Endothelial Factors and Diabetic Nephropathy

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The rising incidence and prevalence of chronic kidney disease (CKD) (glomerular filtration rate <60 mL/min per 1.73 m²) is a major public health concern (U.S. Renal Data System 2010, http://www.usrds.org). Hypertension is the second leading cause of end-stage renal disease (ESRD) in the U.S. and is also a major contributor to diabetic renal disease, which is the leading cause of CKD and ESRD (U.S. Renal Data System 2010). The diabetes-related ESRD annual incidence rate has been decreasing since 1996, suggesting that the net increase in diabetes-related ESRD may be secondary to the documented pandemic of type 2 diabetes (1,2).

In the general population, CKD predicts death and cardiovascular disease (CVD) events, independently of traditional cardiovascular risk factors such as age, sex, prior CVD, diabetes, hypertension, dyslipidemia, and proteinuria (3). CKD in patients with type 2 diabetes is independently associated with an ∼8–10% annual absolute risk for death and CVD (4). The majority of patients with CKD will die of a CVD event before they reach end-stage renal failure and dialysis treatment (5), and an estimated glomerular filtration rate <60 mL/min is now classified as a major independent risk factor for CVD.

Endothelial dysfunction has been implicated as a potential major mechanism for renal chronic microvascular complications both in diabetic and nondiabetic patients with albuminuria. There is a general assumption of a final common biological pathway that results in diabetic kidney disease and renal failure. As shown in Fig. 1, hyperglycemia and hypertension interact at the glomerulus, resulting in glomerular hypertension and, as a consequence, proteinuria, glomerular and interstitial tissue fibrosis (6), progressive decline in glomerular filtration rate, and finally renal failure.

In recent years, it has been suggested that drugs that interfere with the renin angiotensin system and ameliorate metabolic control can prevent this inevitable progression toward renal failure. However, the reality of everyday clinical experience suggests that, despite intensive multifactorial therapeutic approaches, which are essential and proven to reduce/limit progression of cardio renal disease in patients with diabetes and CKD, we still fail to prevent/delay the progression toward ESRF and CVD in a significant proportion of these subjects (7). Therefore, novel intervention strategies are required to address this unmet need in patients with diabetic and CKD.

In this review, we will focus on the link between endothelial dysfunction and diabetic nephropathy. We will discuss the biology of endothelial/vascular mediators in diabetic glomerulopathy and will attempt to translate this knowledge (in some cases still largely experimental) back to diabetic patients with CKD, debating whether these “new vascular pathways” could emerge as potential therapeutic targets for the management of diabetic kidney disease in the future.

VASCULAR DYSFUNCTION IN DIABETIC NEPHROPATHY: IS THE ENDOTHELIUM THE CULPRIT?—An early sign of diabetic nephropathy is an increased quantity of urinary protein, manifested by “albuminuria,” which correlates with, and can predict, the progression of renal damage (8). It is established that albuminuria derives primarily from defects in the glomerular filtration barrier (9). This long-established view has been recently challenged by other hypotheses (e.g., reduced tubular reuptake of albumin); however, these have been heavily disputed (10).

The mammalian glomerulus consists of a core of “pericyte-like” mesangial cells that support capillary loops. Endothelial cells are separated from specialized epithelia called podocytes by the glomerular basement membrane (GBM) (11). Each podocyte has foot processes that attach to the GBM, and its neighboring processes are separated by specialized tight junctions called slit diaphragms. These tight junctions are formed by complexes of proteins (including nephrin, a key protein involved in the regulation of the glomerular filtration barrier), that are themselves tethered to the cytoskeleton (11). Foot processes with the slit diaphragm represent an important size-selective barrier to loss of proteins into the urine, and the GBM itself, negatively charged, confers an additional barrier by repelling anionic molecules such as albumin. The glomerular endothelium also contributes to the glomerular filtration barrier with its glycocalyx and charge-selective properties (9).

Animal and human studies have demonstrated that diabetes leads to ultrastructural alterations in the glomerular filtration barrier, including podocyte foot process fusion and detachment, GBM thickening, glomerulosclerosis (6), and loss of endothelial glycocalyx, as seen in diabetic patients with microalbuminuria (12).

These structural changes correlate with increasing albuminuria, an early feature of diabetic kidney disease, and strategies to reduce albuminuria are considered to be potential renoprotective treatments in diabetes (13).

In diabetes, endothelial dysfunction parallels microalbuminuria and, as suggested...
Figure 1—Principal mechanisms of diabetic glomerulopathy. Hyperglycemia and hypertension interact at the glomerulus, resulting in glomerular hypertension, progressive glomerular and interstitial tissue fibrosis, and decline in renal function. ACEi, ACE inhibitor.

by the Steno hypothesis, this may suggest a common pathogenetic mechanism for renal and extrarenal chronic vascular diabetes complications (14,15).

Markers of endothelial dysfunction such as soluble vascular cell adhesion molecule, von Willebrand factor, and microvascular reactivity can be observed in type 2 diabetic patients before the onset of albuminuria, suggesting that the pathogenetic process of vascular disease could play a role in the development of nephropathy and other microvascular complications in diabetes (16).

Impairment in number and function of endothelial progenitor cells, involved in neovasculogenesis, endothelium repair, and maintenance of vascular homeostasis, has been proposed as a pathogenic mechanism for vascular disease in diabetes, highlighting the important link between endothelial dysfunction and diabetic nephropathy (17).

Studies conducted in unselected groups of patients with diabetes have described a reduction in endothelial progenitor cell number and function in diabetic patients when compared with nondiabetic subjects (18). More recent studies, within populations of type 1 or type 2 diabetic patients, have demonstrated a reduced number and impaired function of circulating vascular progenitor cells in patients with microalbuminuria (19,20). Specifically, in diabetic patients, the biological activity of circulating vascular progenitor cells may be a mean by which some individuals respond to diabetes-mediated increased vascular damage and improve their long-term vascular health, whereas others, unable to adapt and/or respond to insults, are at higher risk for renal and vascular disease.

**ENDOTHELIAL FACTORS IN DIABETIC GLOMERULOPATHY**

It is well established that, in diabetes, metabolic and hemodynamic perturbations (and their interaction) activate various intracellular pathways such as the polyol and hexosamine pathway, increase production of advanced glycation end products, protein kinase C and p38 mitogen-activated protein kinase, and promote an increase in oxidative stress (21). These pathways have been linked to the dysregulation of different vascular/endothelial growth factors that have been implicated in the pathogenesis of diabetic glomerulopathy (22).

As the hemodynamic and metabolic treatments currently available in routine clinical practice are insufficient to completely prevent progression of diabetic renal disease, novel endothelial/vascular mediators of renal disease (Fig. 2) may play important roles in the future as potential therapeutic targets for diabetic kidney disease.

**VASCULAR/ENDOTHELIAL FACTORS IN DIABETIC GLOMERULOPATHY**

Vascular endothelial growth factor A

Vascular endothelial growth factor A (VEGF-A) is implicated in vascular development, maintenance, and remodeling, via its receptors VEGFR-1 and VEGFR-2. The VEGF-A family is very complex, with several isoforms derived from alternative splicing (23).

VEGF-A is constitutively expressed in the glomeruli podocytes in normal physiology, and autocrine/paracrine VEGF-A signaling occurs between podocytes and adjacent endothelial and mesangial cells, which express the VEGF receptors (VEGFR1, VEGFR2) (24).

In diabetes, the early stages of diabetic glomerulopathy with development of proteinuria are paralleled by an upregulation of VEGF-A in the podocytes and mesangial cells (24). The rise in glomerular VEGF-A expression, paralleled by an increase in urinary VEGF-A, as seen in type 2 diabetic patients (25), has been linked, in humans, with an increase in glomerular endothelial cell number (26) and new vessel formation (27). Inhibition of VEGF-A in an experimental animal model of diabetes in the early stage of diabetic glomerulopathy results in amelioration of proteinuria and reduction in glomerular sclerosis (28,29).

Of importance is the concept that constitutive expression of VEGF-A in the podocytes is key for the normal function of the glomeruli: when VEGF-A is inhibited (with genetic ablation) in podocytes of adult mice, animals develop glomerular thrombotic microangiopathy, mimicking the clinical presentation seen in patients receiving VEGF inhibitors, such as bevacizumab, for the treatment of neoplastic diseases (30). A similar presentation is seen in humans in preeclampsia, where elevated circulating levels of soluble VEGF receptor 1, a specific VEGF inhibitor, is associated with proteinuria and glomerular injury (28,31).

Therefore, the balance of VEGF-A expression is extremely important and, at least in the glomerular vasculature, it appears that a tight system is in place to compensate for any changes in VEGF-A expression/activity (28) and avoid any morphofunctional alteration of the glomerular filtration barrier.
The beneficial effects of VEGF-A inhibition in the early phases of diabetic glomerulopathy reside not only in reduction in permeability of the glomerular filtration barrier, but in amelioration of GBM thickening, and of mesangial extracellular matrix volume (28). VEGF-A has been shown to induce transforming growth factor-β, a prosclerotic cytokine, in mouse podocytes in vitro, and to directly act as a stimulus for extracellular matrix production and accumulation (28).

The preservation of vascular integrity seems to result from a fine balance in the regulation of VEGF-A expression/activity in a way that too little (inhibition of VEGF-A with bevacizumab, preeclampsia) or too much (diabetic glomerulopathy) of this cytokine would result in glomerular capillary pathology and increase vascular permeability.

The interaction between VEGF-A, diabetic glomerulopathy, and endothelial dysfunction has been related to the tissue availability of nitric oxide (NO) (32). In normal physiology, NO derives from VEGF-A–mediated endothelial nitric oxide synthase (eNOS) activation and, with VEGF-A, represents an important trophic factor for endothelial cells; specifically, VEGF-A and NO participate in the maintenance of vascular homeostasis, vascular tone, vascular smooth muscle cell proliferation, and leukocyte/platelet adhesion to endothelium. In diabetes, reduction in NO availability can occur via different cellular mechanisms (impaired eNOS activation, eNOS uncoupling, etc.) and has been implicated in the pathogenesis of microvascular complications both in experimental animal models of diabetes and in diabetic patients (32). NO availability regulates the role of VEGF-A on the vasculature: beneficial when NO is present and deleterious in conditions of reduced NO availability. Any treatment aimed at restoring the VEGF-A/NO balance would likely be beneficial in the pathogenesis of diabetic kidney disease, but more studies in both animals and humans are required to confirm this.

The biology of VEGF includes a group of newly identified isoforms with a unique COOH-terminal sequence (VEGFA_{xxxb}) that retains antiangiogenic and antipermeability properties (23). VEGFA_{xxxb} appears to act as an endogenous inhibitor of VEGF-A; therefore, future intervention could be directed at VEGFA_{xxxb}, an emerging important endothelial factor that may be a potential new therapeutic target, as shown in experimental animal model of diabetes (33).

**ANGIPOIETINS**—Evidence from our group and others have identified the angiopoietins (Angs) as playing an important role in the regulation of the glomerular filtration barrier (34–36), and their specific modulation could offer a future strategy for the treatment of albuminuria in addition to current therapeutic approaches.

Angs are vascular growth factors involved in angiogenesis and vasculogenesis. Two isoforms have been described: Ang-1 and Ang-2, both ligands for the
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Tie-2 receptor, found primarily on endothelial cells and podocytes (35,37). The role of Ang-1, the major physiological ligand for Tie-2, includes promotion of endothelial survival, stabilization of supporting perivascular cells, and inhibition of endothelial permeability. Ang-2 is considered to be a natural antagonist of Ang-1 by virtue of its ability to competitively inhibit binding of Ang-1 to Tie-2, hence reducing Tie-2 activation and signaling. Importantly, the in vivo biological effects of the Angs depend on ambient levels of VEGF-A; for example, with respect to the actions of Ang-2, vessel regression occurs when VEGF-A is lacking, whereas vessel destabilization is followed by endothelial cell proliferation and angiogenesis when the local milieu is rich in VEGF-A (38). In addition, VEGF-A has been shown to induce Ang-2 (39) and modulate Ang–Tie-2 signaling by inducing proteolytic cleavage and shedding of the Tie-2 receptor (40). Ang-1, in turn, has been shown to inhibit VEGF-A–induced propermeability biological effects (41) and has been implicated in thickening of the endothelial glyocalyx layer (34).

In the normal adult glomerulus, Ang-1 is constitutively expressed in podocytes, whereas Ang-2 levels are low or undetectable (37). Ang expression in the glomerulus is deregulated (often with Ang-2 > Ang-1) in conditions associated with albuminuria such as diabetic glomerulopathy and other glomerular diseases (35). Therefore, chronic changes in the balance of Ang-1/Ang-2 expression might play an important role in the pathobiology of glomerular diseases associated with damaged capillaries and altered permeability. Specifically, a mouse model with inducible podocyte-specific Ang-2 expression resulted in albuminuria and glomerular endothelial apoptosis (36).

Experimental models of type 1 diabetes are associated with altered renal expression of Angs, where Ang-2, normally not expressed in the normal glomeruli, is upregulated mainly at the glomerular level in glomerular endothelia and podocytes (42).

Individuals with type 2 diabetes have elevated circulating Ang-2 levels (43). High glucose stimulates Ang-2 expression in mesangial and microvascular endothelial cells in vitro, providing one explanation for Ang-2 upregulation in diabetic nephropathy (35). Collectively, these observations are consistent with the contention that a decreased ratio of Ang-1/Ang-2 might play a role in the pathobiology of glomerular disease in diabetic nephropathy.

It is not yet known whether the observed upregulation of Ang-2 in the context of glomerular diseases (e.g., diabetic glomerulopathy) represents a protective antipermeable mechanism or is per se a promoter of permeability as shown previously. Recent work has suggested that Ang-2 could act as a stimulus for Tie-2 signaling and has been proposed to function as an antipermeability factor in “stressed” conditions (35). Ongoing studies will answer some of these questions and will evaluate the potential for the Angs system as a new target for treatment in diabetic glomerulopathy.

**ADIPONECTIN**—Adiponectin, an adipokine expressed and secreted by adipocytes, is a known insulin sensitizer. Reduced adiponectin levels in parallel with a prodiabeticogenic environment (e.g., lack of exercise, obesity) play an important role in the pathophysiology of insulin resistance. Adiponectin binds to its receptor, expressed in both insulin-dependent tissues (skeletal muscle, adipose, liver) and insulin-independent tissues such as endothelial cells and podocytes (44). In view of these effects of adiponectin, an adipose vascular loop was proposed. Interestingly, reduced adiponectin levels have been linked to endothelial dysfunction in humans (45), and adiponectin was shown, in animals, to improve endothelial dysfunction (46). Further, albuminuria was associated with low adiponectin levels in hypertensive and obese patients (47). Adiponectin knockout mice are characterized by albuminuria and podocyte foot process effacement, and treatment with adiponectin normalizes albuminuria and podocyte abnormalities (47).

Further studies are needed to definitively link adiponectin, endothelial dysfunction, and albuminuria in view of conflicting observations (48); however, the existing link between insulin resistance (low adiponectin) and albuminuria (49) makes adiponectin a promising potential future target for the treatment of chronic vascular complications in diabetes.

**ANTIANGIOGENIC MOLECULES (ENDOSTATIN, TUMSTATIN, AND ANGIOSTATIN)**—Endostatin and tumstatin are naturally occurring peptides derived by degradation of type XVIII and IV collagen, respectively. Angiostatin is a cleavage product of plasminogen. All of these factors retain anti-angiogenic properties, interfere with VEGFR2 activation, and have been shown to ameliorate albuminuria and glomerulosclerosis in an experimental animal model of diabetes (50). Interestingly, treatment with endostatin and tumstatin is paralleled by a reduction in diabetes-induced VEGF-A and Ang-2 expression (50), an effect independent of blood pressure and metabolic control. All of these agents could be considered as potential treatments for the early phases of diabetic glomerulopathy, but further work is required in humans to establish their possible role in disease states.

**THE RENIN ANGIOTENSIN SYSTEM, STATINS, AND PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-γ AGONISTS**—Given the importance of hypertension in renal disease, it is not surprising that anti-hypertensive therapy has demonstrated benefits in the prevention and progression of diabetic renal disease, and the effectiveness of tight blood pressure control for reducing the risk of microalbuminuria in patients with type 1 or type 2 diabetes is established (51,52). In diabetes, ACE inhibitors and angiotensin II receptor blockers (ARBs) have demonstrated renoprotection in diabetic patients with and without hypertension. Hence, ACE inhibitors and ARBs are recommended as first-line antihypertensive therapies for patients with diabetes (53). The renoprotective effects of ACE inhibitors and ARBs, which include reduction of albuminuria and improvements in glomerular histology, are paralleled by amelioration of endothelial dysfunction (54), and these changes appear to be at least in part independent of their blood pressure-lowering effects (55).

Whether statins and tight lipid control are similarly beneficial in preventing or delaying diabetic renal disease needs to be confirmed (56), but there is good evidence for the beneficial effects of these agents on reducing endothelial dysfunction (57).

Peroxisome proliferator–activated receptor-γ agonists have also been shown to ameliorate endothelial dysfunction and albuminuria in patients with type 2 diabetes (58,59), but these potential benefits should be carefully assessed against the safety concerns related to the class
effect of these agents on fluid retention and congestive heart failure as well as the possible enhanced cardiovascular risk (60).

CONCLUSIONS—The dysregulation of vascular factors in diabetic glomerulopathy is now much better understood, and we are starting to comprehend the mechanisms downstream of the primary metabolic and hemodynamic insults responsible for the alteration in glomerular capillary permeability. However, before specific interventions can be implemented and used in a clinical setting, further in-depth understanding of the physiology and pathophysiology of the glomerular filtration barrier is needed both in animals and humans.

The challenges ahead in this field include the complexity and variety of interactions between different vascular growth factors in different settings (e.g., in normal physiology and disease states), which require the achievement of a fine therapeutic balance in growth factor(s) expression/action and tissue/organ specificity, to avoid nonspecific unwanted adverse responses.

Importantly, the inherent individual variability of response to specific treatment(s), or the different propensity toward the development/progression of renal disease observed in diabetic patients, suggests diverse involvement of various cellular pathways and highlights the need for an individualized clinical approach in the management of diabetic kidney disease.

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