State of the Art

GLOMERULAR HYPERFILTRATION – CAUSES AND CONSEQUENCES

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ABSTRACT:

An incipient phase of supernormal glomerular filtration rate (GFR) often heralds diabetic kidney disease (DKD) and many other chronic nephropathies. We review the various definitions set for glomerular hyperfiltration (GH) and the concept of renal functional response induced by haemodynamic and/or metabolic stimuli. The clinical applications and limitations for testing of this response are alluded to. The causes of GH are discussed as perturbations of the physiologic mechanisms that control GFR, emphasizing the unique location of the glomerulus between two sets of resistant arterioles. DKD is discussed as a standard example for the role of GH in initiation and progression of the renal insult. The differences between physiologic and pathologic GH are explored and the morbid consequences of persistent GH are explained. GH is an early pathogenetic alteration in a divergent spectrum of renal disorders whose timely recognition and management might help retard occurrence and progression of chronic kidney diseases

Keywords: *Glomerular filtration rate, glomerular hyperfiltration, renal functional reserve, renal plasma flow, chronic kidney disease.*

INTRODUCTION

The daily filtration of about 180 litters of virtually protein- free fluid from plasma is the hallmark of the kidney`s excretory function and the initial step in urine formation. The glomerular filtration rate (GFR) measured in milliliters per minute (mL/min) and normalized for a presumed average adult body surface area is usually regarded as the best overall global indicator of renal function in health and disease. As per K/DOKI guidelines, [1] persistence of either evidence of kidney damage or low GFR (< 60 mL/min/1.73m2) for > 3 months is indicative of chronic kidney disease (CKD), with lower values denoting more advanced stages, and values < 15 mL/ min/ 1.73m2 denoting end- stage renal disease (ESRD) and the need for renal replacement therapy. Many acute and chronic kidney disorders, however, are heralded by a phase of supernormal glomerular filtration, that may involve some or all nephron units. Glomerular hyperfiltration (GH) has been regarded as an important pathophysiologic alteration whose early recognition and timely management constitute integral components of current standard nephrology care. [2]

Definition

Contrary to the established definition and classification of CKD based on GFR reduction, a generally accepted definition for GH is lacking and thresholds ranging from 125 to 175 mL/min/1.73m2 were described. [2] Conventionally, GH can be defined as GFR exceeding 2 standard deviations above mean GFR of the healthy population, which means GFR > 130 mL/min/1.73m2 for men and > 140 mL/min/1.73m2 for women. [3] Such definitions do not consider the age- related decline of GFR nor the differences in single nephron GFR (SNGFR). Metabolic and neurohumoral stimuli that prevail in diabetic kidney disease (DKD) and many other chronic nephropathies may enhance filtration in some single nephrons with an overall decrease of the whole kidney or global GFR (GGFR). [2] The issue is further complicated by intra- and inter- day GFR fluctuations and inaccuracy of available serum creatinine based GFR estimates. [4] A staging system for the degree of hyperfiltration based on whole kidney GFR was suggested by some authors [5], but has not gained wide acceptance.

Alternatively, GH may be defined by an increased filtration fraction (FF) (the ratio of GFR to effective renal plasma flow, RPF). [6] An increased FF is presumed to indicate increased

glomerular capillary hydraulic pressure (PGC) which is a key factor in GH- mediated progressive nephron damage[.(2)]

Pathophysiology

The glomerular capillaries are unique in having extremely high hydraulic conductivity and in being arranged in series between 2 sets of resistant arterioles (afferent and efferent glomerular capillaries). The Starling forces that govern fluid movement from the glomerular capillaries to the Bowman`s capsule are conceptually similar to those in other vascular beds[(7,8)] (Fig. 1). So, at the single nephron level (single nephron GFR):

$$SNGFR = Kf \times PUF$$
$$= Kf \, (\Delta P - \Delta\Box) \, , \text{ where}$$

P_{UF}	Net ultrafiltration pressure	
K_f	glomerular ultrafiltration coefficient $= K \times S$, where:	
	K : hydraulic permeability of the filtration barrier	S : effective filtration surface area
ΔP	transcapillary hydrostatic pressure gradient $= P_{GC} - P_{BC}$, where:	
	P_{GC} : glomerular capillary hydraulic pressure	
	P_{BC} : Bowman`s capsule hydraulic pressure	
$\Delta\pi$	transcapillary oncotic pressure gradient $= \pi_{GC} - \pi_{BC}$, where:	
	π_{GC} : oncotic pressure of fluid in glomerular capillaries	
	π_{BC} : oncotic pressure of fluid in Bowman`s capsule	

So;

$$SNGFR = K_f \, [(P_{GC} - P_{BC}) - (\pi_{GC} - \pi_{BC})]$$

Since π_{BC} is normally almost zero:

$$SNGFR = K_f \, (P_{GC} - P_{BC} - \pi_{GC})$$
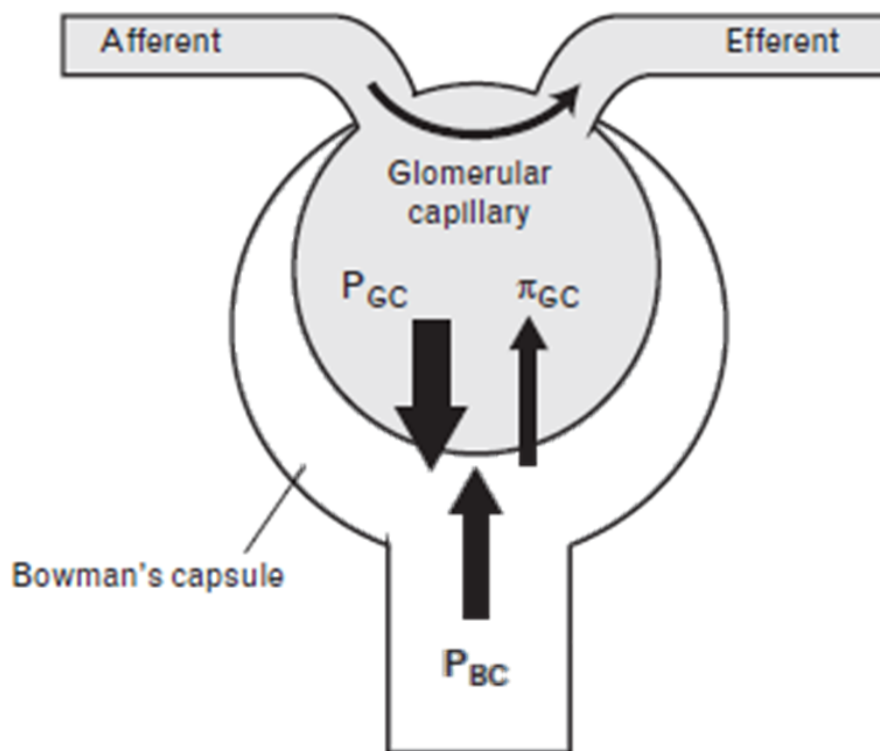
Net Filtration Pressure $= P_{GC} - \pi_{GC} - P_{BC}$

$$= 60 - 30 - 15 \approx 15 \text{ mmHg}$$

Fig. (1): Determinants of net glomerular filtration pressure.[(8)]

The whole process of glomerular filtration is dependent on provision of the kidney with an adequate rate of RPF. Therefore, in theory, an increase in GFR might result from one or a combination of the following factors:[7]

- ↑ RPF: Micropuncture studies in rats have demonstrated that glomerular plasma flow is the most important determinant of GFR.[9] In normal conditions, an increase in renal plasma flow or an increase in hydraulic pressure in preglomerular vessels is offset by a set of automated renal responses that tend to maintain GFR constant and are collectively known as renal autoregulation. An early myogenic and a later tubular response are the main components of this autoregulation.[10]

- ↑ K_f This might result from an increase in hydraulic conductivity of the glomerular filtration barrier (K) and/or its effective surface area (S): It is postulated that mesangial cells are the glomerular capillary equivalent to smooth muscle cells and that they contract and relax in response to various humoral regulatory factors and medications, as for example, contraction in response to angiotensin II (AII) and relaxation in response to natriuretic peptides.[11] It is postulated that mesangial contraction decreases the GFR by decreasing K_f through a decrease in capillary surface area and capillary permeability. Relaxation would have the opposite effects. So, reduced glomerular contractility in early diabetes, may lead to significant glomerular enlargement and hyperfiltration.[12] Another mechanism for increasing the surface area available for filtration at the whole kidney level is the redistribution of renal blood flow so that previously "dormant" nephrons are recruited.[13]

- ↑ P_{GC}: An increase in P_{GC} (glomerular hypertension) is the most significant proximate pathophysiologic mechanism for GH. Changes in P_{GC}, as governed by relative changes in afferent and efferent glomerular arteriolar resistances, are usually responsible for fine tuning GFR and most of its short and long-term changes. Glomerular hyperfiltration and glomerular hypertension are thus 2 closely linked phenomena and occur together in most instances, with some few exceptions. For example, the physiologic hyperfiltration of pregnancy is not associated with glomerular hypertension, because both afferent and efferent arterioles are dilated and FF is reduced.[14] In high altitude renal syndrome (HARS), glomerular hypertension is intended to preserve GFR by increasing the FF from a reduced effective RPF (GFR = FF × RPF). GFR is not increased.[15]

A garden hose with side holes is a simple illustrative model for the differential effects of afferent and efferent arteriolar constriction on P_{GC} and, consequently, on GFR (Fig. 2). [16] Afferent and efferent dilatation would be inferred to have the opposite effects. It should be noticed that changes in afferent arteriolar resistance change both RPF and GFR in the same direction and thus the FF remains practically unchanged. Changes in efferent arteriolar resistance, on the other hand, produce changes in RPF and FF that are opposite to each other. Some typical examples of humoral or pharmacologic factors causing alterations in glomerular arteriolar resistance are the vasodilator prostaglandins causing afferent vasodilatation (VD) and the non- steroidal anti-inflammatory drugs (NSAIDs, anti- prostaglandins) and calcineurin inhibitors causing afferent vasoconstriction (VC). AII is a potent vasoconstrictor with a much higher (10 – 100 times) affinity for efferent over afferent arterioles.[7] Antagonists of the rennin angiotensin aldosterone system (RAS) are widely used to antagonize this action and produce efferent VD, including angiotensin converting enzyme inhibitors, AII receptor blockers and direct rennin antagonists.[16]

- ↓ P_{BC} or ↓ π_{GC}: A decrease in the hydraulic pressure of fluid in Bowman`s capsule and the proximal renal tubule and a decrease in the oncotic pressure of fluid in the glomerular capillaries may possibly contribute to an increase in GFR, but these factors alone are probably of little significance. Changes in oncotic pressure do not appear to be an important factor in the physiologic regulation of GFR. Indeed, π_{GC} tends to increase if GFR is increased for any reason and this would partially offset the GFR increase, thus constituting an additional mechanism of GFR autoregulation.[7, 10]

In most physiologic and pathologic circumstances, alterations in several parameters affecting GFR are concomitant and closely inter- related. These may be additive or offsetting and the final effects on glomerular hemodynamics and GFR depend on their interaction and on the other prevailing factors.[2]

Etiology
GH may be physiologic, pathologic, or stimulated (induced) within controlled conditions to test for renal function reserve (RFR) (Fig. 3). The distinction proposed in table (1) between the typical characteristics of physiologic and pathologic GH may provide a useful framework to understand their causes and consequences, though such a distinction might not be clearly applicable in many clinical situations.

Physiologic GH
- *Protein Meal*
An increase in protein intake was associated with increased GFR in both short- term and long- term studies.[17] Numerous mechanisms are involved in dietary protein- induced GH, [18] including:
− Increased glucagon secretion from the pancreas. Glucagon induces direct dilatation of the afferent arterioles.[19]
− Increased insulin- like growth factor-1 (IGF-1) secretion from the liver. IGF-1 is a potent vasodilator of the renal vessels. Normally, > 99% of plasma IGF-1 is protein- bound. The binding protein level is decreased after protein ingestion, thus increasing its bioavailability.[20]
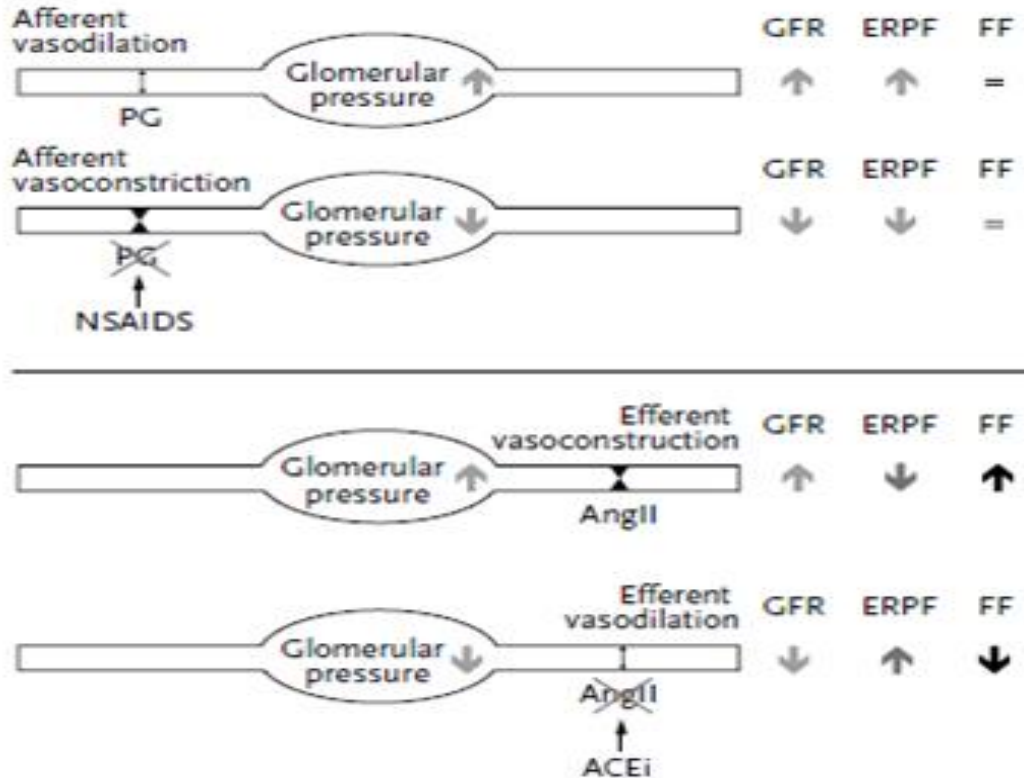
Fig. (2): Effects of periglomerular vasomotor changes on glomerular pressure.(16)

PGC ↑ by afferent dilatation and/or efferent constriction.

AII produces VC of both afferent and efferent arterioles, but the efferent arteriole has 10 – 100 fold greater sensitivity to AII, leading to a net significant increase of PGC

NO and vasodilator prostaglandins inhibit the vasoconstrictor effect of AII on afferent but not efferent arterioles. The production of vasodilator prostaglandins in afferent arterioles is increased by AII, generating another mechanism for the selective constriction of efferent arterioles and increasing PGC in response to AII.
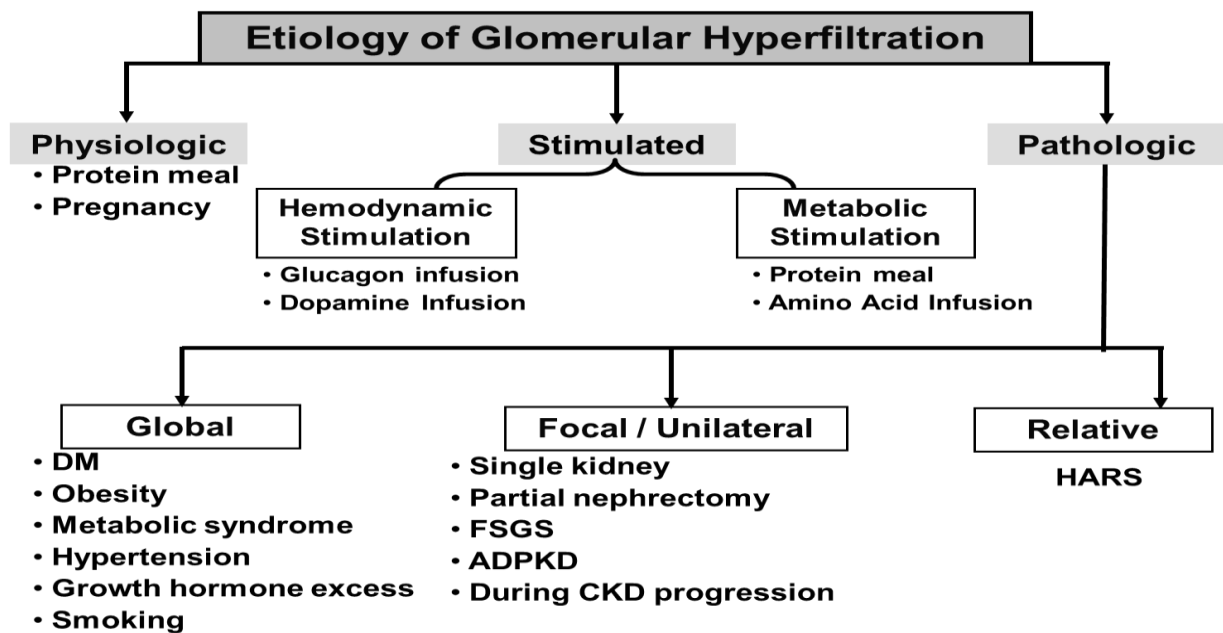

Fig. (3): Main etiologic categories of glomerular hyperfiltration. DM: diabetes mellitus, FSGS: focal segmental glomerulosclerosis, ADPKD: autosomal dominant polycystic kidney disease, HARS: high altitude renal syndrome

(Table 1) Main Differences between Physiologic and Pathologic GH

	Physiologic ↑ GFR	Pathologic ↑ GFR
Principal Underlying Cause	↑ Functional requirements imposed on an intact nephron mass	• ↓ Nephron mass • Intraglomerular hypertension
Predominant Mechanism	Nephron recruitment and ↑ RPF	↑ SNGFR
P_{GC}	Normal	↑
FF	Normal	↑
Proteinuria	--	+
Renal Damage	--	+
Total GFR	N	May ↓
RFR (Total – Current) GFR	↓	↓

GH: Glomerular hyperfiltration, RPF: renal plasma flow, P_{GC}: glomerular capillary hydrostatic pressure, FF: filtration fraction. The detrimental chain of events (GH leading to glomerular injury, proteinuria, and their consequences) would be expected to ensue in pathological, and not in physiologic states of GH.

– Increased plasma rennin activity (PRA), leading to efferent glomerular VC, ↑ P_{GC} , and ↑ FF.[21] However, other investigators found that the increase in GFR is proportional to the increase of RPF, with constant FF,[22] supporting the assumption that recruitment of "dormant" nephrons is the main mechanism rather than alterations in periglomerular (afferent and efferent) arteriolar tone.[23] So, an overall increase in RPF occurs initially, leading to a physiologic increase in GFR. Persistent high protein loading might then open the stage for glomerular hypertension, hyperfiltration, and ensuing nephron damage.

– Inhibition of Tubulo- Glomerular Feedback (TGF) by amino acids (AA): Each tubule that leaves the glomerulus returns again to come in contact with it at a specialized nephron segment lying between the end of the thick ascending limb of loop of Henle (TAL) and the distal convoluted tubule (DCT). The specialized tubular cells in this segment are the macula densa cells and they lie adjacent to the extraglomerular mesangial cells in the angle formed between the afferent and efferent arterioles of the same nephron. The juxta-glomerular apparatus (JGA) comprises the macula densa cells, extraglomerular mesangial cells, rennin-secreting cells of the afferent arteriole (granular or juxta- glomerular cells) and the vascular smooth muscle cells. Macula densa cells are salt sensors that generate paracrine chemical signals (mainly adenosine triphosphate and adenosine) in response to Na^+ and Cl^- ions in the tubular fluid.[24] These paracrine mediators lead ultimately to afferent glomerular VC and inhibition of rennin release. Thus P_{GC} is reduced, decreasing GFR. This TGF is a feedback loop minimizing GFR in case of increased distal tubular salt delivery. Following digestion and absorption of a protein meal, AA concentration is increased in the plasma, and consequently in the glomerular filtrate. Since AA and sodium are co-transported in proximal convoluted tubule (PCT), fractional and absolute proximal sodium reabsorption would increase, parallel with increased AA reabsorption, leading to decreased sodium delivery at the macula densa. Inhibition of the stimulus for TGF would cause afferent arteriolar VD, thus increased P_{GC}.[25] However, the role of TGF inhibition in protein-mediated GH has been questioned.[26]

– Stimulation of dopamine D2 receptors by AA.[27]

• *Pregnancy*[14]
Pregnancy offers the most extensive increment of GFR. Despite increased PRA, a state of generalized VD develops early in pregnancy due to decreased responsiveness to vasopressors as AII, noradrenaline and vasopressin (ADH) and increased vasodilator hormones as oestrogens, progesterone and relaxin. The latter is predominantly released from the corpus luteum. It increases nitric oxide production in the renal circulation leading to dilatation of both afferent and efferent arterioles. The RPF increases about 80% above baseline. GFR increases to a lesser extent (40 – 50% above baseline, to 150 – 200 mL/min/1.73 m²). Therefore the FF actually declines. The kidney volume increases up to 30%.

Stimulated GH (Testing for RFR)
The kidneys are capable of adjusting their performance to haemodynamic and metabolic demands. The ability to test the functional reserve of an organ system is often an excellent tool to uncover subclinical disease, eg, glucose

tolerance test. The 2 main domains of the kidney stress testing are the glomerular and tubular functions. Glomerular reserve testing has been well–established but is used infrequently in clinical practice.[22] RFR represents the capacity of the kidneys to increase GFR in response to a variety of physiological or pathological stimuli or conditions.[23] It is defined as the difference between stimulated and baseline GFR. The difference can be expressed in absolute terms (mL/min) or in relative terms (percentage of increment relative to baseline GFR).[28] A decreased RFR should be interpreted in light of baseline GFR. Loss of RFR may be due to increased basal GFR so that it can not be further increased with stimulation. We can thus assume a hypothetical maximal GFR, which is the sum of basal GFR and GFR increment upon stimulation; a relation expressed mathematically as follows:

Maximal (Peak, Total) GFR = Basal (Resting, Unstimulated) GFR + RFR
In healthy subjects, the kidneys usually operate at about 75% of their maximal GFR.[28] Peak GFR can reach 180 mL/min in case of intact nephron mass. It is reduced to approximately 120 mL/min in case of a solitary kidney (50% of renal mass).[29] Glomerular RFR is an index of the capability of the kidney to increase GFR by arteriolar VD and recruitment of dormant nephrons.[30] In 1930, Verney mentioned the reserve forces of the kidney.[31] In 1983, Bosch et al first coined the term glomerular function reserve, defined as the difference between baseline and stimulated GFR, measured 2 hours after a protein meal.[32] The interest in RFR concept was revived by the recent postulates that decreased RFR contributes to susceptibility for recurrent acute kidney injury (AKI).[23] Study of the diagnostic and prognostic utility of RFR has been mentioned in the roadmap for global kidney health 2017 issued by the International Society of Nephrology.[33]

During the early stages of renal disease, the total kidney GFR is maintained by compensatory hyperfiltration of the remaining intact (or less severely affected) nephrons.[34] Considerable structural damage can occur in the kidney before the GFR falls, suggesting that the reserves are being brought into action and are somewhat obscuring early detection of kidney disease by ordinary GFR assessment. Assessment of RFR may thus be a more sensitive indicator for early detection of renal disease.[32] However, RFR assessments have not been conducted in large cohorts. There is no constant value or nomogram for RFR but it has been shown to vary between 10 and 70% of baseline GFR in healthy subjects.[35]

In most cases, RFR falls relentlessly with progression of CKD. However, RFR may become completely exhausted even with a normal or a minimal decrease in basal GFR. Conversely, RFR may be partially preserved in patients approaching ESRD.[36] Therefore, the concept of renal reserve capacity has not withstood scientific scrutiny. The expression renal function reserve should be replaced by renal functional response.[28]

Stressing the kidney to increase its GFR may be achieved by haemodynamic or metabolic stimuli or a combination of both (Fig. 3). The renal response after a haemodynamic stimulus is immediate, while the maximal effect of a metabolic stimulus is noted after 1 – 3 hours. To maximally guarantee an unstimulated (basal - lowest) GFR, patients are often instructed to adhere to a low protein or vegetarian diet for about 10 days in preparation for a renal stimulation test. Some drugs must be paused before testing for RFR, as NSAIDs, RAS blockers.[28] During the procedure, diuresis of at least 100 mL/h should be maintained by orally administering fluids.[37]

- *Haemodynamic Stimulation of GFR:*

-Glucagon infusion: usually at a dose of 10 – 20 ng/Kg/min.
Glucagon decreases tubular solute concentration at the macula densa leading to downregulation of TGF, and consequently, VD of preglomerular arterioles.[38]

-Dopamine infusion: usually at a dose of 2 – 3 ug/Kg/min "renal dose".

Low "renal" dose dopamine induces a significant decrease in renovascular resistance and increase in RPF. At higher dosages of IV dopamine, a further increase in blood flow appears mainly driven by an increase in systemic blood pressure.[39,40] The dopamine- induced increase in RFR occurs in normal persons, but not in patients with moderate renal dysfunction.[41]

- *Metabolic Stimulation of GFR:*

– **Protein Meal:**
The physiologic diurnal variation in GFR is mainly ascribed to the meals proteins. GFR measured while fasting may thus underestimate the 24 hours average daily GFR, while a GFR obtained following a protein meal may overestimate it.[42] Animal proteins are more stimulating and are generally preferred, although dairy products and egg white proteins are more practical in pediatric subjects.[43] Maximal stimulation occurs 150 minutes after ingestion.[13] The FF increases significantly with moderate to large protein load, but not with low protein load.[44]

– **Amino acid (AA) infusion:**
Usually a mixture of gluconeogenic AA is used,[45] whereas branched- chain AA do not alter GFR or FF.[46] No single amino acid has been implicated as the sole stimulant for RFR, although glycine and arginine seem particularly potent and have occasionally been used solely.[47]

- *Combined Haemodynamic – Metabolic Stimulation of GFR:*
Such a combination would have an additive effect in increasing GFR and is thus recommended, eg, a combination of dopamine and AA infusion. [28] Whereas dopamine decreases total renovascular resistance, AA mainly reduce the tone of afferent glomerular arterioles and barely affect the RPF. AA cause no change or a slight increase in FF. [37]

GFR Determination during Testing for RFR

A focus of difficulty in renal function testing (and particularly RFR testing) is the method used for GFR determination.[28] The RFR is mostly assessed by laboratory means. Alternatively, it may be assessed by imaging techniques, mostly Doppler ultrasound:

- ### Laboratory Assessment of RFR

GFR remains the most widely used indicator for kidney function assessment in healthy subjects and patients with renal disease worldwide.[1] RFR is usually assessed by measuring the GFR twice, under basal then under stimulated or stress condition, then calculating the absolute or the per cent increase. The easiest way is to monitor urinary creatinine excretion by timed urine collection (every 30 or 60 minutes). At least 3 clearance calculations are advised.[28] In cimetidine- aided creatinine clearance, cimetidine was started 1 – 4 days before applying the GFR stimulus, according to a dosing protocol determined by the actual renal function. Cimetidine inhibits tubular secretion of creatinine, thus obviating one source of bias regarding the use of creatinine clearance as a measure of GFR.[48]

- ### Doppler Assessment of RFR(49)

The cumbersome and multiple laboratory analyses required for determination of RFR limit its application in clinical practice. Doppler ultrasonography has emerged as an increasingly available, safe, non- invasive, reliable and relatively inexpensive method for assessment of kidney vascularity and RFR.

Resistive index (RI) is a Doppler- derived indirect but sensitive measure of arterial impedance, which reflects the overall degree of vasoconstriction. It is an easily obtained index that is not affected by vessel diameter or angle of insonation. An increased renal RI (RRI) indicates increased renal vascular resistance. Obtaining several RRI measurements on both sides (to calculate the average) can be accomplished within a few minutes and does not require much training.

$$RI = (PSV – PDV) / PSV \qquad \text{(Normal RRI is} < 0.7)$$
Where PSV and PDV are the peak systolic and diastolic flow velocities, respectively.

During testing for RFR by haemodynamic or metabolic stimulation, increased GFR is principally mediated by renal arteriolar VD and decreased renal arteriolar impedance. This vascular response can be recognized and quantified by assessment of RRI before and 2 hours after application of the stressing stimulus (eg, a protein meal with plenty of fluids). The percent decline in RRI is considered to indicate the RFR. This method has proved useful to study RFR in healthy subjects[49] and to disclose the presence of reduced RFR in subjects with asymptomatic hyperuricaemia and normal basal GFR.[50]

Potential Clinical Applications for RFR Testing [23]
1) CKD patients (especially high risk groups as diabetics and hypertensives) facing an aggressive intervention or dangerous exposure (as radiocontrast injection).

Obliteration of RFR is considered a surrogate marker for the presence of underlying GH and a reduced capability to withstand upcoming renal insults. It has been shown that the RFR falls relentlessly with progression of CKD, from 23.4% in healthy controls, to 6.7% in patients with CKD stage 4.[36] With a basal measurement of GFR, we do not really know the true renal function potential, or the maximal stimulated GFR.[42]

2) To evaluate the extent of recovery following an attack of AKI. The increased utilization of RFR after an attack of AKI may conceal, partially or completely a decline in functional renal mass, RFR testing would thus be a sensitive and early way to assess the functional decline in the kidney following AKI. Recovery may appear complete clinically, but a reduced RFR may be a sign of maladaptive repair or subclinical loss of renal function. [23]

3) Before renal transplantation. It is obvious that renal transplantation should not inflict harm on either the donor or the recipient and any clinically relevant post-operative renal function impairment should, to the maximal possible extent, be avoided in both of them. Accurate prediction of post- operative renal function is crucial to justify the living donation policy and assessment of predonation stimulated GFR during infusion of low dose dopamine and AA (7% AA infusion at a rate of 500 mL/6 hours) became a standard protocol in some centers. A low RFR in a potential kidney donor would suggest a search for a more suitable donor to minimize the future risks of impaired kidney function in both the donor and the recipient. However, compared with assessment of basal (unstimulated) GFR, the added value of stimulated GFR appears to be limited.[51]

4) Before pregnancy. RFR is predictor of pregnancy outcomes, particularly in patients who have sustained previous attacks of AKI.[52]

Pathologic GH

A hall mark of the pathophysiology of many chronic nephropathies is the presence of an initial phase of GH preceding the subsequent phases of progressive nephron destruction and GFR reduction. Since P_{GC} is not measurable outside the experimental settings and appreciation of hyperfiltration by laboratory methods may be elusive, it is the increased protein trafficking across the hyperfiltering glomeruli, manifesting as proteinuria/albuminuria, that is usually considered to provide the earliest clues for the presence of hyperfiltration.

The glomerular capillaries are unique in that they are arranged in series between 2 resistive vessels. Selective modulation of the resistance of these 2 vessels allows the precise and largely independent regulation of RPF and P_{GC}.[53]

GH in DKD

DKD is the single most common cause of CKD and ESRD in most parts of the world, with diabetic patients accounting for 25 – 45% of ESRD patients. It is responsible for a great proportion of cardiovascular events and premature deaths in developing and developed countries.[54] Accumulating evidence suggests a prognostic and pathogenic role of GH in the initiation and progression of DKD. GH is reported to occur early in both type 1 and type 2 diabetes, and to be more frequent and severe in type 1. GFR elevation is particularly pronounced in newly diagnosed diabetic patients and during other intervals with poor metabolic control. Strict glycemic control decreases GFR towards normal.[2]

Increased urinary albumin excretion (UAE) rate short from the detection limits of routine urinalysis (formerly termed microalbuminuria and currently called moderately increased UAE) has long been regarded as the hallmark of the earliest phase of the typical (proteinuric) pathway of DKD. This increased UAE reflects the underlying glomerular hypertension and hyperfiltration in association with multiple other factors increasing the filtration membrane permeability for proteins, particularly albumin. It has now been increasingly recognized that the kidney disease in many diabetic patients, particularly in type 2 disease, does not follow this typical proteinuric pathway, and a non- proteinuric pathway may even be more frequent.[55]

A complex set of inter- related pathogenetic mechanisms underlies the early development of diabetic GH and its consequences. These mechanisms may be categorized as either being primarily causing afferent glomerular VD or efferent VC.[56,57]

Obesity

The histological hallmark of obesity associated renal pathology is glomerulomegaly, which precedes any clinical or laboratory evidence of renal dysfunction.[58]
The significantly increased GFR and RPF values in obesity are normalized when indexed for body surface area.[59]

Metabolic Syndrome

Insulin resistance and hyperinsulinemia induce glomerular hypertension and hyperfiltration and may be the common underlying pathogenetic factor in GH found in DM, obesity and metabolic syndrome.[60]

Hypertension

GH is thought to play a pivotal role in causing renal damage in essential hypertension. GH in hypertensive patients can be modulated by antihypertensive drugs. It could be augmented by nifedipine (calcium channel blocker) and abolished by enalapril (angiotensin converting enzyme inhibitor).[61]

Growth Hormone Excess

Patients with growth hormone hypersecretion (gigantism or acromegaly) have increased kidney weight, glomerular hypertrophy and hyperfiltration. These alterations may be mediated, at least in part, by increased plasma IGF-1.[62]

Smoking

Smoking was reported to be associated with proteinuria independent of blood pressure.[63] Infusion of nicotine into the renal artery increases GFR.[64] Smoking increases plasma ADH level, which may play a role in GH.

Focal / Unilateral GH

Impaired myogenic autoregulation has been described in the remnant kidney model, after reduction of renal mass (as in DKD). Following partial or total unilateral nephrectomy, GH develops in the remaining kidney tissue. Following renal transplantation, both the donor and the recipient are having single kidneys that would undergo hypertrophy and hyperfiltration. A similar phenomenon occurs since early life in patients with a hereditary absent or hypoplastic kidney. Although the GH in these conditions begins as a physiologic response aiming to compensate for the reduced functional renal mass and maintain the overall GFR, the persistence of the extra- load and the hyperfiltration process in the remnant kidney tissue is in itself a risk factor for kidney disease, exhausting the RFR and increasing susceptibility for kidney injury upon exposure to other acute or chronic insults. However, there is evidence that hyperfiltration per se in a completely normal kidney (as in allograft donors) can be well tolerated for years without any clinical sequelae and the risk of ESRD is very low. [65]

The distribution of nephron involvement in many CKDs is not uniform and 2 hypothetical populations of nephrons, one more severely affected and the other better preserved, can be described. The global GFR would be maintained by increasing SNGFR in the remaining surviving nephrons and this would create a state of GH selectively involving some nephrons and sparing the others. [66]

GH in FSGS

FSGS is currently the most common cause of nephritic syndrome in adults. GH occurs in the start as a functional adaptation to reduced functional renal mass, but it then turns maladaptive and leads to glomerular injury, proteinuria, progressive renal fibrosis and deterioration of renal function. [67]

GH in ADPKD

ADPKD is the most common and serious genetic disease leading to CKD and ESRD in adults.[68] GH in children with ADPKD is thought to be mediated by AII, which increases P_{GC} and FF. The increased SNGFR keeps the GGFR normal despite decreased RPF that results from early renal VC. Increased levels of AII might cause both GH and increased cyst size by increasing its epithelial proliferation and oxidant injury. [69]

The long held belief that GH occurs as an early phenomenon in ADPKD has recently been challenged. Cyst formation does not lead to significant nephron loss.

Patients with ADPKD at young adult age or with early CKD stages have a GFR in the normal range and are still able to increase their GFR in response to dopamine. [70]

Relative GH in High Altitude Renal Syndrome (HARS)[15]
HARS develops in persons living at or travelling to a high altitude. It comprises systemic hypertension, polycythaemia, hyperuricaemia, increased UAE with relatively preserved GFR. Reduced atmospheric oxygen at high altitude engenders a pathophysiologic response including polycythaemia and increased blood viscosity. These alterations decrease RPF. To maintain GFR, FF is increased, by increasing P_{GC} through VC of efferent arterioles. The mechanism of VC is unknown and RAS is not consistently activated. GFR is not increased above normal, but is relatively high in relation to the low RPF. Proteinuria ensues due to glomerular capillary hypertension, tissue hypoxia and hyperviscosity.

Other Causes of GH[2]
- Chronic haemolytic anaemias as thalassaemia and sickle cell anaemia.
- Polycythaemia.
- Sleep apnoea syndrome.
- Some malignancies.

Consequences of GH
Although increased P_{GC} may be a physiologic response intended in the short term to maintain ΔP and improve FF in the face of conditions of renal hypoperfusion or hypovolemia, the process may turn in the long term to be maladaptive because both glomerular hypertension and increased protein trafficking across the renal tubules have many deleterious consequences. According to Brenner`s hypothesis,[71] glomerular hypertension leads to mechanical damage of the glomerular capillaries, and progressive glomerulosclerosis. Consequences of GH include:

CKD Progression
Hyperfiltration is a known risk factor for CKD progression. Conversely, there is ample evidence that reduction of GH, by RAS blockers or other interventions, reduces the risks of CKD progression in DKD and many other proteinuric and non- proteinuric chronic nephropathies. [72]

Proteinuria
Urinary protein excretion increases in direct proportion to the increase in P_{GC} and FF. These 3 parameters are closely associated. The amount and duration of proteinuria are key factors in determining CKD progression, and may be more influential than the degree of renal function impairment. Recent KDIGO guidelines have defined 3 categories of increased excretion of urinary albumin or total proteins and have emphasized the necessity of considering these categories together with the 5 K/DOQI categories of GFR reduction in order to evaluate the overall prognosis and the cardiovascular disease risks associated with CKD. [73]

Proteinuria, particularly when heavy and non- selective, is both a marker for and a mechanism of kidney disease progression. It can be nephrotoxic via a variety of mechanisms.[74] Increased tubular reabsorption of filtered proteins induces tubulointerstitial inflammation, leading to tubular atrophy, interstitial fibrosis, and progressive loss of renal function. Moreover, the increased protein reabsorption activates local RAS leading to more proteinuria, thus generating a vicious circle. [75] Reduction of albuminuria in DKD is followed by reduction of renal and CVD risk, especially if the initial level albuminuria was high. [76]

Cardiovascular Disease
Most deaths in the CKD population are attributable to CVD complications. Proteinuria or albuminuria, which may result from GH, are established independent risk factors for increased CVD risk. Albuminuria is one of the most important independent risk factors underlying the cross talk between CVD and renal risks.[77]

Mortality
Recent evidence from diverse populations, including healthy individuals and patients with diabetes or established cardiovascular disease, suggests that renal hyperfiltration is associated with a higher risk of cardiovascular disease and all-cause mortality.[78]

Conclusion
GH may occur as an adaptive response to pregnancy or protein ingestion. It may also occur as an early pathogenetic alteration in DM, hypertension, obesity and many other conditions. Augmentation of GFR and assessment of the resultant increase under controlled conditions is the basis for testing for RFR which helps in functional evaluation of CKD patients and forecasting the prospects of success after renal transplantation. GH is a target for early intervention to halt CKD progression, for which many pharmacological interventions have or are being developed. As such, efforts to revive our knowledge about recognition and management of GH may help reduce the extremely high CVD morbidity and mortality associated with kidney diseases.

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