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EDITORIAL

Renal hyperfiltration related to diabetes mellitus and obesity in human disease

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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. Until now, human studies have primarily focused on the use of medications that inhibit the renin angiotensin system to reduce efferent vasoconstriction and thereby improve 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. In this review, we summarize available data from experimental and human studies of type 1 and type 2 DM and obesity to provide an overview of factors that contribute to the hyperfiltration state. We have focused on the renin angiotensin system, cyclooxygenase-2 system, nitric oxide, protein kinase C and endothelin as vascular determinants of hyperfiltration. We also discuss relevant tubular factors, since experimental models have suggested that inhibition of sodium-glucose cotransport may be renoprotective.

Key words: Diabetes mellitus; Metabolic syndrome; Hyperfiltration; Glomerular filtration rate

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INTRODUCTION

Renal hemodynamic function abnormalities are common in experimental models of diabetes mellitus (DM), including increased intraglomerular capillary pressure and glomerular hyperfiltration[1,2]. 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 vasodilatation, efferent vasoconstriction and suppression of tubuloglomerular feedback[3-5]. 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[4,6]. Similar changes likely occur in experimental obesity[7].

In humans, glomerular hyperfiltration associated with early DM is a risk factor for the development of progressive diabetic nephropathy[8]. Hyperfiltration is typically defined by a glomerular filtration rate (GFR) of between

125 mL/min to 140 mL/min per 1.73 m^2, or greater than 2 standard deviations above the mean GFR in normal, healthy individuals[9,10]. 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[10]. 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[13].

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[8,14].

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[13]. 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 arteriole, 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[15,18]. 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 hyperfiltering type 1 DM patients, consistent with findings from hyperfiltering animals[20,24]. 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[1,25,26]. 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[26]. 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[33-35]. 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[36,37]. 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[38,39]. 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[38]. In clinical studies examining ET-A receptor blockade with avosentan, 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[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[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)[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 vasodilatation, an increase in renal perfusion and a normalization in GFR (tubuloglomerular feedback-TGF)[5,43,44]. 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[5,45,46].

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[47,48]. 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[49-51].

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[43]. For example, adenosine A1 antagonists, which have been used in heart failure studies, would be expected to increase GFR and worsen hyperfiltration[52]. 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[53]. 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[53]. 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[21,54]. We observed that hyperfiltration is associated with high arterial compliance and an impaired vasodilatory response to reactive hyperemia[21,54]. 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[10,55,56]. 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[10,55-60]. 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[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[11,63-65]. For

example, hyperfiltration occurs in individuals with glucose intolerance before the diagnosis of type 2 DM[66,67]. Melsom *et al*[12] 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[7,68-75]. Others have suggested that TGF-related mechanisms are activated in the presence of obesity and the metabolic syndrome, leading to hyperfiltration[66,73,76,77]. 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[11]. 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[73].

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[78,79]. 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 inulin as a gold standard) in patients with uncomplicated type 1 DM, cystatin C does have limitations[80]. 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.

REFERENCES

1 **Anderson S**, Jung FF, Ingelfinger JR. Renal renin-angiotensin system in diabetes: functional, immunohistochemical, and molecular biological correlations. *Am J Physiol* 1993; **265**: F477-F486

2 **Craven PA**, Caines MA, DeRubertis FR. Sequential alterations in glomerular prostaglandin and thromboxane synthesis in diabetic rats: relationship to the hyperfiltration of early diabetes. *Metabolism* 1987; **36**: 95-103

3 **Hostetter TH**, Troy JL, Brenner BM. Glomerular hemodynamics in experimental diabetes mellitus. *Kidney Int* 1981; **19**: 410-415

4 **Zatz R**, Meyer TW, Rennke HG, Brenner BM. Predominance of hemodynamic rather than metabolic factors in the pathogenesis of diabetic glomerulopathy. *Proc Natl Acad Sci USA* 1985; **82**: 5963-5967

5 **Vallon V**, Richter K, Blantz RC, Thomson S, Osswald H. Glomerular hyperfiltration in experimental diabetes mellitus: potential role of tubular reabsorption. *J Am Soc Nephrol* 1999; **10**: 2569-2576

6 **Ziyadeh FN**. Mediators of diabetic renal disease: the case for tgf-Beta as the major mediator. *J Am Soc Nephrol* 2004; **15** Suppl 1: S55-S57

7 **Park SK**, Kang SK. Renal function and hemodynamic study in obese Zucker rats. *Korean J Intern Med* 1995; **10**: 48-53

8 **Magee GM**, Bilous RW, Cardwell CR, Hunter SJ, Kee F, Fogarty DG. Is hyperfiltration associated with the future risk of developing diabetic nephropathy? A meta-analysis. *Diabetologia* 2009; **52**: 691-697

9 **Dahlquist G**, Stattin EL, Rudberg S. Urinary albumin excretion rate and glomerular filtration rate in the prediction of diabetic nephropathy; a long-term follow-up study of childhood onset type-1 diabetic patients. *Nephrol Dial Transplant* 2001; **16**: 1382-1386

10 **Jerums G**, Premaratne E, Panagiotopoulos S, MacIsaac RJ. The clinical significance of hyperfiltration in diabetes. *Diabetologia* 2010; **53**: 2093-2104

11 **Tomaszewski M**, Charchar FJ, Maric C, McClure J, Crawford L, Grzeszczak W, Sattar N, Zukowska-Szczechowska E, Dominiczak AF. Glomerular hyperfiltration: a new marker of metabolic risk. *Kidney Int* 2007; **71**: 816-821

12 **Melsom T**, Mathisen UD, Ingebretsen OC, Jenssen TG, Njølstad I, Solbu MD, Toft I, Eriksen BO. Impaired fasting glucose is associated with renal hyperfiltration in the general population. *Diabetes Care* 2011; **34**: 1546-1551

13 **Cherney DZ**, Scholey JW, Miller JA. Insights into the regulation of renal hemodynamic function in diabetic mellitus. *Curr Diabetes Rev* 2008; **4**: 280-290

14 **Zatz R**, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM. Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest* 1986; **77**: 1925-1930

15 **Chiarelli F**, Cipollone F, Romano F, Tumini S, Costantini F, di Ricco L, Pomilio M, Pierdomenico SD, Marini M, Cuccurullo F, Mezzetti A. Increased circulating nitric oxide in young patients with type 1 diabetes and persistent microalbuminuria: relation to glomerular hyperfiltration. *Diabetes* 2000; **49**: 1258-1263

16 **Bank N**, Aynedjian HS. Role of EDRF (nitric oxide) in diabetic renal hyperfiltration. *Kidney Int* 1993; **43**: 1306-1312

17 **Veelken R**, Hilgers KF, Hartner A, Haas A, Böhmer KP, Sterzel RB. Nitric oxide synthase isoforms and glomerular hyperfiltration in early diabetic nephropathy. *J Am Soc Nephrol* 2000; **11**: 71-79

18 **O'Byrne S**, Forte P, Roberts LJ, Morrow JD, Johnston A, Anggård E, Leslie RD, Benjamin N. Nitric oxide synthesis and isoprostane production in subjects with type 1 diabetes and normal urinary albumin excretion. *Diabetes* 2000; **49**: 857-862

19 **Komers R**, Simkova R, Kazdova L, Ruzickova J, Pelikanova T. Effects of ACE inhibition and AT1-receptor blockade on haemodynamic responses to L-arginine in Type 1 diabetes. *J Renin Angiotensin Aldosterone Syst* 2004; **5**: 33-38

20 **Cherney DZ**, Miller JA, Scholey JW, Bradley TJ, Slorach C,

Curtis JR, Dekker MG, Nasrallah R, Hébert RL, Sochett EB. The effect of cyclooxygenase-2 inhibition on renal hemodynamic function in humans with type 1 diabetes. *Diabetes* 2008; **57**: 688-695

21 **Cherney DZ**, Miller JA, Scholey JW, Nasrallah R, Hébert RL, Dekker MG, Slorach C, Sochett EB, Bradley TJ. Renal hyperfiltration is a determinant of endothelial function responses to cyclooxygenase 2 inhibition in type 1 diabetes. *Diabetes Care* 2010; **33**: 1344-1346

22 **Cherney DZ**, Scholey JW, Nasrallah R, Dekker MG, Slorach C, Bradley TJ, Hébert RL, Sochett EB, Miller JA. 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

23 **Ichihara A**, Imig JD, Navar LG. Cyclooxygenase-2 modulates afferent arteriolar responses to increases in pressure. *Hypertension* 1999; **34**: 843-847

24 **Komers R**, Lindsley JN, Oyama TT, Schutzer WE, Reed JF, Mader SL, Anderson S. Immunohistochemical and functional correlations of renal cyclooxygenase-2 in experimental diabetes. *J Clin Invest* 2001; **107**: 889-898

25 **Brenner BM**, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. *Kidney Int* 1996; **49**: 1774-1777

26 **Sochett EB**, Cherney DZ, Curtis JR, Dekker MG, Scholey JW, Miller JA. Impact of renin angiotensin system modulation on the hyperfiltration state in type 1 diabetes. *J Am Soc Nephrol* 2006; **17**: 1703-1709

27 **Cherney DZ**, Konvalinka A, Zinman B, Diamandis EP, Soosaipillai A, Reich H, Lorraine J, Lai V, Scholey JW, Miller JA. Effect of protein kinase Cbeta inhibition on renal hemodynamic function and urinary biomarkers in humans with type 1 diabetes: a pilot study. *Diabetes Care* 2009; **32**: 91-93

28 **Koya D**, Haneda M, Nakagawa H, Isshiki K, Sato H, Maeda S, Sugimoto T, Yasuda H, Kashiwagi A, Ways DK, King GL, Kikkawa R. Amelioration of accelerated diabetic mesangial expansion by treatment with a PKC beta inhibitor in diabetic db/db mice, a rodent model for type 2 diabetes. *FASEB J* 2000; **14**: 439-447

29 **Ishii H**, Jirousek MR, Koya D, Takagi C, Xia P, Clermont A, Bursell SE, Kern TS, Ballas LM, Heath WF, Stramm LE, Feener EP, King GL. Amelioration of vascular dysfunctions in diabetic rats by an oral PKC beta inhibitor. *Science* 1996; **272**: 728-731

30 **Ohshiro Y**, Ma RC, Yasuda Y, Hiraoka-Yamamoto J, Clermont AC, Isshiki K, Yagi K, Arikawa E, Kern TS, King GL. Reduction of diabetes-induced oxidative stress, fibrotic cytokine expression, and renal dysfunction in protein kinase Cbeta-null mice. *Diabetes* 2006; **55**: 3112-3120

31 **De Mattia G**, Cassone-Faldetta M, Bellini C, Bravi MC, Laurenti O, Baldoncini R, Santucci A, Ferri C. Role of plasma and urinary endothelin-1 in early diabetic and hypertensive nephropathy. *Am J Hypertens* 1998; **11**: 983-988

32 **Shin SJ**, Lee YJ, Tsai JH. The correlation of plasma and urine endothelin-1 with the severity of nephropathy in Chinese patients with type 2 diabetes. *Scand J Clin Lab Invest* 1996; **56**: 571-576

33 **Hopfner RL**, Gopalakrishnan V. Endothelin: emerging role in diabetic vascular complications. *Diabetologia* 1999; **42**: 1383-1394

34 **Peppa-Patrikiou M**, Dracopoulou M, Dacou-Voutetakis C. Urinary endothelin in adolescents and young adults with insulin-dependent diabetes mellitus: relation to urinary albumin, blood pressure, and other factors. *Metabolism* 1998; **47**: 1408-1412

35 **Peppa-Patrikiou M**, Scordili M, Antoniou A, Giannaki M, Dracopoulou M, Dacou-Voutetakis C. Carotid atherosclerosis in adolescents and young adults with IDDM. Relation to urinary endothelin, albumin, free cortisol, and other factors. *Diabetes Care* 1998; **21**: 1004-1007

36 **Rabelink TJ**, Kaasjager KA, Boer P, Stroes EG, Braam B, Koomans HA. Effects of endothelin-1 on renal function in humans: implications for physiology and pathophysiology. *Kidney Int* 1994; **46**: 376-381

37 **Sørensen SS**, Madsen JK, Pedersen EB. Systemic and renal effect of intravenous infusion of endothelin-1 in healthy human volunteers. *Am J Physiol* 1994; **266**: F411-F418

38 **Goddard J**, Johnston NR, Hand MF, Cumming AD, Rabelink TJ, Rankin AJ, Webb DJ. Endothelin-A receptor antagonism reduces blood pressure and increases renal blood flow in hypertensive patients with chronic renal failure: a comparison of selective and combined endothelin receptor blockade. *Circulation* 2004; **109**: 1186-1193

39 **Dhaun N**, Strachan FE, Newby DE, Johnston NR, Ford NF, Hammett JL, Palmisano M, Webb DJ. Vasodilator effects of the endothelin ET receptor selective antagonist BMS-193884 in healthy men. *Br J Clin Pharmacol* 2005; **60**: 611-622

40 **Mann JF**, Green D, Jamerson K, Ruilope LM, Kuranoff SJ, Littke T, Viberti G. Avosentan for overt diabetic nephropathy. *J Am Soc Nephrol* 2010; **21**: 527-535

41 **Wenzel RR**, Littke T, Kuranoff S, Jürgens C, Bruck H, Ritz E, Philipp T, Mitchell A. Avosentan reduces albumin excretion in diabetics with macroalbuminuria. *J Am Soc Nephrol* 2009; **20**: 655-664

42 **Aires I**, Calado J. BI-10773, a sodium-glucose cotransporter 2 inhibitor for the potential oral treatment of type 2 diabetes mellitus. *Curr Opin Investig Drugs* 2010; **11**: 1182-1190

43 **Faulhaber-Walter R**, Chen L, Oppermann M, Kim SM, Huang Y, Hiramatsu N, Mizel D, Kajiyama H, Zerfas P, Briggs JP, Kopp JB, Schnermann J. Lack of A1 adenosine receptors augments diabetic hyperfiltration and glomerular injury. *J Am Soc Nephrol* 2008; **19**: 722-730

44 **Vervoort G**, Veldman B, Berden JH, Smits P, Wetzels JF. Glomerular hyperfiltration in type 1 diabetes mellitus results from primary changes in proximal tubular sodium handling without changes in volume expansion. *Eur J Clin Invest* 2005; **35**: 330-336

45 **Vallon V**, Blantz RC, Thomson S. Glomerular hyperfiltration and the salt paradox in early [corrected] type 1 diabetes mellitus: a tubulo-centric view. *J Am Soc Nephrol* 2003; **14**: 530-537

46 **Vallon V**, Wead LM, Blantz RC. Renal hemodynamics and plasma and kidney angiotensin II in established diabetes mellitus in rats: effect of sodium and salt restriction. *J Am Soc Nephrol* 1995; **5**: 1761-1767

47 **Arakawa K**, Ishihara T, Oku A, Nawano M, Ueta K, Kitamura K, Matsumoto M, Saito A. Improved diabetic syndrome in C57BL/KsJ-db/db mice by oral administration of the Na(+)-glucose cotransporter inhibitor T-1095. *Br J Pharmacol* 2001; **132**: 578-586

48 **Malatiali S**, Francis I, Barac-Nieto M. Phlorizin prevents glomerular hyperfiltration but not hypertrophy in diabetic rats. *Exp Diabetes Res* 2008; **2008**: 305403

49 **Strojek K**, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes Obes Metab* 2011; **13**: 928-938

50 **List JF**, Whaley JM. Glucose dynamics and mechanistic implications of SGLT2 inhibitors in animals and humans. *Kidney Int Suppl* 2011; S20-S27

51 **List JF**, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. *Diabetes Care* 2009; **32**: 650-657

52 **Massie BM**, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Weatherley BD, Cleland JG, Givertz MM, Voors A, DeLucca P, Mansoor GA, Salerno CM, Bloomfield DM, Dittrich HC. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. *N Engl J Med* 2010; **363**: 1419-1428

53 **Vervoort G**, Wetzels JF, Lutterman JA, van Doorn LG, Berden JH, Smits P. Elevated skeletal muscle blood flow in noncomplicated type 1 diabetes mellitus: role of nitric oxide and sympathetic tone. *Hypertension* 1999; **34**: 1080-1085

54 **Cherney DZ**, Sochett EB, Lai V, Dekker MG, Slorach C, Scholey JW, Bradley TJ. Renal hyperfiltration and arterial stiffness in humans with uncomplicated type 1 diabetes. *Diabetes Care* 2010; **33**: 2068-2070

55 **Wesson DE**. Moving closer to an understanding of the hyperfiltration of type 2 diabetes mellitus. *Am J Physiol Regul Integr Comp Physiol* 2006; **290**: R973-R974

56 **Levine DZ**, Iacovitti M, Robertson SJ, Mokhtar GA. 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

57 **Apakkan Aksun S**, Ozmen B, Ozmen D, Parildar Z, Senol B, Habif S, Mutaf I, Turgan N, Bayindir O. Serum and urinary nitric oxide in Type 2 diabetes with or without microalbuminuria: relation to glomerular hyperfiltration. *J Diabetes Complications* 2003; **17**: 343-348

58 **Hiragushi K**, Sugimoto H, Shikata K, Yamashita T, Miyatake N, Shikata Y, Wada J, Kumagai I, Fukushima M, Makino H. Nitric oxide system is involved in glomerular hyperfiltration in Japanese normo- and micro-albuminuric patients with type 2 diabetes. *Diabetes Res Clin Pract* 2001; **53**: 149-159

59 **Pistrosch F**, Herbrig K, Kindel B, Passauer J, Fischer S, Gross P. Rosiglitazone improves glomerular hyperfiltration, renal endothelial dysfunction, and microalbuminuria of incipient diabetic nephropathy in patients. *Diabetes* 2005; **54**: 2206-2211

60 **Premaratne E**, Macisaac RJ, Tsalamandris C, Panagiotopoulos S, Smith T, Jerums G. Renal hyperfiltration in type 2 diabetes: effect of age-related decline in glomerular filtration rate. *Diabetologia* 2005; **48**: 2486-2493

61 **Henegar JR**, Bigler SA, Henegar LK, Tyagi SC, Hall JE. Functional and structural changes in the kidney in the early stages of obesity. *J Am Soc Nephrol* 2001; **12**: 1211-1217

62 **Bivona BJ**, Park S, Harrison-Bernard LM. Glomerular filtration rate determinations in conscious type II diabetic mice. *Am J Physiol Renal Physiol* 2011; **300**: F618-F625

63 **Ritz E**. Metabolic syndrome: an emerging threat to renal function. *Clin J Am Soc Nephrol* 2007; **2**: 869-871

64 **Ritz E**. Metabolic syndrome and kidney disease. *Blood Purif* 2008; **26**: 59-62

65 **Tantravahi J**, Srinivas TR, Johnson RJ. Hyperfiltration: a sign of poor things to come in individuals with metabolic syndrome. *Nat Clin Pract Nephrol* 2007; **3**: 474-475

66 **Pruijm M**, Wuerzner G, Maillard M, Bovet P, Renaud C, Bochud M, Burnier M. Glomerular hyperfiltration and increased proximal sodium reabsorption in subjects with type 2 diabetes or impaired fasting glucose in a population of the African region. *Nephrol Dial Transplant* 2010; **25**: 2225-2231

67 **Wuerzner G**, Pruijm M, Maillard M, Bovet P, Renaud C, Burnier M, Bochud M. Marked association between obesity and glomerular hyperfiltration: a cross-sectional study in an African population. *Am J Kidney Dis* 2010; **56**: 303-312

68 **de Paula RB**, da Silva AA, Hall JE. Aldosterone antagonism attenuates obesity-induced hypertension and glomerular hyperfiltration. *Hypertension* 2004; **43**: 41-47

69 **Dengel DR**, Goldberg AP, Mayuga RS, Kairis GM, Weir MR. Insulin resistance, elevated glomerular filtration fraction, and renal injury. *Hypertension* 1996; **28**: 127-132

70 **Sharma AM**. Is there a rationale for angiotensin blockade in the management of obesity hypertension? *Hypertension* 2004; **44**: 12-19

71 **Hall JE**, Henegar JR, Dwyer TM, Liu J, Da Silva AA, Kuo JJ, Tallam L. Is obesity a major cause of chronic kidney disease? *Adv Ren Replace Ther* 2004; **11**: 41-54

72 **Knight SF**, Imig JD. Obesity, insulin resistance, and renal function. *Microcirculation* 2007; **14**: 349-362

73 **Chagnac A**, Weinstein T, Herman M, Hirsh J, Gafter U, Ori Y. The effects of weight loss on renal function in patients with severe obesity. *J Am Soc Nephrol* 2003; **14**: 1480-1486

74 **Chagnac A**, Weinstein T, Korzets A, Ramadan E, Hirsch J, Gafter U. Glomerular hemodynamics in severe obesity. *Am J Physiol Renal Physiol* 2000; **278**: F817-F822

75 **Hoffler U**, Hobbie K, Wilson R, Bai R, Rahman A, Malarkey D, Travlos G, Ghanayem BI. Diet-induced obesity is associated with hyperleptinemia, hyperinsulinemia, hepatic steatosis, and glomerulopathy in C57Bl/6J mice. *Endocrine* 2009; **36**: 311-325

76 **Chagnac A**, Gafter U, Zevin D, Hirsch Y, Markovitz I, Levi J. Enalapril attenuates glomerular hyperfiltration following a meat meal. *Nephron* 1989; **51**: 466-469

77 **Chagnac A**, Herman M, Zingerman B, Erman A, Rozen-Zvi B, Hirsh J, Gafter U. Obesity-induced glomerular hyperfiltration: its involvement in the pathogenesis of tubular sodium reabsorption. *Nephrol Dial Transplant* 2008; **23**: 3946-3952

78 **Ficociello LH**, Perkins BA, Silva KH, Finkelstein DM, Ignatowska-Switalska H, Gaciong Z, Cupples LA, Aschengrau A, Warram JH, Krolewski AS. Determinants of progression from microalbuminuria to proteinuria in patients who have type 1 diabetes and are treated with angiotensin-converting enzyme inhibitors. *Clin J Am Soc Nephrol* 2007; **2**: 461-469

79 **Cherney DZ**, Lai V, Scholey JW, Miller JA, Zinman B, Reich HN. Effect of direct renin inhibition on renal hemodynamic function, arterial stiffness, and endothelial function in humans with uncomplicated type 1 diabetes: a pilot study. *Diabetes Care* 2010; **33**: 361-365

80 **Cherney DZ**, Sochett EB, Dekker MG, Perkins BA. Ability of cystatin C to detect acute changes in glomerular filtration rate provoked by hyperglycaemia in uncomplicated Type 1 diabetes. *Diabet Med* 2010; **27**: 1358-1365

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