregular thickening	↓production and/or ↑degradation of extracellular matrix proteins
	Decreased negative charge	↓ production and/or ↑ degradation of HSPG
Podocyte	Podocytopenia	Detachment
		Apoptosis
		Lack of proliferation
	Loss of slit diaphragm integrity	Decrease or changes in subcellular localization of nephrin
	Foot process widening and effacement	Disrupted actin cytoskeleton
		Loss of slit diaphragm integrity
		Impaired podocyte GBM interaction
	Loss negative charge	↓Podocalyxin
Proximal tubule	Decreased protein reabsorption	Tubular injury and interstitial fibrosis

AGE, advanced glycosylation end products; DKD, diabetic kidney disease; GBM, glomerular basement membrane; HSPG, heparan sulfate proteoglycan; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

marked exercise or exacerbations of congestive heart failure, or hypertension. Urine protein typically comprises albumin (30–40%), Tamm–Horsfall protein (50%), immunoglobulins (5–10%), and light chains (5%). Any protein filtered at the glomerulus is typically taken up by, and degraded in, proximal tubular cells, then reabsorbed into peritubular capillaries. However, peptide fragments are present in human urine (2–3 g day^{-1}), that are not detected by standard protein assays.[10,11] Patterns of urine protein fragmentation have been investigated and may correlate with specific glomerular diseases.[12]

The term 'microalbuminuria' is widely used to denote low-grade albuminuria (30–300 mg day^{-1}) and identifies those at risk of DKD, and those at risk of cardiovascular