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The Renal Vascular Response to Diabetes

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Abstract

Purpose of review—Diabetes mellitus is the primary cause of end stage renal disease, yet the mechanisms underlying diabetic nephropathy remain ill-defined. The widely accepted opinion holds that events occurring early during the course of diabetes engender the eventual decline in renal function. This review will summarize recent advances (published January 2008 through June 2009) regarding the renal vascular and glomerular functional changes that occur during the early stage of diabetes.

Recent findings—Reduced C-peptide levels and increased cyclooxygenase-2 activity both seem to promote diabetic hyperfiltration, presumably via effects on afferent arteriolar tone. In addition, exaggerated tonic influences of K^+ channels on afferent arteriolar function likely act in concert with impaired Ca^{2+} influx responses to changes in membrane potential to promote vasodilation. Mechanisms underlying these changes remain largely speculative. Diabetes may also alter autoregulation of renal blood flow and glomerular filtration rate, as well as provoke afferent arteriolar dilation secondary to alterations in proximal tubular reabsorption; however, conflicting evidence continues to flood the literature concerning these events.

Summary—New evidence has expanded our appreciation of the complexity of events that promote preglomerular vasodilation during the early stage of diabetes; however, it seems that the more we know, the less we understand.

Keywords

Afferent arteriole; diabetes mellitus; hyperfiltration

Introduction

Both hemodynamic and non-hemodynamic pathogenic pathways contribute to development of glomerulosclerosis in diabetes mellitus (DM). The hemodynamic mechanisms involve changes in arteriolar function that ultimately engender glomerular hyperfiltration early during the course of both type 1 diabetes (T1D) and type 2 diabetes (T2D). While there is some current debate regarding the precise extent to which early hyperfiltration *per se* represents a risk factor for development of diabetic nephropathy [1**,2*], an understanding of the mechanisms through which renal vascular function is impaired during the early stage of DM represents a key goal of research in the field.

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Potential humoral mechanisms of diabetic hyperfiltration

More than 25 years ago, micropuncture studies first provided evidence that DM exerts a complex influence on renal arteriolar resistance and glomerular dynamics. In rats with streptozotocin-induced T1D that were allowed to develop severe hyperglycemia (no insulin replacement), glomerular filtration rate (GFR) was lower than normal [3]. Increased afferent and efferent arteriolar resistance, with no changes in the glomerular ultrafiltration coefficient (K_f) or the hydrostatic pressure gradient across the glomerular capillary wall (ΔP), implicated decreased glomerular plasma flow as the main factor underlying reduced GFR in these severely hyperglycemic rats. If provided partial insulin replacement sufficient to maintain moderate hyperglycemia, the diabetic rats exhibited increased GFR that was evident at the whole kidney and single nephron levels. These animals exhibit reduced preglomerular vascular resistance, with no significant changes in efferent arteriolar resistance or K_f ; hence, the hyperfiltration in moderately hyperglycemic rats could be attributed to elevations in both glomerular plasma flow and ΔP . For reasons not yet fully evident, this precise hemodynamic scenario of diabetic hyperfiltration is not always observed [4], as some studies suggest that increased GFR during DM can arise with little or no change in renal plasma flow [5] or with normal ΔP values [6]. However, most reports indicate that hyperfiltration in DM occurs in concert with increased renal plasma flow and increased filtration fraction. These observations suggest that effects of DM on afferent arteriolar resistance represent a prominent vascular determinant of GFR in animals with moderate vs severe hyperglycemia. Indeed, data from our laboratory confirmed that afferent arteriolar lumen diameter is increased in diabetic rats with moderate hyperglycemia, but normal or decreased if the animals are allowed to develop severe hyperglycemia [7]. Differences in volume status could not explain the surprising disparity in glomerular dynamics unveiled by micropuncture study of moderately and severely hyperglycemic animals [3], as both groups of animals were found to have equivalent plasma volumes (relative to body weight) that were elevated compared with normal rats. Therefore, the preglomerular dilation associated with diabetic hyperfiltration has often been postulated to reflect to altered humoral influences on the vasculature. However, despite intensive investigation, no single vasoactive factor has been shown to fully account for diabetic hyperfiltration.

In the past decade, there has been growing acceptance of the assertion that nitric oxide (NO) drives hyperfiltration early during T1D and that subsequent glomerular damage arises at least in part as the result of progressively developing NO deficiency. However, reports suggesting that NO drives renal vasodilation and hyperfiltration during diabetes [8–10] are difficult to reconcile with studies revealing reduced renal NO bioavailability [11,12] resulting in a diminished impact of endogenous NO on the renal microvasculature even during the first few weeks of streptozotocin-induced T1D [13–16]. This controversial topic is beyond the scope of this short report and has been reviewed elsewhere several times over the past few years; however, interesting new insights have emerged recently regarding other humoral mechanisms that may contribute to altered renal hemodynamics during DM.

Accumulating evidence implicates a reduction in the proinsulin connecting peptide, C-peptide, in several complications of T1D. C-peptide is a 31-residue cleavage product of insulin synthesis, and is secreted from pancreatic β -cells together with insulin. Accordingly, impaired insulin release in type 1 diabetes is associated with similarly suppressed C-peptide release. Once thought to be biologically inert, C-peptide is now recognized to exert renoprotective effects in patients and animals with T1D [17]. C-peptide administration attenuates hyperfiltration, albuminuria and hypertrophy in DM, presumably through effects on the Na^+/K^+ -ATPase [18], but the precise mechanism has remained speculative. In fact, it might at first seem intuitive to suggest that the well-documented ability of C-peptide to stimulate Na^+/K^+ -ATPase activity in the thick ascending limb could alter glomerular function via a TGF-

dependent mechanism; however, such an effect of exogenous C-peptide would actually reduce solute delivery to the macula densa and exacerbate diabetic hyperfiltration. A recent study from Nordquist and colleagues [19*] revealed that C-peptide exerts a direct constrictor influence on isolated perfused afferent arterioles from mice with alloxan-induced T1D, while exerting minimal effect on afferent arterioles from non-diabetic mice. This observation not only raises the possibility that C-peptide administration might represent a useful therapeutic approach to minimize glomerular damage during T1D, but it also suggests that reduced endogenous C-peptide levels may contribute to the afferent arteriolar dilation associated with diabetic hyperfiltration. Moreover, as C-peptide is a vasodilator in most vascular beds [20], its vasoconstrictor impact on the afferent arteriole during T1D underscores the likelihood that novel mechanisms control afferent arteriolar function under these conditions.

New evidence is also expanding our appreciation of the role of arachidonic acid metabolites in the renal vascular dysfunction accompanying DM. Altered arachidonic acid metabolism has long been linked to diabetic hyperfiltration based on the effects of nonsteroidal anti-inflammatory drugs, but evidence suggesting specific involvement of cyclooxygenase (COX)-2 in these events has only emerged in recent years. Key observations by Komers et al [5] established that renal cortical COX-2 expression was increased in rats with streptozotocin-induced T1D and that COX-2 inhibition reversed hyperfiltration in the diabetic rats without altering GFR in normal rats. Subsequent studies have confirmed these observations and implicated peroxynitrite as a contributory stimulus for up-regulation of COX-2 in diabetes [21,22]. In the past few months, the effect of COX-2 inhibition on renal function has been examined in normotensive, normoalbuminuric adolescents and young adults with uncomplicated T1D. In individuals exhibiting hyperfiltration, COX-2 inhibition partially blunted the hyperfiltration, while patients with normal GFR exhibited an increase in GFR under these conditions [23]. These observations attest to the complexity of COX-2-dependent influences on glomerular function in patients with T1D. Interestingly, the renal hemodynamic response to COX-2 inhibition is sex-specific, such that the dependence on vasodilator prostaglandins in T1D is greater in women than in men [24*]. This observation is consistent with accumulating evidence that sex hormones may contribute to the pathogenesis of diabetic nephropathy [25] through renal vascular events that occur early during the course of DM.

Direct effects of diabetes on preglomerular microvascular function

Data from our laboratory support the contention that primary changes in preglomerular microvascular smooth muscle function may underlie afferent arteriolar dilation during the hyperfiltration state of DM. Pharmacological blockade of ATP-sensitive K^+ channels (K_{ATP} channels) contracts afferent arterioles from rats with streptozotocin-induced DM, while having minimal impact on afferent arterioles from normal rats [26]. This observation suggests that open K_{ATP} channels contribute to tonic afferent arteriolar dilation during DM. More recently, we utilized a similar pharmacological approach to survey the role of other K^+ channels in setting afferent arteriolar tone in normal and diabetic rat kidney [27*]. Our experiments revealed afferent arteriolar constrictor responses to blockade of voltage-gated K^+ channels (K_V), inward rectifier K^+ channels (K_{IR} ; likely Kir2.1) and large-conductance Ca^{2+} -activated K^+ channels (BK_{Ca}), indicating the tonic dilator influences of these channels on the normal afferent arteriole. Blockers of small-conductance Ca^{2+} -activated K^+ channels (SK_{Ca}) and renal outer medullary K^+ channels (ROMK; Kir1.1) had no discernible impact on afferent arteriolar tone in normal rat kidney. Streptozotocin-induced T1D altered the relative contributions of specific K^+ channels to afferent arteriolar tone, such that there was an increased tonic dilator impact of K_{IR} channels and the emergence of a tonic impact of ROMK channels. To our knowledge, this is the first evidence that ROMK channels (expressed in the thick ascending limb and distal nephron) also influence renal vascular function – a phenomenon that was evident in kidneys from diabetic rats regardless of solute delivery to the macula densa (i.e. both

before and after acute surgical papillectomy). Importantly, exposure to blockers of K_{ATP} , K_{IR} or ROMK channels reversed the afferent arteriolar dilation characteristic of this streptozotocin-induced model of T1D in the rat. This observation suggests that K^+ channel activation is critical for sustaining tonic afferent arteriolar dilation during the hyperfiltration stage of DM in the rat (3–4 wk after onset), although a possible role for this phenomenon in initiating the hyperfiltration has not been investigated. These K^+ channels likely contribute to afferent arteriolar dilation in DM by promoting vascular smooth muscle membrane hyperpolarization, thereby reducing Ca^{2+} influx through voltage-gated channels and, ultimately, decreasing intracellular $[Ca^{2+}]$. This situation is probably exacerbated by suppressed afferent arteriolar Ca^{2+} influx responsiveness to membrane potential in kidneys from diabetic rats [28].

The mechanisms underlying changes in K^+ and Ca^{2+} channel regulation of afferent arteriolar tone in DM remain speculative. Exposure of isolated afferent arterioles from diabetic rats to a normoglycemic environment restores intracellular $[Ca^{2+}]$ responses to depolarization within a few minutes [28], suggesting that the hyperglycemic milieu *per se* impairs voltage-gated Ca^{2+} channel function in preglomerular vascular smooth muscle during T1D. Preliminary evidence suggests that oxidative stress may play a role in the exaggerated tonic afferent arteriolar dilator impact of K^+ channels during T1D [29]. It is also easy to envision a scenario in which altered K^+ channel influences on afferent arteriolar tone represent the means through which a yet to be identified stimulus achieves preglomerular dilation during DM. Moreover, it is even possible that these changes in ion channel function arise in the preglomerular vasculature secondary to the hyperfiltration state, a scenario that would undoubtedly exacerbate the situation by allowing increased renal blood flow and transmission of systemic arterial pressure to the glomerular capillary network. Regardless of the underlying cause, impaired electromechanical coupling in afferent arteriolar smooth muscle should impair vasoactive responses to multiple humoral agents as well as the myogenic response, tubuloglomerular feedback (TGF) and, ultimately, autoregulation of renal blood flow and GFR. Indeed, diabetes has been alleged to have all of these effects on renal vascular function, although recent evidence does not necessarily support the previously widely-accepted dogma in this regard.

Effects of diabetes on renal autoregulation

Glomerular hyperfiltration and/or glomerular capillary hypertension are generally envisioned to play a role in the pathogenesis of diabetic glomerulosclerosis. These deleterious events should be exacerbated by even modest elevations in systemic arterial pressure that are transmitted to the glomerulus through the vasodilated preglomerular microvasculature. Even transient spontaneous reductions in systemic arterial pressure seem to impede glomerular damage in DM [30]. Indeed, the beneficial impact of lowering blood pressure as a means of reducing glomerular hemodynamic and structural changes in rodents during DM has led to the widespread clinical utilization of antihypertensive therapy as a means of slowing the progression of diabetic nephropathy. Situations characterized by systemic arterial pressure changes being transmitted to the glomerulus imply impairment of renal autoregulatory capability. DM impairs both components of renal autoregulation – the myogenic response [31,32] and the TGF response [33]. Thus, it is not surprising to find multiple reports suggesting that renal autoregulation is impaired in T1D [34–36,37*,38]. Recently, however, Lau et al [39**] utilized both steady-state pressure ramps and assessment of renal blood flow dynamics in a meticulous investigation of renal autoregulation in rats with streptozotocin-induced T1D. Surprisingly, these studies revealed that rats with T1D have significantly augmented renal blood flow autoregulatory capability at low perfusion pressures, compared with non-diabetic rats, confirming two previous reports [40,41] that have heretofore largely been ignored by most investigators. Some [42**,43], but not all [35], studies have detected normal renal autoregulatory capability in T2D. Thus, there currently exists no consensus regarding the

autoregulatory capability of the renal microvasculature during the early stage of DM. The complexity of the situation may reflect, at least in part, the gradual impairment of GFR autoregulation with increasing duration of T1D in both rodents and humans [38,44]. Differences in the pathogenic processes arising in various rodent models, as well as the salt-sensitivity of mechanisms controlling blood pressure and renal vascular function, may also contribute to the confounding array of data regarding the impact of DM on renal autoregulatory function.

The tubulo-centric hypothesis of diabetic hyperfiltration

In recent years, an intriguing “tubulo-centric” hypothesis of diabetic hyperfiltration has emerged [45,46]. This scenario has a strong basis in our understanding of normal renal function and control theory, and positions a primary change in proximal tubular reabsorption as the trigger of a sequence of events that ultimately alter glomerular function: high glucose levels in the glomerular ultrafiltrate stimulate Na^+ -glucose transport by the proximal tubule, thereby reducing solute delivery to the macula densa and provoking a TGF-dependent afferent arteriolar dilation and increased GFR (which tends to restore solute delivery to the distal nephron). Although a number of experimental observations from rodent models of T1D (and, more recently, T2D [47]) are consistent with this postulate, cause and effect have been difficult to establish. Adenosine-1A receptor knock-out mice ($\text{A1AR}^{-/-}$ mice, which lack a functioning TGF mechanism) have recently been exploited as a tool for evaluating the validity of the tubulocentric hypothesis. If hyperfiltration arises by TGF-dependent afferent arteriolar dilation secondary to changes in proximal tubule reabsorption, diabetic hyperfiltration should not arise in these animals lacking a functional TGF mechanism. However, Sällström and coworkers [48] found that alloxan-treated $\text{A1AR}^{-/-}$ develop hyperfiltration, with GFR values similar to those found in wild-type mice with alloxan-induced T1D. These observations seem to refute the contention that TGF plays a major role in the development of diabetic hyperfiltration. Faulhaber-Walter and colleagues [49*] used a genetic model of T1D in their studies comparing wild-type mice, Akita mice that develop T1D due to a mutated insulin 2 gene ($\text{Ins2}^{+/+}$), and Akita mice with A1AR deficiency ($\text{Ins2}^{+/+}/\text{A1AR}^{-/-}$). Their data confirmed hyperfiltration in Akita mice, compared with wild-type (non-diabetic) mice. Moreover, diabetic hyperfiltration was not absent, but in fact was augmented, in Akita mice lacking A1AR . These investigators also documented reduced TGF responsiveness in the Akita mice and confirmed that the double-mutant mice lack TGF-dependent control of stop flow pressure or early proximal flow rate (indices of glomerular hydrostatic pressure and single-nephron GFR, respectively). The inevitable conclusion drawn from these studies is that TGF is not required for development of diabetic hyperfiltration and, moreover, that TGF might actually limit the degree of diabetic hyperfiltration in some models of T1D. In contrast, Vallon and coworkers [50*] found no evidence of hyperfiltration in $\text{A1AR}^{-/-}$ mice with streptozotocin-induced diabetes, an observation consistent with the tubulo-centric hypothesis. These investigators argue that the diabetes model and severity of hyperglycemia may be essential determinants of the role of A1AR s and TGF in the regulation of glomerular filtration during T1D. The conflicting evidence regarding the impact of diabetes on glomerular function in $\text{A1AR}^{-/-}$ mice lacking TGF may also reflect the potentially confounding influence of $\text{A1AR}^{-/-}$ on a variety of other renal processes (proximal reabsorption, renin release, etc). Thus, despite the initial anticipation that studies employing $\text{A1AR}^{-/-}$ mice lacking TGF would prove enlightening with regard to the tubulocentric theory of diabetic hyperfiltration, the validity of this hypothesis remains uncertain and represents an important issue demanding extensive further investigation.

Conclusion

Despite ongoing investigations aimed at delineating the mechanisms underlying preglomerular vasodilation and the resulting glomerular hyperfiltration during DM, no consensus has been

reached. Diabetic hyperglycemia probably exerts an array of direct and indirect influences on the preglomerular microvasculature. Intrinsic, intrarenal processes such as the myogenic and TGF responses, alterations in regulation of membrane potential and Ca^{2+} signaling events in preglomerular vascular smooth muscle, and interactions between tubular transport and vascular function undoubtedly all exert interactive influences on the renal vasculature under these conditions. These events are probably modulated by generation of pro-inflammatory compounds and cytokines, although little is known about the renal vascular influence of these substances during the early stage of DM. Clearly, the field is ripe for continued focused investigation that attempts to overlook accepted dogma in order to unveil the complex sequelae through which DM impairs renal vascular function to engender hyperfiltration and, ultimately, diabetic nephropathy.

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References and recommended reading

- **1. Levine DZ. Can rodent models of diabetic kidney disease clarify the significance of early hyperfiltration?: recognizing clinical and experimental uncertainties. *Clin Sci* 2008;114:109–118. [PubMed: 18062776] This review presents a carefully considered evaluation of the significance of hyperfiltration as a risk factor for development of DN, a brief summary of which rodent models display hyperfiltration and structural lesions of DN, and an evaluation of the potential role of NO in diabetic hyperfiltration.
- *2. Magee GM, Bilous RW, Cardwell CR, et al. Is hyperfiltration associated with the future risk of developing diabetic nephropathy? A meta-analysis. *Diabetologia* 2009;52:691–697. [PubMed: 19198800] This is the first study combining estimates from previous smaller observational studies (thereby having increased power to detect significant differences) regarding the risk of diabetic nephropathy progression in the presence of hyperfiltration. The meta-analysis of 10 cohort studies following 780 patients reveals that T1D patients with hyperfiltration are 2.7 times more likely to progress to incipient nephropathy than those with normal GFR.
3. Hostetter TH, Troy JL, Brenner BM. Glomerular hemodynamics in experimental diabetes mellitus. *Kidney Int* 1981;19:410–415. [PubMed: 7241881]
4. O'Donnell MP, Kasiske BL, Keane WF. Glomerular hemodynamic and structural alterations in experimental diabetes mellitus. *FASEB J* 1988;2:2339–2347. [PubMed: 3282959]
5. Komers R, Lindsley JN, Oyama TT, et al. Immunohistochemical and functional correlations of renal cyclooxygenase-2 in experimental diabetes. *J Clin Invest* 2001;107:889–898. [PubMed: 11285308]
6. Michels LD, Davidman M, Keane WF. Determinants of glomerular filtration and plasma flow in experimental diabetic rats. *J Lab Clin Med* 1981;98:869–885. [PubMed: 7031154]
7. Carmines PK, Bast JP, Ishii N. Altered renal microvascular function in early diabetes. In: Cortes P, Mogensen CE, editors. *The Diabetic Kidney*. Humana Press; Totowa, NJ: 2006. p. 23–36.
8. Bell TD, DiBona GF, Biemiller R, et al. Continuously measured renal blood flow does not increase in diabetes if nitric oxide synthesis is blocked. *Am J Physiol Renal Physiol* 2008;295:F1449–F1456. [PubMed: 18753304]
9. Veelken R, Hilgers KF, Hartner A, et al. Nitric oxide synthase isoforms and glomerular hyperfiltration in early diabetic nephropathy. *J Am Soc Nephrol* 2000;11:71–79. [PubMed: 10616842]
10. Komers R, Allen TJ, Cooper ME. Role of endothelium-derived nitric oxide in the pathogenesis of the renal hemodynamic changes of experimental diabetes. *Diabetes* 1994;43:1190–1197. [PubMed: 7926287]
11. Palm F, Buerk DG, Carlsson PO, et al. Reduced nitric oxide concentration in the renal cortex of streptozotocin-induced diabetic rats: Effects on renal oxygenation and microcirculation. *Diabetes* 2005;54:3282–3287. [PubMed: 16249456]

12. Satoh M, Fujimoto S, Arakawa S, et al. Angiotensin II type 1 receptor blocker ameliorates uncoupled endothelial nitric oxide synthase in rats with experimental diabetic nephropathy. *Nephrol Dial Transplant* 2008;23:3806–3813. [PubMed: 18596126]
13. Ohishi K, Carmines PK. Superoxide dismutase restores the influence of nitric oxide on renal arterioles in diabetes mellitus. *J Am Soc Nephrol* 1995;5:1559–1566. [PubMed: 7756588]
14. Edgley AJ, Tare M, Evans RG, et al. In vivo regulation of endothelium-dependent vasodilation in the rat renal circulation and the effect of streptozotocin-induced diabetes. *Am J Physiol Regul Integr Comp Physiol* 2008;295:R829–R839. [PubMed: 18635451]
15. Schnackenberg CG, Wilcox CS. The SOD mimetic tempol restores vasodilation in afferent arterioles of experimental diabetes. *Kidney Int* 2001;59:1859–1864. [PubMed: 11318957]
16. Dai F-X, Diederich A, Skopec J, et al. Diabetes-induced endothelial dysfunction in streptozotocin-treated rats: Role of prostaglandin endoperoxides and free radicals. *J Am Soc Nephrol* 1993;4:1327–1336. [PubMed: 8130359]
17. Rebsomen L, Khammar A, Raccach D, et al. C-Peptide effects on renal physiology and diabetes. *Exp Diabetes Res* 2008;2008:281536. [PubMed: 18509500]
18. Vague P, Coste TC, Jannot MF, et al. C-peptide, Na^+ , K^+ -ATPase, and diabetes. *Exp Diabetes Res* 2004;5:37–50. [PubMed: 15198370]
- *19. Nordquist L, Lai EY, Sjoquist M, et al. Proinsulin C-peptide constricts glomerular afferent arterioles in diabetic mice. A potential renoprotective mechanism. *Am J Physiol Regul Integr Comp Physiol* 2008;294:R836–R841. [PubMed: 18077505] This is the first study to investigate the direct effect of C-peptide on afferent arteriolar diameter, revealing a constrictor effect on arterioles from diabetic rats but having minimal impact on normal arterioles. This observation suggests that C-peptide treatment may be a useful means of reducing hyperfiltration in DM, and implies that the C-peptide deficiency of DM might contribute to afferent arteriolar dilation and hyperfiltration.
20. Forst T, Kunt T, Wilhelm B, et al. Role of C-peptide in the regulation of microvascular blood flow. *Exp Diabetes Res* 2008;2008:176245. [PubMed: 18670621]
21. Li J, Chen YJ, Quilley J. Effect of tempol on renal cyclooxygenase expression and activity in experimental diabetes in the rat. *J Pharmacol Exp Ther* 2005;314:818–824. [PubMed: 15879008]
22. Chen YJ, Li J, Quilley J. Effect of inhibition of nitric oxide synthase on renal cyclooxygenase in the diabetic rat. *European J Pharmacol* 2006;541:80–86. [PubMed: 16753143]
23. Cherney DZI, Miller JA, Scholey JW, et al. The effect of cyclooxygenase-2 inhibition on renal hemodynamic function in humans with type 1 diabetes. *Diabetes* 2008;57:688–695. [PubMed: 18083781]
- *24. Cherney DZI, Scholey JW, Nasrallah R, et al. Renal hemodynamic effect of cyclooxygenase 2 inhibition in young men and women with uncomplicated type 1 diabetes mellitus. *Am J Physiol Renal Physiol* 2008;294:F1336–F1341. [PubMed: 18400871] This clinical investigation provides the first evidence of sex-dependent responses to COX-2 inhibition in individuals with T1D.
25. Maric C. Sex, diabetes and the kidney. *Am J Physiol Renal Physiol* 2009;296:F680–F688. [PubMed: 19144692]
26. Ikenaga H, Bast JP, Fallet RW, et al. Exaggerated impact of ATP-sensitive K^+ channels on afferent arteriolar diameter in diabetes mellitus. *J Am Soc Nephrol* 2000;11:1199–1207. [PubMed: 10864575]
- *27. Troncoso, Brindeiro CM.; Fallet, RW.; Lane, PH., et al. Potassium channel contributions to afferent arteriolar tone in normal and diabetic rat kidney. *Am J Physiol Renal Physiol* 2008;295:F171–F178. [PubMed: 18495797] This study utilized a pharmacological approach to unveil the K channels that contribute to tonic afferent arteriolar dilation in rats with T1D, specifically implicating K_{IR} and ROMK channels in this phenomenon. As K channel activity is key to establishing membrane potential, dysregulation of K_{IR} and ROMK channels likely engenders afferent arteriolar dilation during DM by promoting hyperpolarization of the resident vascular smooth muscle cells.
28. Carmines PK, Ohishi K, Ikenaga H. Functional impairment of renal afferent arteriolar voltage-gated calcium channels in rats with diabetes mellitus. *J Clin Invest* 1996;98:2564–2571. [PubMed: 8958219]
29. Troncoso, Brindeiro CM.; Fallet, RW.; Carmines, PK. Effect of tempol on inward-rectifier K channel regulation of afferent arteriolar tone in diabetic rat kidney [abstract]. *FASEB J* 2009;23:804.9.

30. Bidani AK, Picken M, Hacıoglu R, et al. Spontaneously reduced blood pressure load in the rat streptozotocin-induced diabetes model: potential pathogenetic relevance. *Am J Physiol Renal Physiol* 2007;292:F647–F654. [PubMed: 16968892]
31. Hayashi K, Epstein M, Loutzenhiser R, et al. Impaired myogenic responsiveness of the afferent arteriole in streptozotocin-induced diabetic rats: Role of eicosanoid derangements. *J Am Soc Nephrol* 1992;2:1578–1586. [PubMed: 1610978]
32. Hayashi K, Kanda T, Homma K, et al. Altered renal microvascular response in Zucker obese rats. *Metabolism* 2002;51:1553–1561. [PubMed: 12489067]
33. Vallon V, Blantz RC, Thomson S. Homeostatic efficiency of tubuloglomerular feedback is reduced in established diabetes mellitus in rats. *Am J Physiol Renal Fluid Electrolyte Physiol* 1995;269:F876–F883.
34. Parving H-H, Kastrup H, Smidt UM, et al. Impaired autoregulation of glomerular filtration rate and renal plasma flow in short-term insulin-dependent diabetics. *Diabetologia* 1981;20:451–456. [PubMed: 7016638]
35. Ishida K, Ishibashi F, Takashina S. Comparison of renal hemodynamics in early non-insulin-dependent and insulin-dependent diabetes mellitus. *J Diabet Complications* 1991;5:143–145. [PubMed: 1770025]
36. Bell TD, DiBona GF, Wang Y, et al. Mechanisms for renal blood flow control early in diabetes as revealed by chronic flow measurement and transfer function analysis. *J Am Soc Nephrol* 2006;17:2184–2192. [PubMed: 16807404]
- *37. Hashimoto S, Yamada K, Kawata T, et al. Abnormal autoregulation and tubuloglomerular feedback in prediabetic and diabetic OLETF rats. *Am J Physiol Renal Physiol* 2009;296:F598–F604. [PubMed: 19106213] This micropuncture study assessed autoregulation of glomerular capillary pressure in superficial and deep nephrons of rats with T2D (OLETF rats) and non-diabetic controls. The results reveal that autoregulation is impaired in OLETF rats even before development of overt hyperglycemia, consistent with the notion that an autoregulatory defect may be a very early event that ultimately leads to diabetic nephropathy in T2D.
38. Hashimoto Y, Ideura T, Yoshimura A, et al. Autoregulation of renal blood flow in streptozotocin-induced diabetic rats. *Diabetes* 1989;38:1109–1113. [PubMed: 2670641]
- **39. Lau C, Sudbury I, Thomson M, et al. Salt-resistant blood pressure and salt-sensitive renal autoregulation in chronic streptozotocin diabetes. *Am J Physiol Regul Integr Comp Physiol* 2009;296:R1761–R1770. [PubMed: 19339676] This systematic investigation of steady state and dynamic renal blood flow control provides strong evidence that the autoregulatory response to changes in systemic arterial pressure is well maintained (and actually extends to lower pressures than normal) in rats with T1D. Effects of dietary salt intake and, hence, volume status are also investigated. The discussion provides a particularly detailed and thoughtful analysis of the observed phenomena.
40. De Micheli AG, Forster H, Duncan RC, et al. A quantitative assessment of renal blood flow autoregulation in experimental diabetes. *Nephron* 1994;68:245–251. [PubMed: 7830864]
41. Mauer SM, Brown DM, Steffes MW, et al. Studies of renal autoregulation in pancreatectomized and streptozotocin diabetic rats. *Kidney Int* 1990;37:909–917. [PubMed: 2313980]
- **42. Park S, Bivona BJ, Feng Y, et al. Intact renal afferent arteriolar autoregulatory responsiveness in db/db mice. *Am J Physiol Renal Physiol* 2008;295:F1504–F1511. [PubMed: 18753291] This study represents the first investigation of afferent arteriolar diameter control in mice with T2D. Afferent arteriolar diameter was greater in db/db mice than in non-diabetic db/m mice. The db/db mice were normotensive and showed unaltered afferent arteriolar diameter responses to changes in perfusion pressure. The data suggest that albuminuria in these animals probably arises as a result of afferent arteriolar dilation and resulting glomerular capillary hypertension, independent of systemic arterial pressure.
43. Griffin KA, Abu-Naser M, Abu-Amarah I, et al. Dynamic blood pressure load and nephropathy in the ZSF1 (*fa/fa^{CP}*) model of type 2 diabetes. *Am J Physiol Renal Physiol* 2007;293:F1605–F1613. [PubMed: 17728379]
44. Schjoedt KJ, Christensen PK, Jorsal A, et al. Autoregulation of glomerular filtration rate during spironolactone treatment in hypertensive patients with type 1 diabetes: a randomized crossover trial. *Nephrol Dial Transplant* 2009:gfp311.

45. Vallon V, Blantz RC, Thomson S. Glomerular hyperfiltration and the salt paradox in early type 1 diabetes mellitus: A tubulo-centric view. *J Am Soc Nephrol* 2003;14:530–537. [PubMed: 12538755]
46. Thomson SC, Vallon V, Blantz RC. Kidney function in early diabetes: the tubular hypothesis of glomerular filtration. *Am J Physiol Renal Physiol* 2004;286:F8–F15. [PubMed: 14656757]
47. Levine DZ, Iacovitti M, Robertson SJ, et al. Modulation of single-nephron GFR in the db/db mouse model of type 2 diabetes mellitus. *Am J Physiol Regul Integr Comp Physiol* 2006;290:R975–R981. [PubMed: 16339386]
48. Sällström J, Carlsson PO, Fredholm BB, et al. Diabetes-induced hyperfiltration in adenosine A₁-receptor deficient mice lacking the tubuloglomerular feedback mechanism. *Acta Physiologica* 2007;190:253–259. [PubMed: 17581137]
- *49. Faulhaber-Walter R, Chen L, Oppermann M, et al. Lack of A₁ adenosine receptors augments diabetic hyperfiltration and glomerular injury. *J Am Soc Nephrol* 2008;19:722–730. [PubMed: 18256360]
This study exploited a genetic approach to investigate the role of TGF in diabetic hyperfiltration. Double-mutant mice lacking the A₁AR (and, hence, lacking TGF) in an Ins2^{+/-} background (Akita model of T1D) were anticipated to display normal GFR, which would be consistent with the tubulo-centric hypothesis of diabetic hyperfiltration. Surprisingly, the double mutant mice exhibited exaggerated hyperfiltration (compared with Akita mice having intact A₁AR). These observations indicate that TGF does not cause hyperfiltration and suggest that TGF may actually limit the degree of diabetic hyperfiltration.
- *50. Vallon V, Schroth J, Satriano J, et al. Adenosine A₁ receptors determine glomerular hyperfiltration and the salt paradox in early streptozotocin diabetes mellitus. *Nephron Physiol* 2009;111:30–38. These investigators examined the role of TGF in diabetic hyperfiltration by studying streptozotocin-induced T1D in mice lacking the A₁AR (and, hence, lacking TGF). In contrast with diabetic mice with intact A₁AR, diabetic mice lacking the A₁AR displayed no evidence of hyperfiltration. These observations provide evidence in support of the tubulo-centric hypothesis.