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Glomerular Filtration Barrier and Mechanism of Proteinuria

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Abstract

The first step in urine formation is the filtration of large amounts of fluid through the glomerular capillaries into Bowman's capsule. It is around 180 liters per day. Most of this filtrate is reabsorbed leaving only about 1 liter of fluid to be excreted each day. Glomerular capillary wall (GCW) or glomerular filtration barrier (GFB) were coined during 1950. The GCW consists of three distinct but closely interacting layers: the fenestrated endothelium, with its glycocalyx; the podocytes, with their interdigitated foot processes and slit diaphragm; and the intervening glomerular basement membrane (GBM). Proteinuria is associated with kidney disease and cardiovascular mortality. It can be categorised as glomerular, tubular and overflow proteinurea.

Keywords: Glomerular capillary wall (GCW); Glomerular filtration barrier (GFB); Proteinuria.

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Introduction

The first step in urine formation is the filtration of large amounts of fluid through the glomerular capillaries into Bowman's capsule. It is around 180 liters per day. Most of this filtrate is reabsorbed leaving only about 1 liter of fluid to be excreted each day.[1] Glomerular capillary wall (GCW) or glomerular filtration barrier (GFB) were coined during 1950.[2]

Glomerular Filtration Barrier/Glomerular Capillary Wall

The GCW consists of three distinct but closely interacting layers: the fenestrated endothelium, with its glycocalyx; the podocytes, with their interdigitated foot processes and slitdiaphragms; and the intervening glomerular basement membrane (GBM).[1] Data generated over decades suggest that normal macromolecular filtration requires the contribution of all three layers of the GFB:Endothelium, GBM and a layer of Podocytes.[3]

Glomerular Capillary Endothelium

It is fenestrated and has a role in determining protein sieving. The fenestrae are too large to form any meaningful barrier and lack a diaphragm. The luminal surface has glycocalyx forming negatively charged coat that covers the fenestrae with plugs. These are central for charge selectivity. Pre-eclampsia/eclampsia and Diabetic nephropathy are the classic proteinuric diseases associated with endothelial dysfunction.[3]

Golmerular basement membrane

It is composed of three layers viz. Lamina rara interna (LRI) which consists of sulfated proteoglycans, Lamina densa (LD) consisting of Type IV collagen (COL4) and laminin, and Lamina rara externa (LRE).[3]

Podocytes with foot process and slit diaphragms

These are highly specialized epithelial cells of mesenchymal origin. Surface of podocytes is covered by anionic glycocalyx, constituted by podocalyxin. Podocytes are characterized by foot processes which interact at specialized cell-to-cell junctions called slit diaphragms.[3]

Slit diaphragm consist of multiple layers of nephrin strands connecting adjacent foot processes (FPs). Pores within this meshwork form elongated channels. In Nephrin mutation, the slit pores become narrower with shorter, thinner, less organized strands bridging adjacent FPs and forming relatively larger pores and channels. Slit diaphragm is located most distally in the GFB and unlikely to function as restrictive barrier. Proteinuria has also been reported in the absence of FP and SD changes.[3]

Glomerular sieving coefficient (GSC)

The GSC is the ratio of a molecule concentration in Bowman's space to that in plasma. As albumin is the most abundant plasma protein, albuminuria is one of the most important signs of glomerular disease.Determining albumin's GSC is central to understanding the GFB.[4]

Controversies regarding glomerular filtration barrier

The controversies related to glomerular filteration barrier revolves around (1) the size verses charge selectivity (2) the Slit Diaphragm verses Glomerular Basement Membrane as predominant albumin barrier and (3) the Glomerular barrier verses Tubular reabsorption.[4]

Size vs. charge selectivity

The existence of size selectivity is universally accepted. Studies done with inert tracers such as Ficoll and dextran indicate that the Glomerular Sieving Coefficient (GSC) is inversely related to molecular weight and radius. Negatively charged dextran was more restricted than neutral dextran, which was more restricted than positively charged dextran of similar size[4]

Charge selectivity is not universally accepted and has been challenged by different workers. As reducing fixed anionic charge sites in the GBM by more than 50% has no consequences on urinary albumin concentration[4].

Slit Diaphragm vs. Glomerular Basement Membrane

The interaction between α3-β1 integrin and β-2 lamininis important for normal podocyte-GBM function. Activation of α3-β1 integrin results in recruitment of a integrin-linked kinase (ILK). When ILK is deleted in a podocyte the proteinuria developed with foot process effacement and glomerulosclerosis[4]

On the other hand, blocking (Transforming Growth Factor)TGF-β1 or adriamycin induced activation of ILK preserved podocyte and ameliorated albuminuria. Together, these findings suggest that the regulation of α3-β1 integrin/ILK may be important in optimal podocyte and GFB function[5].

Glomerular barrier vs. Tubular reabsorption

Mechanism of protein filtration

As per "Gel Permeation/Diffusion Hypothesis" laid down by Oliver Smithies, diffusion through the GBM, is the predominant force governing macromolecular movement through the GFB. Diffusion is independent of fluid flow (i.e., GFR), but dependent on the gel's properties. According to this hypothesis, increased protein concentration in the glomerular filtrate can occur by two different pathways.[6]

The first is by an increase in the rate of passage of protein by changes in the gel's properties (i.e. by alterations to the GBM and perhaps also to the endothelial glycocalyx).[6]

The second is by reduction in the available surface area for filtration, as occurs either with FP effacement or reduced endothelial fenestration. The increased protein concentration in the filtrate then overwhelms the tubular reabsorption capacity, resulting in albuminuria.[5]

Role of tubular absorption

There is significant post glomerular processing of albumin by tubules. 94% of the filtered albumin is absorbed by proximal tubules. Studies concluded that proteinuria is a tubular rather than a glomerular disorder[5].

Proteinuria

Urinary protein excretion in the normal adult humans is less than 150 mg/day[7]. Proteinuria is associated with kidney disease and cardiovascular mortality[8].

It can be Glomerular due to impairment of the glomerular filtration apparatus, tubular due to diminished tubular reabsorption of low molecular weight proteins and overflow when large loads of filtered proteins exceeds resorbptive capacity[5].

Glomerular proteinura can be categorized as Non pathological and Pathological. The Non pathological proteinuria is further divided into transient and orthostatic.[5]

Transient proteinuria occurs in patients with normal renal function with bland urine sediment and normal blood pressure. The quantitative protein excretion is less than 1 g/day. The proteinuria is not indicative of significant underlying renal disease. This is precipitated by high fever or heavy exercise.[9]

Orthostatic proteinuria means no proteinuria in early morning samples but low-grade proteinuria at the end of the day. Usually occurs in tall, thin adolescents or adults younger than 30 years. Patients have normal renal function and proteinuria usually is less than 1 g/day with no hematuria[5].

Pathological proteinuria can be categorized by protein quantity into Non-nephrotic proteinuria i.e. proteinuria <3.5 g/24 h and Nephrotic proteinuria i.e. proteinuria >3.5 g/ 24 h.[5]

Tubular proteinuria occurs most commonly in disease processes affecting the tubulo-interstitial component of the kidney. It comprises low molecular weight proteins such as beta-2 microglobulin, which in normal conditions are completely reabsorbed by proximal tubules. The amount of proteinuria is <2 g/ 24 h and dipstick test may be negative[5].

Overflow proteinuria is associated with increased production of abnormal low molecular weight proteins (eg. light chains in multiple myeloma, myoglobin in rhabdomyolysis) that exceeds the reabsorption capacity of the tubules, leading to spilling of the protein into the urine. These low molecular weight proteins can be toxic to the tubules and can cause acute kidney injury.[5]

Conclusion

It is concluded that the GFB as a functional unit consists of three different elements. It is suggested that it should be viewed as a dynamic sieve, rather than as physically inert. Normal GFB function requires not only three intact GCW layers, but also a hemodynamic steady state in the glomerular capillary and the urinary spaces. A change in any factor (GBM, cell, glycocalyx, local GFR, or plasma albumin concentration) will alter albumin's concentration in the primary filtrate. When the level of albumin in the filtrate exceeds the tubular absorption threshold, albuminuria will ensue.

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