The Kidney; a Primary Approach

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The kidney see everything that enters or is generated from the body at some time.

Every 24 hours the kidney can process about 200 quarts of blood to sift out about 2 quarts of waste products and extra water. Only .1% of the blood volume becomes urine.

The kidneys have a higher blood flow than the brain, liver, or heart.
The typical volume of urine is between 1000-2000 ml daily.

Half of one kidney could do the work of both kidneys if it had to. This is accomplished by nephron hypertrophy.

The urine we produce has been stored in the bladder for about 1-8 hours.

If nephrons were stretched end to end they would stretch 5 miles.

Individuals who donate a kidney have the same life expectancy and those who have two kidneys.
A natomy of the Nephron

Diagram showing the anatomy of a nephron with blood flow, glomerulus, tubule, and waste (urine) flowing to the bladder.
The Nephron

- Function of the Nephron - YouTube
“Simplistically, the glomerulus functions like a kitchen strainer. Blood passes over a series of holes in the kidney blood vessels, and a small amount of it is allowed to flow through the more complicated regions of the kidney, where more detailed filtering occurs. Though later filtering steps are more complex, this initial filtering functions to exclude certain blood components based solely on size.”

Proteinuria represents a breakdown in early filtering apparatus of the kidney.
Glomerular capillary

Permeable:
- Glucose
- Small cations: Na, K, H
- Small anions: Cl, HCO₃

Kidney tubule

Impermeable:
- Red cells
- Proteins
The Kidneys releases three important hormones:

- **Erythropoietin**, or EPO, which stimulates the bone marrow to make red blood cells.
- **Renin**, which regulates blood pressure
- **Calcitrol**, the active form of vitamin D, which helps maintain calcium for bones and for normal chemical balance in the body
What is in urine?

Substances excreted from the kidneys are urea, uric acid, creatinine, toxins, drugs, plasma inorganic ions, (Na+, K+, Ca2+..ect.) H+, HCO3-, of course H2O, and anything else the body doesn't need that's found in the blood plasma.

Substances that are reabsorbed are amino acids, proteins, glucose, water, plasma inorganic ions and anything the body needs that is found in the blood plasma.

Nephrons are nonselective and secrete everything in the plasma, and the capillaries then reabsorb the vitamins minerals nutrients ect. that the body needs back into the blood, everything the body doesn’t need goes to the bladder.
What is GFR?

- The flow rate of fluid through the kidney; which estimates the excretory function of the kidney.

- Specifically the volume of fluid filtered through the capillaries of the glomerular capillaries into the Bowman’s capsule per unit of time.

- It is determined by using any chemical that shows a concentration in the urine times the urine flow and comparing it to the level in the plasma.

- Individuals with low GFR does not Equal Kidney Failure
In practice the creatinine clearance is used to determine the estimated GFR.

Serum creatinine is compound from muscle creatinine phosphate breakdown that maintains a steady state in the body and can easily used to measure the GFR by its appearance in urine.

A common mistake when analyzing serum creatinine is not taking into account muscle mass of the individual.
After the age of 40 the kidney nephrons stop functioning about 1% per year. The remaining nephrons will tend to compensate or hypertrophy.

The Glomerulus has large pores, allowing filtration of large volumes of fluid. The number of nephrons declines with age, to about 50% at age 60; this causes the GFR to drop to 50% of the value in a young person.
Kidney Disease

- Acute Renal failure is a decrease of kidney function caused by a reversible insult such as medication, infection, trauma, dehydration, obstruction, or metabolic conditions.

- Chronic Renal failure is a progressive loss of kidney function that is irreversible.
  - Most common cause: HTN, and Diabetes
  - Secondary causes: Autoimmune, Anatomical, Medications, and Infections.

- 1 in 9 adults have chronic kidney disease.
How do you classify CKD?

Chronic Kidney Disease is defined as GFR of less than 60mL/min/1.73m for greater than 3 months and positive serum and urine markers of kidney damage.

You can have chronic kidney disease with a normal GFR and just markers of kidney damage.

Classification of CKD is based on stages 1-5.

117 million Americans have Stage 1-5 with 500,000 stage 5.
Stages of CKD

S Stage One       Damage with normal or increase GFR >90
S Stage Two       Damage with mild decrease GFR 60-90
S Stage Three     Moderate decrease GFR 30-59
S Stage Four      Severe decrease GFR 15-29
S Stage Five      Kidney failure GFR <15 dialysis

If you have High BP without kidney damage, then drop 1 stage

(Kidney damage is structural or functional damage of the kidney; proteinuria decreased blood flow)
Proteinuria

Proteinuria that occurs is most commonly protein albumin due to its small size, and negative charge.

Albuminuria refers to albumin in the urine and is often used interchangeably with proteinuria. Just a UA can show the presence of protein but not the amount.

Albuminuria is a very sensitive indicator of damage and scarring within the delicate filtering capillaries of the kidneys known as glomeruli. A 24 hour urine collection may be necessary to measure the actual level of protein.

Proteinuria is without symptoms and may be a sign of silent kidney disease or damage.

Rockford Nephrology Associates on “Proteinuria” Dr. James Stim
Obesity or significantly being overweight may also result in proteinuria. There may be hormonal effects that promote proteinuria in obesity in particular excess insulin production due to insulin resistance of fatty tissue. Sustained weight loss may reduce proteinuria and provide general health benefits as well.

Mild proteinuria may be present in children or young adolescents as they undergo active growth. This is termed orthostatic proteinuria and is benign and harmless.
Nephrotic Syndrome

The urine protein level reflects the degree of damage occurring within the glomeruli.

Nephrotic syndrome is albuminuria is greater than 3000 milligrams or 3 grams.

Symptoms are swelling in the legs or face, low albumin in the blood, foamy urine, and high cholesterol levels.

Most common cause Diabetes type 2 which is secondary Nephrotic Syndrome, but can be caused by infections and autoimmune disease.
The Case of the well meaning Orthopedic Surgeon

55 year old white male, HTN, Pre renal Stage 3, Type 2 Diabetes for 10 years on Pioglitazone, Metformin Bydureon, Losartan, Diltiazem, and recently Lasix 20mg.

Presents to office with Hypertension, Fluid retention of the legs/face, and Elevated Blood sugars,

Recent Medrol dose pack for a bad arthritic knee

“Feels Lousy”
### Then and Now

**Base line labs Jan 2013**

- **GFR**: 53
- **CR**: 1.3, **BUN**: 30
- **A1c**: 6.5
- **Micro albumin**: 148 high mg/dl (*<2 ideal*)
- **BP**: 134/92, **Weight**: 236
- **Stage 3 Renal Failure**

**Current labs**

- **GFR**: 29
- **CR**: 2.34, **BUN**: 60
- **Serum Glucose**: 400
- **BP**: 180/100, **Weight**: 262
- **LFT**: 43/48, **AST/ALT**
- **Serum albumin low**: 2.2
- **Nephrotic Syndrome with acute Renal Failure**
Treatment Recommendations

- Stopped Steroid Treatment (was on 5mg dose portion)
- D/C Lasix and Initiated Torsemide at 10mg
- Considered Spironolactone because of elevating LFT and edema
- Placed patient on a “clean diet” No NSAIDS and lower salt
- Treated Glucose levels with Insulin and held Exenatide LA
- Referral to Nephrology
Renal US, UA, repeat Chem., Vit D level, PTH, Light Chain urine study

Echo (normal no diastolic heart fail), C-pap titration,

Increased Torsemide to 40mg in am 20mg in the PM

Spironolactone 25mg Daily

PCP replaced Vit D with 50,000 weekly
Blood pressure is the force that causes blood to move through the kidney’s filter.

Blood pressure too low, and there isn’t enough force to push adequate amounts of blood through the filter, causing a decrease in the amount of blood filtered and lowering the amount of urine produced.

Anything that causes resistance or decreased flow can cause kidney disease.

How is Proteinuria Related to High Blood Pressure
From Craig Weber, M.D.,
One would expect, increasing the blood pressure would deliver more blood to be filtered and thus increase urine production.

The kidney has a built-in gate system that resists increased blood pressures and keep the filtration rate fairly constant rate.

In situations where the blood pressure is chronically elevated, this gating mechanism starts to break down. the delicate filtering structures of the kidneys are exposed to abnormally high pressures,
Pressure a Delicate Balance

S The increased pressure gradually deteriorates the vessel structures of the actual filter.

S It's like making the holes on a kitchen strainer larger. As the size of the holes increases, progressively larger substances are able to pass through this initial barrier into the kidney, where they eventually become part of the urine.

S The presence of these “foreign” substances indicate kidney damage
Diabetes and CKD

- The most common cause of kidney disease.
- Glucose size forces larger proteins into the urine causing proteinuria.
- The kidney filtering process begins to drop as the albumin appears in the urine.
- Comorbid conditions increase kidney damage.
Diabetes and the Kidney

Over time hyperglycemia causes sclerotic vascular changes in the kidney which causes albuminuria and declining renal function due decreased blood flow into the nephron.

Combine this with associated hypertension that often accompanies DM 2 as well as obesity and hyperlipidemia one can see how this disease is the most common cause of kidney failure.

Type 1 Diabetics can get kidney disease in the absence of HTN or other Co-morbid conditions.
The treatment of proteinuria is somewhat dependent on the cause; diabetes with or without hypertension.

High blood pressure (greater than 140/85) worsens proteinuria and kidney function.

Ideal blood pressure is 130/80 using (ACEI) / (ARB). Other hypertensive medications may worsen or improve proteinuria.

Low protein diets, higher fruits and veggies.

In Diabetes Mellitus the goal is to get ideal glucose control, BP control, and improvement in Proteinuria.
Dyslipidemia shifts in the uremic patient and the LDL particle size shifts to a more athrogenic particle size.

The occurs through oxidation and modification.

Triglycerides increase through depletion of the enzyme pool.

HDL levels drop due to lower particle conversion rate.
HTN, CKD and African Americans

**Leading Cause of Kidney failure** Higher in African Americans and results in structural damage to the kidney.

Can be present with or without diabetes or other co-morbid conditions and is a condition of low renin, and expanded intravascular volume, resulting in poor salt excretion and elevated intracellular calcium.

Treatment consists of diuretics, and long acting calcium channel blockers. ACE and ARB are still superior to Beta blockers and should be used in African Americans with proteinuria.
Renal Excreted Diabetes Medication

**Metformin** - primarily excreted through the kidney. It is not metabolized by the kidney but excreted unchanged. The primary fear of lactic acidosis is really from the predecessor drug phenformin which has a 10 fold higher incidence than metformin. Nearly all of the 47 reported cases of lactic acidosis involving metformin were due to other causes such as kidney disease or infection (innocent by-standard).

**Januvia** - 100mg Normal GFR, 50mg Mild Impairment, 25mg End stage disease. Hepatically metabolized but renally excreted.

**GLP1 analogs** - excreted as intact molecule through renal system so decrease in GFR lead to sustained serum concentrations. However GLP1 are not toxic in large quantities in the body.
Addition of Vitamin D

More recent animal and human studies suggest that treatment with vitamin D may be associated with reduction of inflammation and urinary protein loss as well as reduction the activity of the renin angiotensin system (RAS) in addition to its effects on the bone metabolism.

Effects of Vitamin D on Renal Blood Flow, Proteinuria and Inflammation in Patients With Chronic Kidney Disease. University of Virginia
Kidneys; the New Frontier in Diabetes Treatment
Glucouretics

S SGLT2 inhibitors-Block this sodium glucose transport protein in the Proximal tubule

S Using the kidney to urinate out glucose up to 180g per day.

S Several are in development: Canagliflozin (Invokana) only currently FDA approved
When the blood glucose level exceeds about 160 - 180 mg/dl (8.9 - 10 mmol/l), the proximal tubule becomes overwhelmed and begins to excrete glucose in the urine.

This point is called the renal threshold of glucose (RTG).
Impaired Renal Threshold

In Diabetes the kidney upregulates the expression of SGLT2 receptors in the kidney in response to hyperglycemic state.

As a result, the Renal Glucose Threshold increases, so glucose will not be off-loaded into the urine until the serum glucose approaches 220 mg/dl.

Diabetics re-absorb “more glucose” or rather off load less.
Effects and Side Effects

S Off loading of excess glucose in the urine - A1c drop .9-1.3
S 8 oz. of fluid diuresis in 24 hour period
S Drop in serum BP “has a diuretic effect”
S Weight loss due to calorie wasting
S Mycotic infections greatest side effect.
Summary

Kidney disease is generally a slowly progressive, preventable condition.

Management of diseases such as HTN, Diabetes, and CAD can prevent kidney damage.

Monitoring prescription and over the counter medications, coupled with early detection of serum and urinary markers can identify patients at risk.