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Hyperfiltration-Associated Biomechanical Forces in Glomerular Injury and Response: Potential Role for Eicosanoids

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Abstract

Hyperfiltration is a well-known risk factor in progressive loss of renal function in chronic kidney disease (CKD) secondary to various diseases. A reduced number of functional nephrons due to congenital or acquired cause(s) results in hyperfiltration in the remnant kidney. Hyperfiltration-associated increase in biomechanical forces namely pressure-induced tensile stress and fluid flow-induced shear stress (FFSS) determine cellular injury and response. We believe the current treatment of CKD yields limited success because it largely attenuates pressure-induced tensile stress changes but not the effect of FFSS on podocytes. Studies on glomerular podocytes, tubular epithelial cells and bone osteocytes provide evidence for a significant role of COX-2 generated PGE_2 and its receptors in response to tensile stress and FFSS. Preliminary observations show increased urinary PGE_2 in children born with a solitary kidney. FFSS-induced $COX2$-PGE_2-EP_2 signaling provides an opportunity to identify targets and, for developing novel agents to complement currently available treatment.

Keywords

Hyperfiltration; Fluid flow shear stress; Tensile stress; Podocytes; Prostaglandin E_2; Prostanoid receptors

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1. Introduction

Glomerular hyperfiltration is considered to be a major risk factor in progressive loss of renal function in chronic kidney disease (CKD) patients. Despite decades of familiarity with the concept [1], the mechanical and rheological aspects of glomerular hyperfiltration remain unclear. Specifically, the role of hyperfiltration-associated increase in biomechanical forces needs to be explored in the context of glomerular intra-capillary space and extra-capillary Bowman's space. Cells of these two compartments namely capillary endothelial cells and podocytes in Bowman's space and the glomerular basement membrane constitute the glomerular filtration barrier. The glomerular filtration barrier is a complex structure that facilitates a close interaction between endothelial cells in the glomerular capillary lumen and podocytes in Bowman's space. The GBM with its porous structure provides a spatial separation and functional connectivity between the endothelial cells and podocytes [2,3]. Scanning electron micrographs show segments of capillary lumen with sieve-like arrangement of endothelial cells (Figure 1A) and interdigitated foot processes of podocytes that cover the capillary (Figure 1B). Such multicomponent architecture (Figure 1) of the filtration barrier generates the ultrafiltrate under physiological conditions withstanding much higher capillary pressures compared to non-glomerular capillaries. However, the changes in biomechanical forces under physiological or pathological conditions are not well-understood. Each component of the filtration barrier is important to maintain barrier function. Mesangial cells for their close interaction with their close interaction with endothelial cells and podocytes [4,5] and the GBM for its role as a matrix for endothelial cells and podocytes as well as a barrier [6–8]. The significance of capillary endothelial cells in glomerular function is also discussed in excellent reviews [9–11].

Effect of hyperfiltration-associated increase in fluid flow on non-endothelial cells such as podocyte may also have significant consequences on cellular integrity and in onset of glomerular dysfunction. While defects and/or damage to any component of the filtration barrier may compromise its function, podocytes are especially highly vulnerable to hyperfiltration as outlined here [12]. Hyperfiltration causes damage to podocyte structure and function indirectly through increase in capillary stretch as well as directly through elevated fluid flow shear stress (FFSS).

Of the two biomechanical forces associated with hyperfiltration, effects of pressure-induced tensile stress are more familiar and better understood because of extensive work in the past on renal blood flow, glomerular capillary pressure and systemic blood pressure to address the gradual loss of glomerular function. Indeed, the significance of glomerular capillary pressure and glomerular hypertension defined the role for renin angiotensin aldosterone system (RAAS) [1,13]. Renin, a product of the cells of the juxtaglomerular apparatus, activates the RAAS by converting angiotensinogen to angiotensin II (ANG II) in response to sympathetic activity and low blood pressure or sodium. Juxtaglomerular structures and their function continue to remain significant for ongoing research evidenced by recent reviews on the subject [14–16]. Previous work related to the RAAS resulted in the development of mainstream drugs such as angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEI) for treating hypertension that are also used to control pressure-related hyperfiltration-mediated renal dysfunction. These drugs are effective in delaying the

progression of CKD in some but not all kidney diseases. On the other hand, changes in glomerular cells (podocytes) caused by hyperfiltration-mediated increase in ultrafiltrate flow have not been targeted to treat renal dysfunction. Technical advances for studying biomechanical forces and a better understanding of podocyte biology have encouraged investigations into additional mechanisms to further improve the outcomes in patients with CKD.

This brief review outlines the significance of biomechanical forces in hyperfiltration with special reference to the increasing recognition of the effects of FFSS. We summarize results from studies on podocytes and other epithelial cells to distinguish effects of pressure-induced tensile stress and flow-induced shear stress on PGE_2, prostanoid receptors and key elements of their signaling pathway. Preliminary studies show that changes in urinary PGE_2 and other eicosanoids may be useful indicators to follow progression of CKD. Recent findings in renal tubular epithelial cells and bone osteocytes are provided as examples to demonstrate similarities in the mechanism(s) of the effect of biomechanical forces across different cell systems. The review summarizes the recent findings on the differential effects of biomechanical forces in glomerular dysfunction viewed through eicosanoid-mediated changes in podocytes. Considering the mechanism of hyperfiltration-induced injury of podocytes in terms of FFSS, hitherto unaddressed in the mainstream literature, will likely provide new directions for future investigations and drug development.

2. Single nephron glomerular filtration rate (SNGFR) and hyperfiltration

Approximately 1 million nephron units in each human kidney extract fluid from ~1500 liters of blood in 24 hours from glomerular capillary and generate ~180 liters ultrafiltrate into the Bowman's compartment. The ultrafiltrate is then processed down to ~1.5 liters in the tubular compartment and excreted as urine. Thus, plasma filtration in each glomerulus i.e. single nephron glomerular filtration rate (SNGFR) is a key indicator of renal function. SNGFR is determined by ultrafiltration coefficient (K_f), a product of total filtration area and hydraulic permeability (L_p) as well as net ultrafiltration pressure (P_{UF}). P_{UF} represents the difference between the net integrated hydraulic pressure and net plasma oncotic pressure [17].

An adaptive increase in SNGFR is immediately observed after unilateral nephrectomy that decreases the number of functional nephrons by half and results in increased blood flow, increased glomerular capillary pressure (P_{GC}) and filtration area [18] in the remnant functional kidney. Persistent adaptive hyperfiltration may become maladaptive and contribute to glomerular injury which, in turn, further propagates and exacerbates the magnitude of hyperfiltration. Hyperfiltration remains a loosely defined term but threshold levels of glomerular filtration rate (GFR) between 90.7 to 175 ml/min/1.73 m^2 with a median value of 135 ml/min/1.73 m^2 are reportedly indicate hyperfiltration [19,20]. Increased SNGFR entails greater ultrafiltrate flow through Bowman's space. Consequently, both pressure and flow related mechanical forces are relevant for the present discussion.

3. Biomechanical forces associated with hyperfiltration

Biomechanical forces generally connote musculoskeletal structure-function. Forces associated with fluid mechanics have been largely studied in terms of blood/gas flow-related pressure and shear. Plasma filtration in renal glomeruli exemplifies a unique interaction between blood flow in vasculature and ultrafiltrate flow in non-vascular space i.e. Bowman's space. Here, blood flow in the capillary indirectly affects podocytes. Capillary pressure generates tensile stress on capillary wall while plasma fluid filters into Bowman's space as the ultrafiltrate. Next, ultrafiltrate flow within Bowman's space directly exerts FFSS on podocytes (a.k.a. visceral epithelial cells) localized in Bowman's space (Figure 1C). Basal tensile stress and FFSS are integrated with physiological glomerular filtration but a decrease in the number of functional nephrons in CKD induces hyperfiltration in the remnant functional nephrons with a parallel rise in both tensile stress and FFSS. Glomerular hyperfiltration provides an interesting study of the temporal relationship between tensile stress and FFSS *vis-a-vis* their effects on podocytes.

(A) Tensile stress

Blood flow through capillary loops generates force radially at 90° to the direction of flow causing capillary wall stretch that radiates to podocyte foot processes attached to the GBM that covers the outer aspect of the capillary. To study the effect of experimental stretch, cells are cells grown on the flexible surface of specially designed petri dishes and subjected to computer-controlled application of vacuum generate uniaxial or biaxial stretch (Flexcell International Corporation, Burlington NC) [21], hydrostatic pressure [22], hypo-osmotic stretch [23], or magnetic pull to iron-coated cells [24].

(B) Fluid flow shear stress (FFSS)

Ultrafiltrate flow from capillary to the proximal tubule causes on major processes and cell bodies of podocytes in Bowman's space. To study the effect of experimental FFSS, cells are grown on glass slides and subjected to a fluid column of defined viscosity and dimensions. Thus, under defined conditions, flow rate is the only determinant of FFSS. The nature of the fluid column can be designed to deliver laminar, pulsatile or oscillating shear stress. Commercially available equipment can be used for treating multiple slides simultaneously (Streamer System, Flexcell Corporation). We have developed a special flow chamber for studies using FFSS-treated isolated glomeruli [25].

4. Hyperfiltration and arachidonic acid metabolites

Arachidonic acid metabolites are key regulators of renal blood flow, GFR, salt and water absorption, and renin secretion from the juxtaglomerular apparatus in kidneys [26, 27, 28,29]. Cyclooxygenases 1 and 2 (COX-1, COX-2), lipoxygenases (LOX) and cytochrome P450 (CYP2 epoxygenases and CYP4 ω-hydroxylases) generate prostaglandins, leukotrienes and epoxyeicosatrienoic acids (EETs) and hydroxyeicosatetraenoic acids (HETEs), respectively. Isoprostanes, prostaglandin-like eicosanoids, are formed by free radical-catalyzed peroxidation of arachidonic acid. Among these, PGE_2 has been found to have significant role in cellular response to hyperfiltration-mediated changes.

PGE_2 is generated from arachidonic acid by COX-1 and COX-2 activities. COX-1 is expressed constitutively whereas COX-2 is generally an inducible enzyme [30]. Podocytes express both COX-1 and COX-2 [31,32] and, we found that the $COX2-PGE_2-EP_2$ axis plays an important role in hyperfiltration-mediated glomerular injury in mouse models of solitary kidney as well as in cultured podocytes [25, 33]. PGE_2 is the major prostanoid under physiological conditions and interacts with four E-prostanoid (EP) receptors that have been cloned and characterized in both human and mouse [34,35].

Figure 2 summarizes the expression and functions of PGE_2 receptors EP_1-EP_4. EP_1 mRNA is restricted to kidney, lung and stomach [36]; EP_2, mainly found in vascular compartment of the kidney, and is induced in response to stimuli [34] while EP_3 and EP_4 are widely distributed [37,38]. In mouse kidneys, EP_1 is localized to the collecting ducts from the cortex to the papilla, EP_2 to glomeruli and arterioles, and EP_3 to tubules of outer medulla and the cortex [38,39]. Renal cells such as podocytes simultaneously express several EP receptors, and their relative levels determine the overall cellular response. Mouse podocytes express three of the four receptors for PGE_2 namely, EP_1, EP_2 and EP_4 [25]. In podocytes, basal expression of EP_4 is higher compared to that of EP_2 [25, 40]. While EP4 expression was found to increase in response to tensile stress [10], we found that FFSS results in increased expression of EP_2 not EP_4 [25]. Previous studies identified expression of EP2 in mesangial cells and infiltrating cells [41,42].

Pharmacological and gene targeting techniques have been used for determining the role of PGE_2 receptors [43]. Reported findings seem to vary. PGE_2 receptors are G-protein coupled proteins. EP_1 is coupled to calcium mobilization, EP_2 and EP_4 are linked to G_s protein, and EP_3 to G_i protein [34, 39]. EP_2 stimulates adenylate cyclase while both EP_2 and EP_4 cause vasodilatation of mouse afferent arteriole and buffer vasoconstrictor effects of EP_1 and EP_3 [44]. In addition, EP_4 mediates renin release [45]. EP_2 knock-out (KO) mice develop salt sensitive hypertension [46]. An anti-apoptotic/pro-survival role of EP_2 receptors have been implicated in renal cysts in ADPKD [47]. Glomerular size is reduced in EP_4, EP_2 or EP_1 deficient mice emphasizing the importance of PGE_2 in early postnatal period [48]. On the other hand EP_4 null mice were found protected from the injurious effects of 5/6 nephrectomy [49]. Prostacyclin receptor KO mice have no phenotype [50] but prostacyclin synthase KO mice have elevated levels of PGE_2 and a renal phenotype with cysts, sclerosis and vascular changes [51]. Although the foregoing section summarizes known changes potentially mediated by each receptor, the role of each receptor appears to be influenced by several factors including cell-type, study model and experimental conditions. These factors seem to result in overlapping and sometimes contradictory findings. Thus, assigning a definite role for each receptor would require validation in the context of specific disease model and experimental settings including gene deletion.

While tensile and shear stress involve distinct mechanisms, interactions between key molecules involved in pressure regulation and shear-induced add another level of complexity. Release of renin was found to be stimulated by COX-2 and PGE_2 mediated by EP_4 [45]. EETs and HETEs formed by the CYP450 enzymes interact with ANG II [52,53,54]. These findings suggest a significant cross-talk and modulatory interaction between eicosanoids and the RAAS in glomerular function. Likewise, similarities,

differences and cross-talk between EP receptors are also indicated by their effects on blood pressure and fertility. Although both EP_2 and EP_4 are G_s-coupled receptor proteins, they are differentially expressed in tissues, and their responses to stimuli are diverse. Additionally, genetic background, techniques used for gene deletion, sex hormones may influence the observed effects of PGE_2 receptors [55].

5. Effect of biomechanical forces on podocytes and PGE₂ as a mediator of fluid flow shear stress in podocytes

Podocytes provide the most structural resistance to the passage of plasma proteins from blood into urine. Podocytes are large terminally-differentiated epithelial cells localized in Bowman's space. Podocytes are characterized by an elaborate actin cytoskeleton and associated proteins such as nephrin, podocin, synaptopodin and podoplanin. With the cell body lies freely exposed within the Bowman's space, podocytes anchor on the GBM-covered capillary loops through primary processes that branch into foot processes and form slit pore junctions by interdigitating with foot processes from adjacent podocytes. Slit pore junctions restrict the passage of plasma macromolecules into Bowman's space (Figure 1C) [56]. The low/absent mitotic activity, large cell body, location in Bowman's space and vulnerability to tensile stress and FFSS make intact podocytes a critical but fragile component of the glomerular barrier function [57,58].

Recent reports from others have emphasized the significance of podocyte vulnerability to persistent capillary stretch and FFSS. Kritz and Lemley observed that capillary stretch is largely experienced at slit junctions between foot processes. In parallel, the cell body and primary processes of podocytes provide large area for sensing and transmitting the effects of FFSS which causes structural and functional changes within the cells. Increased biomechanical forces associated with hyperfiltration may contribute to podocyte detachment [59].

(A) Potential temporal difference in tensile stress and FFSS

Based on results from cell culture and animal models we have proposed that shear stress on podocytes due to increased ultrafiltrate flow is an important component of hyperfiltration-induced glomerular injury [4,25,33,60]. Thus, hyperfiltration can be visualized as a continuum with its early effects mediated by shear stress due to increased ultrafiltrate.

Persistent increase in tensile stress gradually overcomes impedance posed by the GBM and increasingly adds to the effects of hyperfiltration [Figure 3]. Other investigators have also emphasized the significance of shear stress in damage and loss of podocytes [59,61]. It is noteworthy that children born with a solitary kidney generally develop hypertension, albuminuria and/or decreased eGFR during late adolescence/young adulthood suggesting that FFSS drives the early loss of glomerular function in these children.

Such observations raise the possibility that early effects of hyperfiltration in some conditions may be largely due to effects of FFSS on podocytes. Endothelial fenestrae and GBM may, in part, dampen the transmission of capillary stretch before it reaches podocytes. Thus, capillary stretch during early hyperfiltration may cause insignificant tensile stress to

podocyte structures covering the capillary. This would imply that tensile stress makes a significant impact on podocytes only at later stages when capillary stretch overcomes the impedance posed by the GBM.

(B) Effects on podocyte morphology and proteins

Studies using cultured podocytes have begun to shed light on the differences between the mechanism(s) involved in the cellular effects of tensile stress and FFSS. Briefly, tensile stress decreases transverse actin fibers and increases radial fibers [57]. Tensile stress was shown to upregulate the expression of secreted protein acidic and rich in cysteine (SPARK i.e. Osteonectin) [62] and, of osteopontin [63,64]. Both proteins are mechanoprotective and decrease cell detachment caused by tensile stress. Cell stretch induces signaling by p38 MAPK, ERK1/2 and JNK but not AKT and GSK3β [21,62, 64–68]. These observations require further investigation to confirm the role of and interaction(s) among signaling molecules.

In contrast, actin cytoskeleton forms a cortical ring structure in podocytes exposed to FFSS [33]. We also detected increased PGE$_2$ in FFSS-treated podocytes that was blocked by indomethacin [33]. FFSS increased COX-2 expression without altering COX-1 expression. However, FFSS resulted in upregulated the expression of EP$_2$ but not EP$_4$ [60].

(C) Effect on glomerular protein permeability

Podocytes are key constituents of the filtration barrier and changes in cellular structure would be reflected in filtration barrier characteristics. We used an *in vitro* assay to assess the effect of FFSS on glomerular albumin permeability as an indicator of filtration barrier characteristics. Further work to determine a direct effect of FFSS on intact glomerular filtration barrier showed increased albumin permeability in isolated glomeruli following FFSS [25]. These findings are in accordance with previously reported increase in albumin permeability in glomeruli incubated with PGE$_2$ [69]. Recent updates show that COX2-PGE$_2$-EP$_2$ axis with the activation of AKT- GSK3β- β catenin and c-src-PLD-mTOR are considered mediators of the effects of FFSS [61].

(D) Effects on signaling mediators

Other investigators showed that tensile stress activates arachidonic acid metabolism through upregulation of COX-2 expression without changing COX-1 expression. Induction of 1–8% stretch caused a small increase in cAMP levels that was enhanced by exogenous PGE$_2$. Parallel experiments showed that addition of PGE$_2$ to cells immediately after stretch also increased cAMP production. Tensile stress increased the expression of EP$_4$ receptor of PGE$_2$ [21,66,67]. Activation of Gq-coupled signaling was also found to result in podocyte injury [68]. These observations support the role of COX-2 and EP$_4$ in tensile stress-induced cellular signaling without an increase in PGE$_2$.

(E) Effects on mouse models

Observations on the role of COX2-PGE$_2$-EP$_2$ pathway using cultured cells and isolated glomeruli were confirmed in mouse models of hyperfiltration. We used two different models of reduced functional nephron mass namely, unilaterally nephrectomized mice and mice

born with low nephron number. Unilaterally nephrectomized sv129 mice as well as Os/+ mice born with low nephron number showed albuminuria and increased glomerular expression of COX-2 enzyme and PGE_2 receptor EP_2 proteins [25,60].

Thus, podocytes respond to tensile stress and FFSS using distinct receptors and signaling mechanisms involving PGE_2. Biomechanical forces have been extensively studied in endothelial cells for their role in homeostasis, vascular remodeling and cardiovascular diseases. Effects of biomechanical forces on endothelial cells summarized in books [e.g. 70, 71] are beyond the scope of this brief discussion. On the other hand, evidence for a role of PGE_2-initiated signaling in mechanotransduction of shear stress in other epithelial cells such as osteocytes in the bone and tubular epithelial cells in the nephron is currently accumulating in parallel with our findings using podocytes.

6. PGE_2 as a mediator of fluid flow shear stress in osteocytes

Osteocytes, epithelial cells derived from osteoblast lineage, are embedded in mineralized bone matrix and function as the major mechanosensory cells in bone tissue. Osteocytes, like podocytes, are terminally differentiated and express podoplanin. Cytoplasmic processes (dendrites) from osteocytes traverse within the canaliculi of mature bone and connect with other osteocytes and with cells on bone surface through adhesion molecules and gap junctions. Computational modeling suggests that FFSS causes greater deformation of intracellular structures compared to stretch in osteocytes [72].

Several molecules/pathways involving nitric oxide [73], ATP [74], intracellular calcium [75] and COX-2 [76] have been identified in osteocyte response to stress. One model outlines a release of PGE_2 via calcium fluxes involving integrins and the cytoskeleton [77]. Another model describes FFSS-induced release of ATP that binds to P2Y and $P2X_7$ purinoceptors resulting in Ca^{+2} mobilization and PGE_2 release, respectively [78].

As with podocytes, the effects of mechanical stretch and FFSS in osteocytes are mediated through distinct pathways [72]. FFSS on osteocytes results in increased production of PGE_2, and increased expression of COX-2 and EP_2 but not EP_4 [79]. FFSS-induced release of PGE_2 activates EP_2 in osteocytes leading to activation of the AKT-GSK3β-β-catenin pathway and, to a lesser degree, of the cAMP-PKA pathway [80–83]. Thus, osteocytes sense mechanical strain and release PGE_2 which acts in a paracrine/autocrine fashion to engage EP_2 followed by GSK-3β phosphorylation and inactivation resulting in increased intracellular β-catenin that is translocated to the nucleus.

Similarities between podocytes and osteocytes in their responses to FFSS suggest that PGE_2-EP_2-Wnt/β-catenin signaling maybe a conserved mechanism for responding to mechanical stress in wider biological systems.

7. PGE_2 as a mediator of flow-induced shear stress in renal tubular cells

As in podocytes, tensile stress and shear stress induce distinct effects on the tubular segment of the nephron. Biomechanical forces secondary to tubular flow regulate sodium and potassium transport in renal epithelial cells [84]. Increased tubular urine flow caused by

diuretics and extracellular isotonic volume expansion causes circumferential stretch and shear stress on tubular cells and induces segment-specific signaling changes. Increased flow in cortical collecting duct results in greater sodium reabsorption and potassium secretion into urine. Circumferential stretch applied to cortical collecting duct decreases PGE_2 release while FFSS increases PGE_2 [85,86]. FFSS but not stretch upregulates COX-2, neutral sphingomyelinase, endothelin, phospho-ERK and phospho-p38 in cortical collecting duct cells [85–89]. Cilia or microvilli act as mechanosensors of shear and alter intracellular calcium resulting in cPLA2 activation [88,90] in renal cortical collecting duct principal and intercalated cells [85,91]. In proximal tubular cells, cyclical stretch results in ERK-dependent release of arachidonic acid [92] and FFSS promotes cytoskeletal re-organization by redistributing stress fibers from the basolateral membrane to apical surface and forming new apical junctional complexes [93,94].

These studies on tubular cells also support the differences in the mechanism of tensile stress and shear stress. Here again, PGE_2 causes a significant change in cellular responses to shear stress. Thus, it is apparent that podocytes, osteocytes and tubular epithelial cells invoke COX2-PGE_2 in response to biomechanical forces. While EP_2-Wnt/β-catenin signaling seem to be critical in podocyte and osteocytes, p38 MAPK and ERK signaling seems to be utilized by tubular epithelial cells. These examples serve to support the occurrence of a common mechanism of cellular response to biomechanical forces in diverse epithelial cells.

8. Hyperfiltration and eicosanoids in kidney disease

Loss of functional nephrons due to developmental defects, hereditary disorders, surgical ablation, kidney donation, acute kidney injury and systemic diseases results in hyperfiltration leading to further damage to and loss of functional nephrons. Thus, adaptive hyperfiltration begets more hyperfiltration and eventually becomes maladaptive and leads to progression of CKD (Figure 4). Glomerular hyperfiltration is considered to be a major factor in renal injury from diabetes, hypertension and obesity, and a contributing factor in secondary focal segmental glomerulosclerosis [19]. The following paragraphs summarize the significance of hyperfiltration and eicosanoids in animal models and human diseases.

Animal models are commonly used to study the effect of hyperfiltration on glomerular function and renal disease. Several factors such as genetic characteristics, experimental gene manipulations, target cells and surgical manipulations need to be considered for selecting appropriate models to study expression and function of each receptor type [95–98]. Rat and mouse models have been used extensively to determine changes in arachidonic acid metabolism in models of acute and chronic kidney diseases. Synthesis of PGE_2, prostacyclin (PGI_2) and expression of COX-2 are increased in animal models of glomerular hyperfiltration, including subtotal nephrectomy [1,99–107], high protein intake [108,109], diabetes [110–116], hypertension [1,113,117] and obesity [109, 118–120]. A recent review suggests that microsomal prostaglandin E synthase (mPGES-1) contributes to reduction in renal function, urine concentrating ability and elevation in BP [121]. Renal function may also be affected by treating many of the conditions mentioned. For example, sodium glucose co-transporter 2 (SGL T2) inhibitors used for treating type 2 diabetes may benefit renal function through a slight reduction in blood pressure [122].

(A) Congenital anomalies of the kidney and urinary tract (CAKUT)

Hyperfiltration appears to be the main reason of initial progression of CKD in children born with a solitary kidney or other CAKUT. Between 20% and 40% of children born with a solitary kidney develop ESRD as young adults, with manifestations of renal injury starting only at ~15 years of age [123,124]. Preliminary work in our laboratory using liquid chromatography-mass spectrometry analysis showed increased urinary PGE_2 (p=0.14) and decreased PGI_2 (p=0.04) in this small group of children with a solitary kidney (Table 1).

(B) Surgical resection resulting in solitary kidney

Fifteen healthy humans had a significant increase in GFR, effective renal plasma flow (ERPF), urine flow, sodium and potassium excretions, urinary excretion rate of PGE_2 and 6-keto prostaglandin F1 alpha (6-keto PGF1 alpha) in the remaining kidney (p<0.01) at 10 days after unilateral nephrectomy. Indomethacin administered at 75 mg/day for 3 days abolished the increase in GFR, ERPF and sodium excretion with reduced urinary excretion rate of PGE_2 and 6-keto PGF1 alpha but not the increase in urine flow and potassium excretion. These findings suggest that renal prostaglandins may play a role in renal functional adaptation following unilateral nephrectomy [125].

(C) Kidney donors

Approximately a third of all renal transplants are obtained from living donors [126]. Currently there are ~50,000 individuals who have donated one kidney and their number increases each year by ~5000 [127,128]. Kidney donors have increased risk of developing end stage renal disease (ESRD) with a median period of ~15 years after kidney donation [129]. This suggests that the conditions remain benign for a long time and that younger donors (<35 years) would be at a greater lifetime risk for ESRD [130,131]. Likewise, hyperfiltration would be a key determinant of long term outcome of renal function in transplant recipients who face additional risk due to potential adverse effects of post-transplantation medications.

Examples from animal studies and observations in human subjects suggest that eicosanoids play a role in mediating the effects of biomechanical forces associated with hyperfiltration that remains a serious challenge in the management of kidney disease.

9. Amelioration of hyperfiltration-induced glomerular dysfunction

COX inhibitors, prostanoids or their analogs have been used for minimizing the effect of hyperfiltration in different settings including hypertension and diabetes.

(A) Treatments to modulate prostanoid levels

Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce intractable proteinuria [132]. However, NSAIDs also cause loss of renal function. Therefore, these drugs are not popular as first or second line of treatment. Proteinuria is reduced by COX inhibition from NSAIDs drugs, and this improvement is associated with decreased PGE_2 excretion [133,134]. NSAIDs that reduce renal PGE_2 excretion also decrease proteinuria, whereas sulindac which does not influence PGE_2 levels has no impact [135–137].

Prostacyclin analog Beraprost-Na delayed the doubling of creatinine in 5/6 rat nephrectomy model [138], anti-GBM model [138,139] and has a possible effects in humans with chronic glomerulonephritis [140]. Urinary PGI_2 showed no relationship with the development of hemolytic uremic syndrome and was not protective [141]. PGE_1 infusion reduced albuminuria and proteinuria in diabetic nephropathy in six studies included in Cochrane Review [142]. PGE_1 infusion was not helpful in 8 adults with CKD [143] or in 9 adults with GN [144] but PGE1 with ACEI was helpful in 52 adults with CKD [145].

(B) Treatments directed at the renin angiotensin aldosterone system (RAAS)

RAAS antagonists are the major class of drugs currently used to treat hyperfiltration-mediated injury in progression of CKD. However, ACEI and ARBs were not effective in delaying the progression of disease in children with CAKUT in ItalKid study [146]. RAAS blockade is also not the standard of care in children with CAKUT as evident from the NIH CKiD study where fewer than 50% of children were on the treatment [147]. Thus, there is a need to further understand the basic mechanism of hyperfiltration that could complement the RAAS-mediated changes from early to late stages of the disease.

10. Summary

Hyperfiltration is considered a common underlying mechanism for progression of CKD associated with a number of diseases. Tensile stress and fluid flow shear stress are biomechanical forces associated with hyperfiltration. The effect of these biomechanical forces on glomerular podocytes and cellular mediators their effects are not clear. ACE inhibitors and ARBs are commonly used as renoprotective drugs to delay progression of CKD. However, these drugs are not favored for treating progression of CKD in children with a solitary kidney or transplant donors where hyperfiltration is the dominant cause of renal dysfunction. Therefore, effects of tensile stress and shear stress on podocytes need to be addressed for a comprehensive approach to treat CKD. Several lines of evidence demonstrate that tensile stress and shear stress invoke distinct mechanisms in podocytes and other cells. In this regard, we have shown that fluid flow shear stress upregulates COX2-PGE_2-EP_2 in podocytes. Similar signaling mechanisms appear to mediate the effect of biomechanical forces in other epithelial cells as well. Further research on tensile and shear stress-induced cellular pathways that address interaction between PGE_2 receptors may lead to identification of additional targets for novel treatments that will complement the current RAAS therapy.

Acknowledgments

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Highlights

- Hyperfiltration is responsible for progression of CKD in several diseases.

- Tensile stress and fluid flow shear stress (FFSS) mediate the effects of hyperfiltration on podocytes.

- Tensile stress and FFSS induce distinct changes in podocytes via separate mechanisms.

- FFSS activates COX2-PGE$_2$-EP$_2$ axis in podocyte, osteocyte and tubular epithelial cell.

- Current therapy does not address podocyte injury that stems from FFSS in early hyperfiltration.
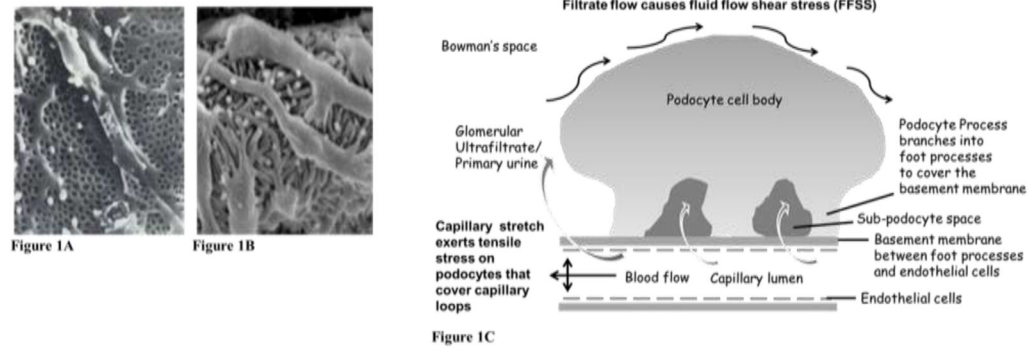
Figure 1.
(A) Luminal aspect of the glomerular capillary showing highly porous sieve-like structure. Capillary endothelial cell lining acts a highly fenestrated porous filter and plasma filtrate moves to podocyte slit junctions through the basement membrane. **(B)** Outer aspect of the glomerular capillary showing branches from podocyte processes. These branches then further branch into foot processes that interdigitate to form slit junctions that tightly cover the capillary surface and restrict the passage of plasma macromolecules into Bowman's space. **(C)** Glomerular hyperfiltration damages podocytes in Bowman's space. Podocytes cover capillary loops by interdigitating foot processes. Blood flow in the capillary causes tensile stress due to circumferential stretch at the capillary bends (biaxial) in the direction of blood flow and at 90° (uniaxial) to the direction of blood flow, while the resulting flow of ultrafiltrate causes fluid flow shear stress.

- Expression: Kidney>lung, spleen, skeletal muscle, testes, brain, heart, eye, distributed in parallel with smooth muscle cells
- Function: Vasoconstriction
- General mechanism: PLCβ activation, PIP2-DAG-IP$_3$, Ca^{+2}release

- Expression: Kidney tubules, gastrointestinal tract neurons, myometrium
- Function: Smooth muscle contraction, constriction of vessels, venules and airway; pain sensation, Duodenal bicarbonate secretion
- General mechanism: cAMP mediated signaling

- Expression: EP$_2$ and EP$_4$ overlap in distribution and function with tissue/cell-specific differences. Vascular smooth muscle, brain, kidney, leukocytes; sclera, corneal epithelium, and choriocapillaries in the eye
- EP$_2$ >EP$_4$ in spinal cord , articular cartilage
- EP$_4$ >EP$_2$ in osteoblasts; corneal endothelium and keratocytes, conjunctival and iridal stroma cells of the eye
- Function: vasorelaxation
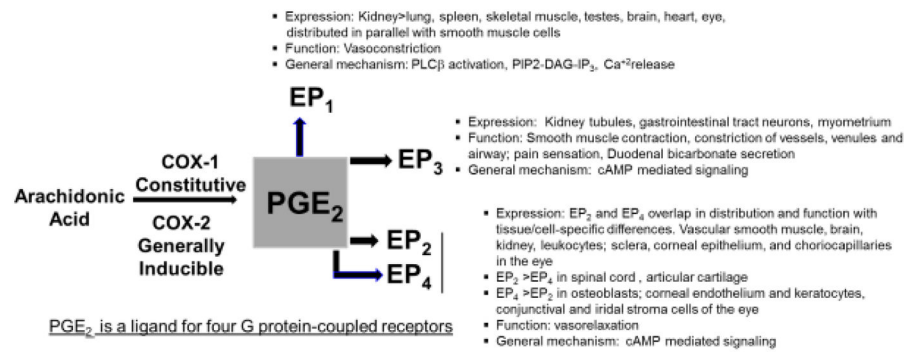- General mechanism: cAMP mediated signaling

Figure 2.
Prostaglandin E$_2$ (PGE$_2$) functions in an autocrine/paracrine manner through the four G-protein coupled receptors. Localization, expression and main signaling pathways of EP$_1$, EP$_2$, EP$_3$ and EP$_4$ are outlined.

Glomerular Filtration Rate

HYPERFILTRATION CONTINUUM

Basal SNGFR	↑ SNGFR	↑↑SNGFR	↑↑↑ SNGFR
Basal tensile stress (σ)	↑ σ	↑↑σ	↑↑↑ σ
Basal shear stress (τ)	↑ τ	↑↑τ	↑↑↑ τ

Loss of podocyte structure and function

In early stages, shear stress due to increased ultrafiltrate flow affects podocytes located in Bowman's space. Capillary pressure that causes circumferential stretch of the capillary wall and GBM to generate tensile stress on podocytes is minimum and increases gradually.

In later stages, increasing capillary pressure raises circumferential tensile stress and podocytes are damaged by both tensile stress and shear stress.
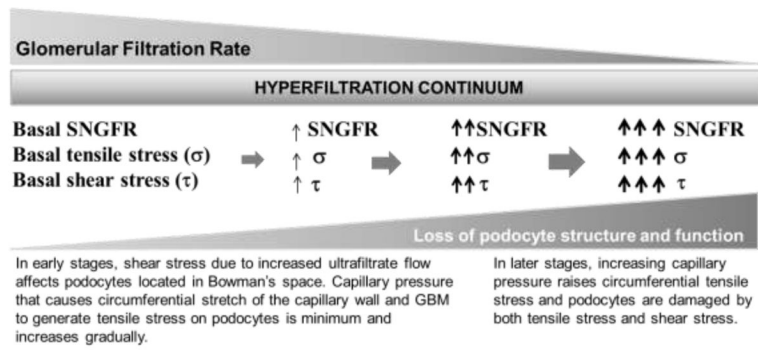
Figure 3.
Hyperfiltration, a result as well as a cause of glomerular dysfunction, can be visualized as a continuum. Overtime, net glomerular filtration rate (GFR) decreases with increasing loss of renal function, but results in increasing single nephron GFR (SNGFR) and increasing injury to podocyte structure and function from increasing tensile and shear as indicated by vertical arrows. Early effects are likely due to increased ultrafiltrate flow which is joined by tensile stress caused by increasing capillary stretch.
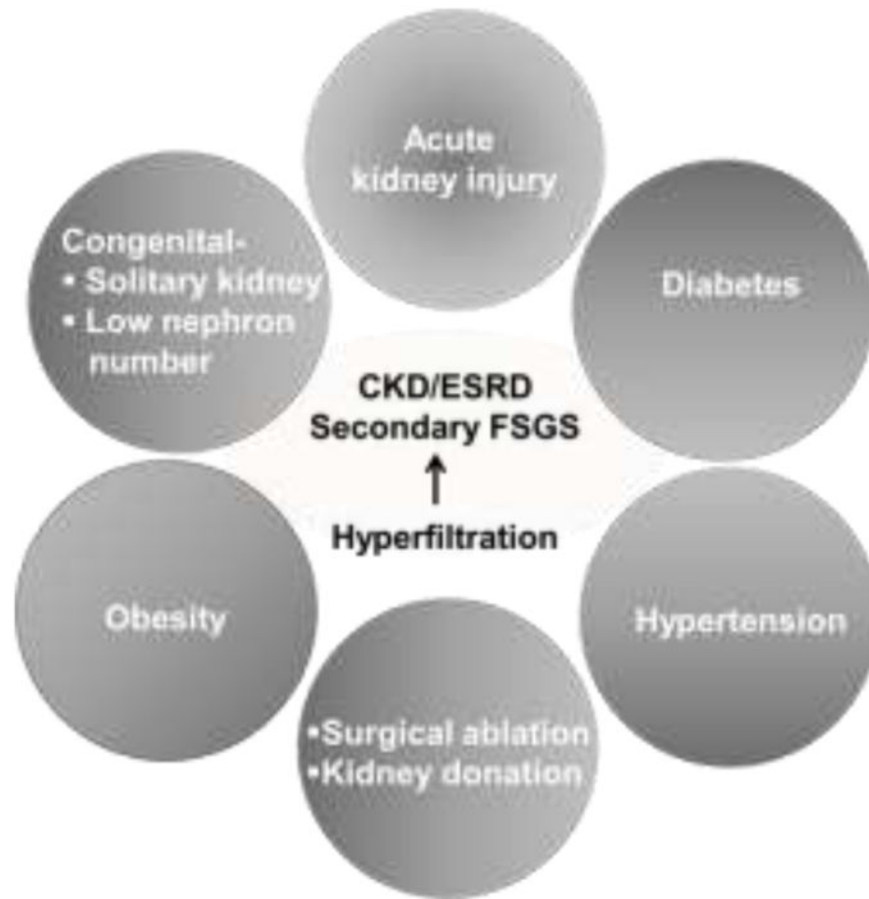
Figure 4.
Reduction in the number of functional nephrons occurs in many conditions and results in hyperfiltration. Hyperfiltration is considered the underlying cause of CKD leading to secondary focal segmental glomerulosclerosis (FSGS) and end-stage renal disease (ESRD). A constellation of diseases result in decreased number of functional nephrons. Congenital anomalies of kidney and urinary tract (CAKUT) including solitary kidney and low nephron number endowment are the main reasons of CKD in children. Unilateral nephrectomy for removing malignant tumors or for kidney donation causes an immediate loss of 50% of nephrons. Diabetes, hypertension or obesity may gradually lead to loss of functional nephrons. AKI due to a variety of causes may result in loss of functional nephrons.

Table 1

Urinary eicosanoids profile is altered at early stages of CKD in children born with solitary kidney

Urine samples from children with solitary kidney with normal kidney function (n=6) and from healthy children who were seen in the clinic for bedwetting (control, n=6) were analyzed. Metabolites of the COX pathway (PGE-M, PGD-M, PGI-M, TXB$_2$-M), LOX (LTE$_4$) and CYP 450 pathway (14,15-DHET, 11,12-DHET, 8,9-DHET, 20-HETE) and isoprostanes were analyzed using LC-MS/MS (ng/mgCr, Mean ± SD). Increased concentration of PGE$_2$ metabolite (*, p=0.14) and lower concentrations of PGI$_2$ metabolite (**, p=0.04) were detected. Increase in 14,15-DHET and decrease in 8-isoprotane in children with solitary kidney was statistically not significant.

	PGE-M	PGD-M	PGI-M	TXB$_2$-M	LTE$_4$
Solitary Kidney (n=6)	8.9 ± 5.7*	2.3 ± 1.2	0.09 ± 0.06**	0.3 ± 0.1	0.07 ± 0.07
Control (n=6)	5.9 ± 2.5	2.0 ± 0.7	0.20 ± 0.11	0.3 ± 0.1	0.06 ± 0.06