Lecture-4

The Kidneys

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Renal Functions

Excretion of waste - Production of urine
- elimination of metabolic end products (Urea, Creatinine, uric acid ...etc)
- elimination of foreign materials (Drugs)

Control of volume & composition of ECF
- Water and electrolyte balance
- Acid/Base status

Renal Functions

Endocrine Functions
- renin
- erythropoietin
- Calcitriol (activation of vitamin D)

Why Test Renal Function?

- To identify renal dysfunction.
- To diagnose renal disease.
- To monitor disease progress.
- To monitor response to treatment.
- To assess changes in function that may impact on therapy (e.g. Digoxin, chemotherapy).

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Renal Anatomy and Physiology

- A pair of fist-sized organs located on either side of the spinal column just behind the lower abdomen (L1-3).

- Consists of renal cortex and renal medulla.

- The functional unit of the kidney is the nephron;

- 10^6 nephrons /Kidney.

Blood is separated from the lumen of the nephron by three layers.

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The glomerular filtrate is an ultra filtrate of plasma, that has similar composition of plasma, except for proteins.

endothelium is impermeable to blood cells as well as large proteins. Proteins with MW lower than that of albumin (68KDa) are filterable.

What gets filtered in the glomerulus?

- **Freely filtered**
  - $H_2O$
  - $Na^+$, $K^+$, $Cl^-$, $HCO_3^-$, $Ca^{++}$, $Mg^+$, $PO_4^{3-}$, etc.
  - Glucose
  - Urea
  - Creatinine
  - Insulin

- **None filtered**
  - Proteins >68KDa
  - Immunoglobulins
  - Ferritin
  - Blood Cells
The filtration is a passive process.

The filtration rate of the kidneys depends on the difference between blood pressure in the glomerular capillary and the hydrostatic pressure in the lumen of the nephron.

Kidneys receive ~2,000 L/day (25% of cardiac output).

GFR = 110 ml/min

Kidneys receive
200 Liters
Of plasma ultra filtrate formed per day.

-% Reabsorbed
Water 99.2
Sodium 99.6
Potassium 92.9
Chloride 99.5
Bicarbonate 99.9
Glucose 100
Albumin 95-99
Urea 50-60
Creatinine 0 (or negative)

Reabsorption from glomerular filtrate

Reabsorption can be active or passive, and occurs in virtually all segments of the nephron.

Nephron performed three functions.
1. Glomerular filtration
2. Tubular secretion
3. Tubular reabsorption
Biochemical Tests of Renal Function

Diseases affecting kidneys can be selectively damage glomerular or tubular function.

Test of glomerular function
- Measurement of GFR
  - Clearance tests
  - Plasma creatinine
  - Blood urea

Tubular function tests

Urinalysis

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Measurement of Glomerular Filtration Rate (GFR)

Measurement is based on concept of clearance:

"Measuring urinary excretion of a substance (X) that is completely filtered from the blood by the glomeruli."
Measurement of Glomerular Filtration Rate (GFR)-conti

- If clearance = GFR then substance \( x \) properties: -
  - freely filtered by glomeruli
  - Not secreted or reabsorbed or metabolized by tubular cells
  - Non-toxic and easily measurable

Determination of Clearance

\[ \text{Clearance} = \frac{\text{U} \times \text{V}}{\text{P}} \]

Where

- \( \text{U} \) is the urinary concentration of substance \( x \)
- \( \text{V} \) is the rate of urine formation (mL/min)
- \( \text{P} \) is the plasma concentration of substance \( x \)

Inulin Clearance

- Gold Standard
- Plant polysaccharide
- measurement of inulin clearence requires the infusion of inulin into blood
- clinically is not suitable

Creatinine Clearance

- Creatine is a nitrogen containing compound
- formed from glycine, arginine, methionine in the liver
Creatinine Clearance conti.

1-2% of muscle creatine converted to creatinine (Cr) each day

- Amount of Cr produced relates to muscle mass
- Freely filtered at the glomerulus
- Creatinine clearance = 110 ml/min
- Corrected to standard body surface area of 1.73 m²

Some active tubular excretion (10%).

This is of little significant for normal GFR

When GFR < 10 ml/min, GFR is over estimated
Creatinine Clearance: advantage and disadvantage

- Timed urine collection for creatinine measurement (usually 24h)

**Problems:**
- Practical problems of accurate urine collection and volume measurement.
- Time consuming, inconvenient and potentially unreliable
- Carried out for transplanted kidneys & degree of renal impairment

Plasma Creatinine Concentration

- Most reliable simple biochemical test of GFR
- Plasma Cr level remains fairly constant through adult life

Plasma Creatinine Concentration conti.

**Problems**

- Plasma Cr can increase by 30% 7 hrs after meal.

- Cr level can be changed independently to renal disease
- Decreased in:
  - starvation
  - wasting disease
  - pregnancy
  - immediately after surgery
  - steroid therapy
Plasma Creatinine Concentration conti.

- Cr Normal reference value
  - 60-120 μmole/l
  - Or 0.7-1.4 mg/dl
- Concentration inversely related to GFR.

Plasma Creatinine Concentration conti.

- Plasma Cr level can be misleading
- GFR can decrease by 50% before plasma Cr rise beyond normal range

Blood Urea

- Urea is nitrogen containing compound formed in the liver as the end product of protein metabolism and digestion.
- Eliminate in urine as a major nitrogen waste product (85%)
UREA contd.
- freely filtered but about 50% reabsorbed by through passive diffusion
- tubular reabsorption increases at low rate of urine flow
- often used an index of renal function along with plasma Cr

Blood Urea
- Blood Urea level can be changed independently to renal disease
  - high protein intake
  - GIT hemorrhage
  - hypovolemia, burns
dehydration
  - congestive heart failure
  - Catabolic state

Blood Urea
- blood Urea level reduced in
  - starvation
  - Low protein diet
  - Sever liver disease
- Thus, BU needs to be compared to cr to determine true renal dysfunction
- The levels of urea and Cr almost always are paralleled to each other

High plasma Urea (Uremia or Azotemia) (azotemia = elevated BU)
The causes can be subdivided to
Prerenal
- Renal
  - intrinsic renal disease
Postrenal
- obstruction to urine outflow
Other Methods for Assessing GFR

- $^{51}\text{Cr-EDTA}$, $^{99}\text{Tc-DTPA}$
  - Exogenous: need to be administered
  - Not readily available
  - Radioactive

Cystatin-C
- Protease inhibitor (MW 13 kDa)
- Freely filtered at glomerulus
- Reabsorbed and degraded by proximal tubule
- Plasma concentration reflects GFR
- Constant production rate by all nucleated cells
- No known extra-renal excretion routes
- Not influenced by muscle mass, diet or subjects' sex

$\beta_2$-Microglobulin (BMG)
- Small protein (MW=11.8K)
- Not affected by muscle mass or diet
- BMG is filtered in the glomerulus, but is reabsorbed in the renal tubules.
- Urinary BMG levels are a sensitive measure of renal tubular function
- Increased in renal failure

Tests of Tubular Function

- Performed less frequently
- Proximal Tubular Function
  - Aminoaciduria
  - Glycosuria with normal blood glucose
- Distal Tubular Function
Urinalysis (UA)
General urine examination (GUE)
- it is a general test for evaluation of renal function
- Fresh sample = Valid sample

- Physical,
- chemical and
- macroscopic examination

Physical examination includes
- Appearance
  - Colour, turbidity
- pH
- Specific gravity and osmolality

Appearance – clear

- Turbidity: (infection, nephrotic syndrome, proteinuria)

- Colour: amber light
  - Coloured-haemoglobin, myoglobin, Jaundice, drugs, beet
Urine pH

- Normally acidic
  - Normal: 4.5-8
  - Acidic: 4.5-5.5
  - Alkaline: 6.5-8

- pH that is >8 or less <4 is physiological impossible. In general urine parallels serum pH.

Urine Osmolality

- Normal Average:
  - 400-900 mOsm/kg H2O
  - Max 1200 mOsm/kg

- Purpose = Assess the ability of kidneys to dilute or concentrate urine-tubular function.

Urine Osmolality-conti.

- **Increased values**
  - Dehydration
  - Diabetes mellitus
  - Hyperglycemia
  - Hypernatremia

- **Decreased values**
  - Overhydration
  - Hyponatremia
  - Diabetes insipidus

Specific Gravity

1.005-1.030

- A measure of the DENSITY of urine compared with the density of water.

- The higher the number = the more concentrated the urine.
Specific Gravity- conti

- **Increased Specific Gravity**
- Lacking fluids
- Increased ADH

- *Falsely high* = glucose, protein, or dye in urine

- **Decreased Specific Gravity**
- Dilute urine
- Decreased ADH (diabetes insipidus)

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Urinalysis (UA)

**Chemical examination includes**

- Protein
- Glucose
- Ketone bodies
- Bilirubin
- Blood
- Nitrites

Urine protein

Normal value up to 150mg/day

- (30% albumin, 30% globulins and 40% Tamm-Horsfall)
- Normally, Urine sticks -ve
- Urine sticks +ve = >300mg/L

Urine protein

**Proteinuria**

- *overflow (raised plasma Low MW Proteins, Bence Jones, myoglobin)*

- Renal diseases
Urine glucose

- Normally –ve
- +ve urine glucose
  - Increased blood glucose
  - Low renal threshold or other tubular disorders
- False +ve
  - Ascorbic acid

- Ketone bodies –Ve
- Bilirubin –ve
- Nitrite –Ve,
  +ve during UTI by gram +ve bacteria

Microscopic examination Urine sediment

Freshly passed urine. looking for

- Cells,
- Casts (Tamm-Horsfall protein)
- Crystals

Microscopic examination Urine sediment-cont

Cells

- RBCS
- WBC
- epithelial
**WBC 0-1 HPF**

- The presence of more than 5 WBC's / hpf may suggest infection, pyelonephritis or inflammation of the genitourinary tract.

**RBCS 0-1 HPF**

- Large no. of RBC's in the urine may be associated with (i) renal disease, (ii) lower urinary tract disease, (iii) external disease, (iv) physiologic causes including exercise.

**Epithelial 0-2 HPF**

- Increased in bladder inflammation.

**Casts (Tamm-Horsfall protein)**

Microscopic examination Urine sediment-cont
Granular cast

White cell cast + polymorphs + Bacteruria = **pyelonephritis**

Red Cell casts

Hematuria - glomerular disease

White blood Cell casts

Hylan cast
Crystals such as phosphates, urates, and oxalates occur in normal urine sediment, and are of limited clinical significance.

Triple phosphate and amorphous phosphate of normal urine

Triple phosphate crystals are seen only in alkaline urine. They have a characteristic crystal shape, often referred to as "coffin lids."

Calcium oxalate crystal

Calcium oxalates appear at any pH. They are octahedrons that resemble envelopes.

Urate crystals
Renal Disorders

Failure of renal function may occur rapidly or over a period of time

- Acute renal failure (ARF)
- Chronic renal failure (CRF)

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Signs and Symptoms of Renal Failure

- Symptoms of Uraemia (nausea, vomiting, lethargy)
- Disorders of Urine volume (polyuria, oliguria, anuria)
- Alterations in urine composition (haematuria, proteinuria, calculi)
- Pain
- Oedema

ARF

Divided into three categories

- Pre-renal failure
due to decreased blood supply
- Renal- intrarenal
due to intrinsic damage to kidney
- Post renal
due to urinary tract obstruction
Causes of pre-renal failure
Kidney hypo-perfusion (circulatory insufficiency)
- severe haemorrhage
- burns
- dehydration
- cardiac failure
- hypotension

Causes of pre-renal failure - continued
consequence
- reduced GFR and increased RAS
- urine osmolality high low in Na (<20mmol/l)
- if adequate perfusion is not rapidly restored PRF progress to CRF

Renal or internal renal failure
most common causes
- nephrotoxine (drugs)
- renal hypo-perfusion which leads to tubular necrosis
- internal obstruction (BJP)

Renal or internal renal failure - continued
- Specific renal (glomerulonephritis)
- and systemic diseases (systemic lupus erythematosus - SLE)
### glomerulonephritis
- A group of renal diseases that characterized by pathological changes in the glomeruli with immune bases
- May presented as
  - Acute nephritic syndrome with hematuria, HT, & edema
  - ARF or CRF
  - Proteinuria < 3 gm/day which leads to NS

### Biochemical Consequences of ARF
- Increased serum urea & creatinine
- Increased serum $K^+$
- Increased serum $H^+$ (Metabolic acidosis)
- Increased serum phosphate
- Reduced bicarbonate
- Reduced serum Na (dilutional)
- Reduced serum calcium (usually)

### Course of ARF
- **Oliguric phase**: Urine flow < 400 mL/24 hr
- **Diuretic phase**: Urine output increases $\uparrow$ GFR
- **Recovery phase**

### Oliguria:
**Features Indicating Pre-renal Cause**
- Urinary Na $< 20$ mmol/L
- Urinary/serum urea $> 20:1$
- Urine osmolality $> 600$ mmol/L (as response to hypovolemia)
Pre-Renal ARF?
Pre = functioning tubules

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>Urine Na⁺ (mmol/L)</td>
<td>Pre-renal &lt;20</td>
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<tr>
<td></td>
<td>Renal &gt;40</td>
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<tr>
<td>Ratio urine/plasma osmolality</td>
<td>Pre-renal &gt;1.5</td>
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<tr>
<td></td>
<td>Renal &lt;1.1</td>
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<td>Ratio urine urea/plasma urea</td>
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<td>concentration</td>
<td>Pre-renal &gt;10</td>
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<tr>
<td></td>
<td>Renal &lt;5</td>
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Chronic Renal Failure: Causes

- Glomerulonephritis
- Diabetes mellitus
- Hypertension
- Chronic pyelonephritis
- Etc.

Chronic Renal Failure: Prognosis
· GFR is proportional to 1/[Plasma creatinine]

Many patients may remain asymptomatic until GFR<15 ml/min

Chronic Renal Failure: Volume Problems

- Can't regulate urine volume /composition → urine of fixed osmolality, similar to serum (300 mOsm/kg)
- Retention of waste products
- Decreased erythropoietin and calcitriol synthesis
Laboratory Features of CRF
- Increased serum urea /creatinine
- Increased serum K+
- Metabolic acidosis
- Hypocalcaemia (usually)
- Hyperphosphataemia
- Osteodystrophy (alk phosphatase raised, 2° or 3° hyper PTH)
- Normochromic normocytic anaemia

Proteinuria and nephrotic syndrome
Normal glomerular:
7 - 10g/24hr protein filtration
Normal urinary protein excretion:
up to 150mg/24hr

Mechanisms of Proteinuria
- **Overflow**: Bence Jones, Hb, Myoglobin
- **Glomerular**: increases Glomerular permeability-Albumin-NS
- **Tubular**: impaired reabsorption β2-microglobulin
- **Secreted**: kidney epithelium, Tam-Horsfall

Proteinuria: Non-renal Factors
- Strenuous exercise
- Fever
- Burns
- Posture or orthostatic proteinuria (early morning vs afternoon)
Nephrotic Syndrome

- Proteinuria ≥ 5g/24hr

Nephrotic syndrome: Causes

- Glomerulonephritis (various types)
- Diabetes
- SLE
- etc.

Nephrotic Syndrome: Consequences

- Proteinuria
- Oedema
- Hyperlipidaemia
- Thrombotic tendency
- Increased susceptibility to Infection
- ± Uraemia

Renal Tubular Disorder

- Can be acquired or congenital
- Consequences losses substances which normally completely or partially reabsorbed
- Fanconi syndrome: is a general Tubular dysfunction
  - Amino acids- Cystinuria
  - Glucose
  - Phosphate
  - Proximal renal tubular acidosis
Renal Tubular Disorder-conti

- Rare but many causes: heavy metals inborn errors (e.g. Galactosaemia, Wilson's disease, cystinosis) paraproteins, amyloid etc.

Specific PT Transport Defects

- Cys slightly water soluble - precipitate in the kidney forming Cys-stone
- Type 2 proximal renal tubular acidosis

Urinary calculi

- One in every 20 people develop Urinary calculi at some point in their life.
- Is a hard mineral and crystalline material formed within the kidney or urinary tract.
- Are a common cause of blood in the urine and pain in the abdomen

Urinary calculi (UC)

Kidney stones form when there is a decrease in urine volume or an excess of stone-forming substances in the urine.
Causes of urinary calculi
- Dehydration
- Urinary tract infection
- Hypercalciuria
- Hyperuricoseuria
- Hyperoxaluria
- Lack of urinary inhibitors of crystallization

Composition of UC
- Calcium in combination with either oxalate or phosphate (common)
- Magnesium ammonium phosphate (triple phosphate)
- Uric acid 5-10%
- Cystine-1%

Biochemical investigation
- Most kidney stones eventually pass through the urinary tract on their own within 48 hours, with ample fluid intake.
- A 4 mm stone has an 80% chance of passage while a 5 mm stone has a 20% chance
- UC analysis

How can kidney stones be prevented?
- Drink more water. (The National Institutes of Health recommend drinking up to 12 full glasses of water a day, if you’ve already had a kidney stone.) Water helps to flush away the substances that form stones in the kidneys
www.just.edu.jo/~kkalani