Renal hyperfiltration related to diabetes mellitus and obesity in human disease

Alexa N Sasson, David ZI Cherney

Abstract
High intraglomerular pressure is associated with renal hyperfiltration, leading to the initiation and progression of kidney disease in experimental models of diabetes mellitus (DM). In humans, hyperfiltration is observed in patients with type 1 and type 2 DM, and is also seen in patients with pre-diabetic conditions, such as the metabolic syndrome. From a mechanistic perspective, both vascular and tubular factors likely contribute to the pathogenesis of hyperfiltration. More recent advances in the development of investigational adenosine antagonists and inhibitors of sodium-glucose co-transport may help to elucidate tubular factors that contribute to afferent vasodilatation.

INTRODUCTION
Renal hemodynamic function abnormalities are common in experimental models of diabetes mellitus (DM), including increased intraglomerular capillary pressure and glomerular hyperfiltration. Micropuncture studies have suggested that these hemodynamic abnormalities are on the basis of high renal blood flow and glomerular transcapillary hydraulic pressure due to afferent arteriolar vasodilation, efferent vasoconstriction and suppression of tubuloglomerular feedback. These hemodynamic changes have been associated with activation of pro-inflammatory cytokines such as transforming growth factor-β (TGF-β), leading to proteinuria and kidney disease. Similar changes likely occur in experimental obesity.

In humans, glomerular hyperfiltration associated with early DM is a risk factor for the development of progressive diabetic nephropathy. Hyperfiltration is typically defined by a glomerular filtration rate (GFR) of between...
125 mL/min to 140 mL/min per 1.73 m², or greater than 2 standard deviations above the mean GFR in normal, healthy individuals[8,10]. Hyperfiltration is typically observed in 25%-75% of prevalent patients with type 1 DM and may depend on factors such as age, diabetes duration and glycemic control[8]. In patients with the metabolic syndrome and type 2 DM, the occurrence of hyperfiltration is likely lower and ranges from 5%-40%[10,11]. More recently, hyperfiltration has been associated with impaired fasting glucose in the general population, suggesting a link between high intraglomerular pressure and the development of chronic kidney disease[12]. The pathogenesis of diabetic hyperfiltration is incompletely understood but has been attributed to glomerular hemodynamic and tubular factors[12].

Given the deleterious effect of renal hyperfiltration on the risk of diabetic nephropathy and the possible clinical benefit derived through a reduction in intraglomerular pressure, it is of the utmost clinical importance to elucidate physiological mechanisms that are responsible for this condition[14].

**HEMODYNAMIC HYPOTHESIS FOR HYPERFILTRATION IN TYPE 1 DM**

As reviewed elsewhere, the hemodynamic hypothesis suggests that hyperfiltration is caused by changes in pre-glomerular (afferent) and post-glomerular (efferent) arteriolar tone. A variety of vasoactive mediators regulate glomerular arteriolar tone, including the nitric oxide (NO) system, cyclooxygenase 2 (COX2)-derived prostanoids, the renin angiotensin system (RAS), protein kinase C (PKC) and endothelin (ET). Strong experimental evidence has suggested that hyperglycemia increases the production and/or bioavailability of these factors, leading to changes to segmental resistance, thereby influencing renal function[13]. While pre- and post-glomerular arteriolar resistance cannot be measured in human studies, a similar change in levels of vasoactive mediators has been postulated in human integrative physiology studies involving patients with type 1 DM. These studies used inulin and para-aminohippurate clearances to measure GFR, filtration fraction, renal blood flow and renal vascular resistance[13].

At the afferent arteriolo, experimental evidence has strongly implicated a primary increase in NO production and bioactivity, which is mediated by hyperglycemia[15,17]. Less is known regarding the NO system in patients with uncomplicated type 1 DM, as reviewed elsewhere[13]. For example, increases in urinary and serum levels of NO metabolites are present in patients with type 1 DM and are associated with the degree of chronic hyperglycemia[13,15]. These studies have, however, been limited by the inclusion of both normal buminuric and albuminuric participants, who may have underlying differences in NO bioactivity[13]. Studies examining the interaction between NO and hyperfiltration have been further limited by a lack of dynamic testing, such as the inhibition of NO synthase or the use of acute hyperglycemic clamping[19]. Such physiological maneuvers are necessary to clarify the role of the NO system in early type 1 DM.

In addition to the NO system, COX2-derived prostanoids likely mediate an important impact on the afferent arteriolar function, leading to hyperfiltration[13,20,22]. COX2 is constitutively expressed in vascular endothelial cells in renal tissue and mediates important renal autoregulatory effects at the macula densa[23]. We have previously demonstrated that COX2 inhibition during clamped euglycemic conditions result in a partial reduction in GFR in hyperfiltrating type 1 DM patients, consistent with findings from hyperfiltering animals[23,24]. Interestingly, COX2 inhibition did not ameliorate the GFR increase mediated by hyperglycemia. Despite compelling animal data, the use of COX2 inhibitors in humans is limited by partial hemodynamic effects and a side effect profile which prevents long term use of these agents.

In addition to factors in the pre-glomerular circulation, efferent vasoconstriction related to RAS activation plays a critical role in the pathogenesis of glomerular hyperfiltration in animal and human studies[13,25,26]. For example, we have previously demonstrated that angiotensin-converting-enzyme (ACE) inhibition for 21 d is associated with a significant decline in hyperfiltration in patients with uncomplicated type 1 DM[27]. We were unable, however, to normalize GFR in our cohort. In contrast, GFR was not influenced by ACE inhibition in participants with normofiltration. We have extended this work by examining the effect of adding an investigational PKC-β inhibitor (ruboxistaurin) to pre-existing RAS blockade therapy in patients with microalbuminuria[27]. Our rationale for this study was that the hemodynamic effects of hyperglycemia and angiotensin II, including hyperfiltration, are mediated by PKC-β intracellular signaling cascades[28,29]. Similar to the effects of ACE inhibition, the addition of ruboxistaurin partially reduced, but did not normalize hyperfiltration, suggesting the need for the blockade of multiple pathways to abolish the hyperfiltration state.

Other vasoactive mediators have been associated with renal hyperfiltration in experimental models of DM, including ET-1[30]. Plasma ET-1 levels are increased in patients with DM due to the influence of hyperglycemia, RAS activation and PKC-β[31,32] and have been associated with microalbuminuria and the development of chronic kidney disease[33,34]. From a hemodynamic perspective, administration of exogenous endothelin is associated with increases in renal vascular resistance (RVR) and filtration fraction (FF), and a decline in effective renal plasma flow (ERPF) in healthy patients, suggesting a renal hyperfiltration response[35,36]. Blockade of the ET-A type receptor leads to reductions in systemic blood pressure and RVR and a rise in ERPF with no change in FF, suggesting a renal vasodilatory effect[35,36]. Importantly these effects are lost in the presence of ET-B type receptor antagonists, which cause an opposite rise in blood pressure and RVR.
and sodium retention leading to edema\textsuperscript{[38]}. In clinical studies examining ET-A receptor blockade with avosetan, these hemodynamic observations have translated into anti-proteinuric effects and preservation of renal function in patients with type 2 DM. Unfortunately, these promising clinical effects have been accompanied by an increased risk of sodium retention and edema, which may ultimately limit the use of these agents\textsuperscript{[40,41]}. This adverse effect likely occurs because available agents exhibit ET-B receptor antagonism at doses that have been studied, leading to increased proximal tubular sodium reabsorption\textsuperscript{[40,41]}. To our knowledge, human mechanistic studies examining the effect of ET antagonists on renal hyperfiltration in patients with type 1 DM have not been performed.

**TUBULAR HYPOTHESIS FOR HYPERFILTRATION IN TYPE 1 DM**

In contrast with the hemodynamic hypothesis, the tubular hypothesis proposes that hyperfiltration is initiated by increased sodium reabsorption in the proximal tubule, which is mediated by the sodium-glucose cotransporter-2 (SGLT2)\textsuperscript{[42]}. This increase in proximal reabsorption reduces delivery of sodium to the macula densa, which senses a decline in effective circulating volume and renal perfusion. To “maintain” GFR under conditions of effective circulating volume contraction, a physiological response would be to reduce adenosine generation in the juxtaglomerular apparatus, leading to afferent arteriolar vasodilation, an increase in renal perfusion and a normalization in GFR (tubuloglomerular feedback-TGF)\textsuperscript{[43,44]}. In DM, the decrease in distal delivery is not on the basis of effective circulating volume contraction, but instead due to increased proximal reabsorption of sodium, independent of volume status. Consequently, increased proximal reabsorption is associated with a supranormal rise in GFR into the hyperfiltration range\textsuperscript{[44]}. Animal studies have also elucidated the role of the tubular hypothesis by administering SGLT2 inhibitors in experimental models of type 1 and type 2 DM\textsuperscript{[45-48]}. These studies have suggested that SGLT2 inhibition decreases hyperfiltration and histological evidence of diabetic nephropathy. In humans, while these agents have demonstrated glycemic, blood pressure and weight lowering effects, effects on direct measures of GFR are not yet known\textsuperscript{[40,41]}

In addition to the SGLT2, adenosine has been implicated as an important factor that mediates TGF. The use of agents that modulate adenosine activity may therefore provide mechanistic insights into the pathophysiology of renal hyperfiltration\textsuperscript{[49]}. For example, adenosine A1 antagonists, which have been used in heart failure studies, would be expected to increase GFR and worsen hyperfiltration\textsuperscript{[50]}. While adenosine A1 antagonists have not, to our knowledge, been used in mechanistic studies in patients with DM, short-term administration of these agents may help to clarify the role of tubular factors in the pathogenesis of renal hyperfiltration.

**RENAL HYPERFILTRATION AND CHANGES IN MACROVASCULAR FUNCTION**

In addition to increased renal perfusion leading to hyperfiltration, patients with type 1 DM, not analyzed on the basis of filtration status, exhibit elevated blood flow in skeletal muscle\textsuperscript{[51]}. Furthermore, some of the same factors that cause hyperfiltration have been implicated in the pathogenesis of the early systemic vascular abnormalities that have been described in type 1 DM, including increased NO bioactivity\textsuperscript{[52]}. To determine if renal hyperfiltration is associated with exaggerated systemic vascular abnormalities, we measured endothelial function and arterial stiffness in our cohort of patients with uncomplicated type 1 DM\textsuperscript{[23,34]}. We observed that hyperfiltration is associated with high arterial compliance and an impaired vasodilatory response to reactive hyperemia\textsuperscript{[23,34]}. We interpreted these observations to reflect an underlying state of generalized maximal vasodilatation and a subsequent inability to dilate further in response to an ischemic stimulus. Whether medications that reduce hyperfiltration, such as ACE inhibitors, also preferentially increase endothelial function in hyperfiltering patients is unknown. Regardless of the underlying mechanisms, hyperfiltration related to type 1 DM reflects a generalized change in vascular function leading to renal and systemic vascular abnormalities that may predispose to the initiation and progression of diabetic nephropathy.

**HYPERFILTRATION, TYPE 2 DM AND PRE-DM CONDITIONS**

Hyperfiltration is not unique to type 1 DM. Type 2 DM is also associated with hyperfiltration. As in type 1 DM, hyperfiltration related to type 2 is likely to be a significant risk factor for the progression of diabetic nephropathy\textsuperscript{[50,58-60]}. Many of the mechanisms that have been implicated in the pathogenesis of hyperfiltration related to type 1 DM have also been demonstrated in the context of type 2 DM, including hemodynamic and TGF-related factors\textsuperscript{[21,54,60-62]}. Most of the evidence in this area is, however, based on experimental data, possibly because patients with type 2 DM are considerably more heterogeneous in terms of co-morbid conditions and vascular diseases, and are therefore more difficult to include in mechanistic human physiology studies.

Obesity-related metabolic abnormalities, including impaired glucose tolerance, have been strongly associated with progressive renal disease\textsuperscript{[61,62]}. Furthermore, obesity, the metabolic syndrome and impaired glucose tolerance are associated with mechanisms of renal injury that are similar to those identified in overt type 2 DM\textsuperscript{[63-64]}. For
example, hyperfiltration occurs in individuals with glucose intolerance before the diagnosis of type 2 DM[6,7]. Melsom et al.[5] demonstrated an increased risk of hyperfiltration in middle-aged non-DM patients with impaired fasting glucose. Interestingly, insulin levels were not associated with hyperfiltration in this cross-sectional, population-based study. The authors could not, however, rule out the possibility that hyperinsulinemia/insulin resistance were intermediary factors associated with the development of hyperfiltration, as suggested by others based on experimental and human data[5-9]. Others have suggested that TGF-related mechanisms are activated in the presence of obesity and the metabolic syndrome, leading to hyperfiltration[10-13]. Whatever the underlying mechanism, individuals with obesity and the metabolic syndrome exhibit a significant increase in GFR, predisposing a growing segment of the population to progressive renal disease[14]. Additional human research is required to study both the effect of pharmacotherapy and weight loss strategies, including bariatric surgery, on physiological and long-term clinical outcomes[15].

CONCLUSION

Since agents that modulate afferent arteriolar tone are either not practical (IV administration of L-NMMA) or associated with an unacceptable side effect profile after long term use (COX2 inhibitors), future attempts to ameliorate the hyperfiltration state will likely focus on the efferent arteriole and tubular factors. As reviewed elsewhere, ACE inhibitors and angiotensin receptor blockers only result in partial renal protection, partially due to compensatory pathways that are activated with the use of these agents[16-19]. In contrast, direct renin inhibition has theoretical physiological advantages that may avoid some of these pitfalls. Whether these agents result in a more complete reduction in hyperfiltration is currently not known. As mentioned above, experimental evidence in type 1 and 2 DM has suggested that inhibition of the SGLT2 co-transporter influences TGF and may reduce hyperfiltration. Whether this occurs in humans is unknown and requires further study.

Perhaps a larger issue related to studying hyperfiltration is the absence of a good marker of kidney function within the hyperfiltration range. Although we have demonstrated that cystatin C compares favorably to creatinine-based measurements (using insulin as a gold standard) in patients with uncomplicated type 1 DM, cystatin C does have limitations[20]. A greater understanding of the role cystatin C and the identification of additional markers of GFR that are accessible and cost-efficient are required to perform larger therapeutic trials designed to better elucidate the clinical importance and treatment of renal hyperfiltration.

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