Consequences of Glomerular Hyperfiltration: The Role of Physical Forces in the Pathogenesis of Chronic Kidney Disease in Diabetes and Obesity

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Keywords

Obesity · Diabetes mellitus · Shear stress · Tensile stress · Mechanical forces · Hydrodynamic forces · Glomerular hypertrophy · Tubular hypertrophy · Segmental glomerulosclerosis · Diabetes

Abstract

Background: Glomerular hyperfiltration (GH) is a hallmark of renal dysfunction in diabetes and obesity. Recent clinical trials demonstrated that SGLT2 inhibitors are renoprotective, possibly by abating hyperfiltration. The present review considers the current evidence for a cause-to-effect relationship between hyperfiltration-related physical forces and the development of chronic kidney disease (CKD). **Summary:** Glomerular hyperfiltration is associated with glomerular and tubular hypertrophy. Hyperfiltration is mainly due to an increase in glomerular capillary pressure, which increases tensile stress applied to the capillary wall structures. In addition, the increased ultrafiltrate flow into Bowman's space heightens shear stress on the podocyte foot processes and body surface. These mechanical stresses lead to an increase

in glomerular basement membrane (GBM) length and to podocyte hypertrophy. The ability of the podocyte to grow being limited, a mismatch develops between the GBM area and the GBM area covered by foot processes, leading to podocyte injury, detachment of viable podocytes, adherence of capillaries to parietal epithelium, synechia formation and segmental sclerosis. Mechanical stress is also applied to post-filtration structures, resulting in dilation of glomerular and tubular urinary spaces, increased proximal tubular sodium reabsorption by hypertrophied epithelial cells and activation of mediators leading to tubulointerstitial inflammation, hypoxia and fibrosis. **Key Messages:** GH-related mechanical stress leads to both adaptive and maladaptive glomerular and tubular changes. These flow-related effects play a central role in the pathogenesis of glomerular disease. Attenuation of hyperfiltration is thus an important therapeutic target in diabetes and obesity-induced CKD.

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Introduction

Glomerular hyperfiltration (GH) is a hallmark of renal dysfunction in obesity and diabetes mellitus. Obesity-related glomerulopathy and other adaptive nephropathies have been referred to as hyperfiltration nephropathies [1] – a name that emphasises the central role of hyperfiltration in the pathogenesis of these conditions. Recent clinical trials demonstrated that SGLT2 inhibitors abate GH and protect the kidney in diabetic nephropathy. The present review considers the current evidence for a cause-to-effect relationship between hyperfiltration-related physical forces and the development of chronic kidney disease (CKD).

Obesity and diabetes mellitus are associated with increased renal plasma flow, filtration fraction and glomerular filtration rate [2, 3]. The fact that renal plasma flow increases to a lesser extent than glomerular filtration rate implies the presence of renal vasodilation involving predominantly the glomerular afferent arteriole. The assumption that whole-kidney hyperfiltration reflects an increase in single-glomerulus filtration rate was recently confirmed in humans [4]. The structural counterpart of renal hyperfiltration is renal hypertrophy, characterized at the nephron level by an increase in the volume of glomerular tuft, Bowman's space, tubular epithelium and tubular lumen [5, 6].

GH is mainly due to an increase in net filtration pressure. This increased filtration pressure, as well as the consequent increased ultrafiltrate flow rate, affects the filtration barrier as well as post-filtration glomerular and tubulo-interstitial structures. This review will focus on the way by which physical forces engendered by GH lead to glomerular and proximal tubular injury.

The Mechanical Forces at Work on the Filtration Barrier

The physical forces at work in hyperfiltration states arise from 2 different fluid movements affecting the glomerular structures: blood flowing in the glomerular capillaries and ultrafiltrate streaming from capillaries into Bowman's space. These movements lead to mechanical stress on the capillary wall. Stress is calculated as the amount of force per unit area applied to a structure's surface. Two types of stress act on glomerular structures – tensile stress and shear stress [7]: (1) Tensile stress is applied on the capillary wall by blood flowing in capillaries, either as axial stress, that is, a force applied

perpendicularly to an area or as hoop stress, that is, a circumferential stress. Endothelial cells, the glomerular basement membrane (GBM) and podocytes are subjected to tensile stress. Its magnitude is a function of pressure, radius and thickness of the capillary wall; (2) Shear stress results from a force applied in parallel to the surface of the cells. It is applied on endothelial cells by the passage of blood in capillaries and on podocytes by the flow of ultrafiltrate between the podocytes. Its intensity is a function of fluid viscosity, flow velocity and size of the ultrafiltrate column flowing along the podocyte boundaries [8].

Effects of Hyperfiltration-Related Mechanical Forces at the Filtration Barrier

Tensile Stress

An increase in glomerular capillary perfusion pressure and in hydrostatic pressure difference between the glomerular capillary and Bowman's space creates an increased tensile stress leading to immediate increase in GBM length and area [9]. This change in geometry occurs due to elastic expansion of the GBM and recruitment of GBM stored in wrinkles in peri-mesangial areas. This increase in GBM is associated with an increase in length of the podocytes' foot processes and with unchanged filtration slits width. Thus, following acute strain of the GBM, the foot process cytoskeleton is modified in a way that maintains an adequate coverage of the GBM by the foot processes.

Shear Stress

An increase in the ultrafiltrate flow applies tangential forces and increased shear stress to the podocyte at 2 different sites – the foot processes, as ultrafiltrate flows through the filtration slits, and the podocyte's body surface, as ultrafiltrate pursues its way within Bowman's space [7, 9, 10].

As shown by Kriz and Lemley [9], the tensile stress-induced expansion of GBM prompts adaptive podocyte hypertrophy [11] aimed at covering the increased surface of GBM. Since podocytes are unable to divide and since dedifferentiation of glomerular parietal epithelial cells into podocytes is limited, cell hypertrophy is the only way the podocyte can adapt to the increase in GBM length. As the magnitude of podocyte hypertrophy is lower than that of the capillary wall, a mismatch develops between the GBM area and the GBM area covered by foot processes [9]. The podocyte body is stretched,

foot processes are deformed and cell body thinned, with bulging into the urinary space. It has been suggested that the mild to moderate foot process effacement that develops is an adaptive phenomenon improving podocyte adhesion and hindering its detachment [9, 12]. Extensive bare segments of GBM appear with local detachment of podocytes. In normal glomeruli, about 60% of the ultrafiltrate reaches the peripheral glomerular urinary space through sub-podocyte spaces [13]. The resistance to outflow from the sub-podocyte space is high compared to that of the inter-podocyte space. In hyperfiltration states, the fraction of ultrafiltrate flowing through the sub-podocyte space increases, at the expense of flow through inter-podocyte spaces. Both the preferential ultrafiltration through this space and the hypertrophy-induced narrowing of outflow from this space result in increased resistance to outflow and further increased stress on podocytes, leading to pseudocyst formation. These changes lead to podocyte detachment, extensive denudation of the GBM, adherence of the capillary wall to Bowman's capsule, synechia and finally segmental sclerosis [3, 7, 9, 11]. The central role played by hypertrophy mismatch in the pathogenesis of CKD was demonstrated by in vivo models of hyperfiltration [14]. Mechanical stress modifies cell function and structure by mechanotransduction – a process through which cells sense and respond to mechanical stimuli by converting them into biochemical signals that elicit specific cellular responses. The ability of the podocyte to sense mechanical forces that remodel its actin skeleton was first demonstrated by Endlich et al. [15]. Since then, a large number of in vitro studies brought to light the activation of signalling pathways by mechanical stress, among them mitogen-activated protein kinases, prostaglandins, angiotensin II, mTOR and TGF- β , resulting in reorganization of the actin cytoskeleton, dysregulation of integrins expression and cell hypertrophy. A description of the involved pathways can be found in extensive reviews [7, 8, 10, 14].

Effects of Hyperfiltration-Related Mechanical Forces Distal to the Filtration Barrier

GH is associated with increased Bowman's space volume and increased proximal tubular cells and lumen volume [6]. Glomerular urinary space expansion – the structural corollary of hyperfiltration – is the result of increased pressure and flow causing mechanical stress on post-filtration structures.

Effects of Hyperfiltration on the Parietal Layer of Bowman's Capsule

Tensile stress applied to the parietal layers of Bowman's capsule is increased as a consequence of the increased Bowman's space hydrostatic pressure and the increased distance between podocytes and parietal epithelial cells. Shear stress is increased as a consequence of the increase in ultrafiltrate flow velocity. The effects of stress on parietal epithelial cells have not been demonstrated. However, considering the role played by these cells as a source of recruited podocytes and as a barrier preventing periglomerular ultrafiltrate leak, it is possible that mechanical stress-induced dysfunction of these cells contributes to the progression of hyperfiltration nephropathy.

Effects of Hyperfiltration on the Proximal Tubular Epithelium

Flow-Related Increase in Sodium Reabsorption

The increased proximal tubular ultrafiltrate flow rate entailed by GH causes an increase in shear stress on the tubular epithelium [16]. The expansion of the tubular urinary space [6] implies an elevated tubular wall tensile stress. Thus, both tensile and shear stress act upon tubular structures in hyperfiltration states. The elevated shear stress applied on proximal tubule microvilli creates a rotational force (torque), which is transmitted to the brush border cytoskeleton, generating biochemical signalling that activates the luminal NHE3 transporter and the basolateral Na⁺/3HCO₃ cotransporter [16]. The resulting increase in sodium reabsorption is made possible by the increased number and density of luminal and peritubular sodium transporters in hypertrophied tubular epithelium [16] and by the GH-induced increase in peritubular capillary oncotic pressure [17]. A consequence of the enhanced fractional proximal reabsorption of sodium in diabetes and obesity is a decreased delivery of solutes to the macula densa that prompts deactivation of the tubuloglomerular feedback and ensuing GH [18, 19]. Thus, the combination of an increased flow-mediated torque effect on microvilli and an increased density, in part flow-related, of sodium transporters in hypertrophied renal proximal tubules, plays a central role in the development of hyperfiltration. This creates a self-perpetuating system, where hyperfiltration and the consequent increased proximal tubular flow apply physical forces that increase sodium reabsorption and deactivate tubuloglomerular feedback, thus maintaining GH. The increased tubular flow and tubular reabsorption initiates fibrinogenesis [20]. In addition, the enhanced proximal sodium transport load and

consequent elevated oxygen consumption may be one of the mechanisms contributing to renal hypoxemia, oxidative stress, inflammation and fibrosis [18, 21]

Increased Proximal Tubular Reabsorption of Small Organic Solutes

In addition to the direct effect of flow-mediated shear stress, GH affects tubular function by increasing the filtered load of organic solutes and their delivery to the proximal tubule. The increased load of reabsorbed amino acids induces tubular growth by activation of mTORC1 [22]. The increased delivery of glucose leads to increased reabsorption by upregulated glucose transporters [18, 23]. Glucose uptake results in the inhibition of AMPK that drives tubular growth, lipid accumulation and activation of PKC, mTOR pathway and TGF- β [18, 24]. These molecular pathways lead to tubular hypertrophy, lipid cytoplasmic inclusions, tubulo-interstitial inflammation, hypoxia and fibrosis [18, 24, 25].

Decreased Proximal Tubular Reabsorption of Albumin; Early Stage

Albuminuria may increase at early stages of renal involvement in diabetes and obesity to the so-called microalbuminuric range – 30 to 300 mg/day. This increase in albumin excretion may be accounted for by an increase in proximal tubular flow resulting in impaired physiologic proximal tubular reabsorption [26]. An increased tubular flow secondary to GH lowers the contact time between protein and tubular epithelium and generates an increased radial gradient of albumin concentration within the tubule lumen, resulting in reduced albumin reabsorption that may occur without evidence for glomerular dysfunction. Thus, the administration of pharmacologic agents that ameliorate GH may reduce albuminuria owing to decreased tubular flow rate and not to an improvement in glomerular permselectivity.

Increased Proximal Tubular Reabsorption of Proteins: Advanced Stage

GH induces an increase in glomerular permeability that markedly enhances the delivery of proteins to the tubular epithelium, among them protein-bound lipids, cytokines and growth factors. The resulting excessive reabsorption of proteins promotes apoptosis, renal oxidative stress, inflammation, hypoxia, lipid accumulation and tubulo-interstitial fibrosis [27].

The tubular flow rate flowing out the proximal tubule plays a physiological regulatory role on distal tubular epithelial cell function [28]. It should be pointed out that the

flow rate delivered to the loop of Henle in diabetes and obesity is variable, being decreased [29], normal or increased [calculated from 17], depending on the magnitudes of increase in GFR and proximal reabsorption. We refer to a review on distal hydrodynamic effects of tubular flow [16] and to a modelling analysis of distal adjustment to GH [28].

Therapeutic Implications; Targeting GH in Diabetes and Obesity-Related CKD

The identification of the mechanisms that causally link GH to kidney damage provides a rationale for targeting GH in the treatment of diabetes and obesity-induced CKD. Non-specific antihypertensive agents and agents reducing the activity of the renin-angiotensin-aldosterone system have been used for decades to decrease glomerular pressure. Recent clinical studies showed that decreasing proximal reabsorption of glucose and sodium by SGLT2 inhibition improves GH and slows the progression of diabetic CKD [19]. The glomerular and tubular hemodynamic and hydrodynamic effects of SGLT2 inhibition play a major role in the afforded renoprotection. Inhibition of proximal tubular reabsorption abates GH in obese non-diabetic subjects [30]. Thus, SGLT2 inhibition could theoretically have a renoprotective effect in obesity-induced GH.

Conclusions

GH-related physical forces play a central role in the pathogenesis of CKD in diabetes and obesity by applying mechanical stress on the filtration barrier and on post-filtration structures. This leads to podocyte loss and focal segmental glomerulosclerosis. The increased proximal tubular flow ensuing from GH increases the delivery and reabsorption of small and large molecular weight solutes with ensuing hypertrophy, tubulointerstitial inflammation and fibrosis. Attenuation of hyperfiltration is thus an important therapeutic goal in diabetes and obesity-induced proteinuric CKD.

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