REVIEW RENAL FUNCTION

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What are some of the functions of the kidneys?

• **Regulation of water / fluid balance:**
  • Arginine Vasopressin (AVP) stimulates formation of Aquaporins in Tubular cell, increasing reabsorption of Water from Glomerular filtrate;

• **Regulation of Electrolyte:**
  • Aldosterone acts on Tubules causing reabsorption of Na\(^+\) ions in exchange for secretion of K\(^+\) ions and H\(^+\) ions,

• **Regulation of Acid-Base balance:**
  • Maintenance of pH in blood and other body fluids,

• **Excretion of metabolic waste** products of Protein and Nucleic acid:
  • Urea, Creatinine, Creatine, Uric acid, Sulphate, Phosphate
• **Parathyroid Hormone (PTH):** Acts via the Kidneys:
  • To promote Tubular Reabsorption of Calcium ions,
  • For biosynthesis of 1,25-Dihydroxy-Cholecalciferol (Vit D₃) that regulates Calcium absorption in GIT;
• **Renin** from Juxtaglomerular cells in kidneys regulate Aldosterone production:
  • Renin converts Angiotensinogen to Angiotensin-1,
  • Angiotensin Converting Enzyme (ACE) converts Angiotensin-1 to Angiotensin II,
  • Angiotensin II stimulates biosynthesis of Aldosterone in Adrenal Cortex,
• **Erythropoietin** that promotes biosynthesis of Hb is partly regulated by kidneys,
What are the Renal Function Tests?

- **Renal Function Tests**: Procedures and Tests to evaluate Functional State of kidneys:
  - Tests for Glomerular Function;
  - Tests for Tubular Function;

- Specimens used are:
  - Urine,
  - Plasma or Serum,
• Renal Function Tests Include the following:
  • **Urinalysis**: First line test for Renal Function,
  • **Creatinine Clearance (CC)**: to measure Glomerular Filtration Rate (GFR),
  • **Inulin Clearance**: to measure GFR,
  • **Para-Amino-Hippuric Acid (PAH)**: to measure Renal Plasma Flow (RPF),
  • Urine Osmolality,
  • Plasma Creatinine,
  • Plasma Urea,
  • Plasma Electrolyte;
What test are carried out during urinalysis?

• Randomly collected urine sample is examined:
  • **Physically** for:
    - Color, Odor, Appearance, Concentration (specific gravity) or Osmolarity;
  • **Chemically** for:
    - Protein, Glucose, Urine pH (acidity/alkalinity);
  • **Microscopically** for:
    - Cellular elements (RBC, WBC, Epithelial cells),
    - Bacteria, Crystals, Casts (deposit of protein, cells, and other substances in kidney tubules);
What is Glomerular Filtration Rate (GFR)?

- GFR: useful index of numbers of functioning Glomeruli,
- GFR: amount of filtrate kidneys made per minute,
- GFR: maximum rate that plasma can be ‘Cleared’ of a substance;
- GFR is related to body size and age, higher in males compared to females; reduced rate in elderly,
- Reduction in GFR can be caused by:
  - Restriction of Renal blood supply,
  - Low Cardiac Output,
  - Destruction of Nephrons by Renal Diseases, etc
- Reduction in GFR results in Retention of Waste Products of Metabolism in blood;
How is GFR (Creatinine Clearance) calculated?

• GFR is directly related to Clearance,
• GFR can be calculated from Clearance of a compound in Plasma that is freely filtered at Glomerulus, and is not reabsorbed or Secreted by Tubules,
• Creatinine: normal product of muscle metabolism in blood is used to calculate GFR (Creatinine Clearance);
• GFR is calculated from Creatinine content of 24-hrs urine collection, and Plasma concentration of Creatinine within the 24-hrs period,
• **Inulin** can be used to measure GFR because it is filtered but not re-absorbed or secreted by Renal Tubules,
Take Note:

- GFR must be corrected for body surface area of patients;
  - Correction factor is calculated from Age and Height of patient in relation to “Standard” Average Body Surface Area of an adult;
- ‘Standard’ average body surface area = 1.73m$^2$;
- It is a common mistake to consider V as urine volume;
- V is Urine Flow Rate: Volume of Urine collected in 24hrs, expressed in ml/min
• Calculation of GFR or Creatinine Clearance (CC):
  \[ GFR = CC = \frac{(U \times V)}{P} \]

• Where **U** = Urine concentration of Creatinine (mmol/L);
• **P** = Concentration of Creatinine in Plasma or Serum (mmol/L; \(\mu\)mol/L)
• **V** = Urine Flow Rate (ml/minute);
How is GFR or CC calculated using Cockcroft and Gault equation?

\[(140 - \text{Age in yrs}) \times \text{Weight (Kg)}\]

\[\text{CC (ml/min)} = \frac{0.814 \times \text{Serum Creatinine (umol/L)}}{}\]

- To correct for muscle mass:
  - For Female multiply result by 0.85
  - For Male multiply by 1.22
Another form of the Cockcroft and Gault equation

\[ (140 - \text{Age in yrs}) \times \text{Weight (Kg)} \]

- \( \text{CC (ml/min)} = \frac{72 \times \text{Serum Creatinine (umol/L)}}{} \)

- NB: For Female multiply result by 0.85

- Limitations of Cockcroft and Gault equation:
  - Patients should not be severely malnourished,
  - Patients should not be very obese,
  - Renal Function should not be severely impaired (GFR < 20 ml/min)
What is Proteinuria?

• Glomerular filtrate is an ultra-filtrate of plasma;
• Glomerular basement membrane does not allow passage of albumin and large molecular weight proteins,
• Small amount of protein, (<25mg/24h) may be in urine,
• Positive screening test for protein (routine urinalysis) on random urine sample should be followed-up with test on 24-h urine sample that precisely measures quantity of protein in urine,
• Protein, in excess of 250mg/24h urine sample indicates significant damage to Glomerular membrane,
• Persistent presence of significant amounts of protein in urine, is an indicator of kidney disease;
What are the different types and causes of Proteinuria?

• **Glomerular Proteinuria:**
  • Abnormal leaking of large and small molecular weight proteins into filtrate resulting from damaged of Glomerular membrane,
  • May be due to:
    • Exercise,
    • Fever (Febrile Proteinuria),
    • Congestive Cardiac Failure,
    • Glomerulonephritis,
    • Renal Stenosis,
• **Glomerulonephritis**:  
  • Common cause of persistent Proteinuria  
  • Amount of protein in urine depends on:  
    • Extent of Glomerular damage,  
    • Molecular mass of protein,  
    • Capacity of Tubule to reabsorb or metabolize proteins  
  • May be mild, moderate or Severe Proteinuria  
  • **Severe Proteinuria:**  
    • Protein loss in urine exceeds synthetic capacity of liver to replace protein, resulting in Hypo-Proteinemia  
  • **Severe persistent Proteinuria is one of the features of Nephrotic Syndrome,**
• **Nephrotic Syndrome:**
  - Large amount of protein loss in urine,
  - Leads to Hypo-Proteinemia and Edema,
  - Edema may be caused by low albumin or secondary Hyper-Aldosteronism,
  - Patients may also develop Hyperlipidemia,

• **Some causes of Nephrotic Syndrome:**
  - Glomerulonephritis,
  - Systemic Lupus Erythematosus,
  - Diabetes Nephropathy
• **Tubular Proteinuria:**
  • Failure of Tubules to reabsorb filtered plasma proteins,
  • Abnormal secretion of protein into urinary tract,
    • May be due to Tubular or Interstitial damage,
  • Proteins with low molecular wt are excreted by Tubules,
  • Loss of protein is mild about 2.0g/24h urine sample,
  • Sensitive test for assessment of Renal Tubular damage:
    • **Measure Urinary β₂-Microglobulin:** Values greater than 0.4mg/24h indicates tubular damage
• **Overflow Proteinuria:**
  • Large amount of low molecular weight proteins in urine,
  • Proteins are filtered at Glomerulus, but not reabsorbed or metabolized completely by Tubules,
  • Some causes of Overflow Proteinuria:
    • Acute Pancreatitis,
    • Multiple Myeloma,
    • Intravascular Hemolysis,
    • Myelomonocytic Leukemia,
    • Crush Injuries

• **Orthostatic (Postural) Proteinuria:**
  • Proteinuria occurs after standing for a long time,
  • Protein absent in early morning urine samples,
Use of Plasma Creatinine in Renal Function Test

- Creatinine is a by-product of muscle energy metabolism,
- Creatinine is cleared from blood and excreted in urine,
- Level of creatinine in plasma depends on muscle mass, thus normally Creatinine in blood remains relatively constant,
- Plasma Creatinine level is inversely proportional to CC or GFR,
- Plasma Creatinine level is not affected by Liver function,
- **Elevated Plasma Creatinine is sensitive indicator of impaired Renal function,**
- Normal Plasma Creatinine conc. of a patient does not always indicate normal Renal function,
- Progressive rise in serial Plasma Creatinine levels may indicate impaired Renal function,
Use of Blood Urea Nitrogen (BUN) \(\{\text{H}_2\text{N-CO-NH}_2\}\)

- **Urea** is a by-product of protein metabolism,
- Urea is formed in liver, released in blood then filtered by Glomerulus and excreted in urine,
- **BUN** is the amount of Nitrogen contained in Urea,
- High BUN indicates kidney dysfunction, but because BUN is also affected by Protein intake and Liver Function, the test is done in conjunction with Plasma Creatinine, a more specific indicator of kidney function
- Elevated BUN is suggestive, but not diagnostic of kidney dysfunction, because BUN is affected by other factors;
Other parameters in blood for assessing kidney function

• Measurement of blood levels of other compounds that are regulated in part by kidneys are useful in evaluating kidney function:

• These include:
  • Electrolytes: Sodium, Potassium, Chloride;
  • Bicarbonate, Calcium, Magnesium, Phosphorus,
  • Protein,
  • Uric Acid,
  • Glucose
RENAL TUBULAR FUNCTION TESTS

• Glomeruli provide an efficient filtration mechanism for removal of waste products and toxic substances;

• Tubular reabsorption must be efficient to ensure that important constituents such as: Water, Sodium, Glucose, and Amino Acids are not lost in urine;
  • About 180 liters of fluid is filtered by Glomerulus each day, and more than 99% is reabsorbed by Tubules;

• Of all tubular functions, the most frequently affected by disease is ability to concentrate the urine;

• Tubular function can be assessed by comparing Osmolality of Urine and Plasma;
• For “healthy” person under normal Physiological conditions Urine is more concentrated than Plasma
Urine Osmolality > Plasma Osmolality

• Urine-Plasma Osmolality Ratio is between 1.0 and 3.0,
• Urine / Plasma ratio < 1.0,
  • Indicates poor reabsorption by Renal Tubules,

• Some disorders of Tubular function are inherited;
  • Some patients cannot reduce their urine pH below 6.5, because of specific failure of Hydrogen ion secretion;
How is Acid-Base balance regulated by the kidneys?

• Kidney regulates Acid-Base Balance by controlling:
  • Re-absorption of Bicarbonate ions (HCO₃⁻)
  • Secretion of Hydrogen ions (H⁺)
• Both processes depend on formation of HCO₃⁻ and H⁺ ions from CO₂ and H₂O within Renal Tubular cells:

  Carbonic Anhydrase
  \[
  \text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^- 
  \]
• H⁺ ions formed are actively secreted into Tubule fluid in exchange for Na⁺ ions,
What mechanisms are used in the kidney for elimination of Acids?

• Mechanisms for elimination of Acids:
  • **Re-absorption** of Sodium Bicarbonate (NaHCO$_3$) by Proximal Renal Tubules, *(Fig. 1)*;
  • **Regeneration** of HCO$_3^-$ by Distal Renal Tubules *(Fig. 2)*;
  • Formation of **Phosphate buffer** in Distal Tubules *(Fig. 3)*;
  • Production of **Ammonia (NH$_3$)** by Distal Renal Tubules for formation of Ammonium buffer *(Fig. 4)*;
  • Secretion of H$^+$ ions by Tubular cells serves initially to reabsorb HCO$_3^-$ ions from the Glomerular filtrate;
  • After all the HCO$_3^-$ ions have been reabsorbed, any deficit that occurs is regenerated;
Fig. 1: Reabsorption of Bicarbonate by Renal Tubules

Diagram to illustrate Reabsorption of Bicarbonate in the renal tubules

- Blood vessel
- Glomerulus (Glomerular Membrane)
- Glomerular filtrate

1. **HCO₃⁻** → **Na⁺** → **Na⁺** (Renal Tubular Cells)
2. **H⁺** (Glomerular filtrate) → **H₂CO₃** → **H₂CO₃⁻** → **CO₂** → **H₂O**
3. **H₂CO₃⁻** (Renal Tubular Cells) → **H⁺** → **H₂CO₃** → **CO₂** → **H₂O** (Interstitial Fluid)

**Carbonic Anhydrase**
Fig. 2: Regeneration of Bicarbonate ions by Renal Tubules

Diagram to illustrate Regeneration of Bicarbonate ions in the renal tubules

Blood vessel

Glomerulus (Glomerular Membrane)

Glomerular filtrate

Renal Tubular Cells

Interstitial Fluid (Peritubular capillary)

Na+

H⁺

H⁺

H₂CO₃

H₂O

CO₂

Na⁺

HCO₃⁻
Fig. 3: Formation of Phosphate Buffer in Renal Tubules

Diagram to illustrate excretion of $H^+$ ions by Phosphate buffer in the renal tubules

Blood vessel

Glomerulus (Glomerular Membrane)

Glomerular filtrate

HPO$_4^{2-}$ Na$^+$

$+$ Na$^+$

HPO$_4^{2-}$ + $H^+$

$H_2$PO$_4^-$

Carbonic Anhydrase

Renal Tubular Cells

$Na^+$

$HCO_3^-$

$H_2CO_3$

$H_2O$

$CO_2$

Interstitial Fluid (Peritubular capillary)

$CO_2$

$HCO_3^-$
Fig. 4: Formation of Ammonium Buffer in Renal Tubules

Diagram to illustrate excretion of H⁺ ions by Ammonium buffer in the renal tubules
What is Anion Gap?

• Anion Gap (AG) calculation is the sum of routinely measured Cations minus routinely measured Anions:

\[
\text{Anion Gap} = (\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)
\]

• However, because \( \text{K}^+ \) is a small value it is usually omitted from the AG equation; the most commonly use equation is:

\[
\text{Anion Gap} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)
\]
• Venous value of HCO$_3^-$ should be used in calculation;
• Venous value of CO$_2$ can be used in place of Bicarbonate

The equation will then be:  $\text{AG} = \text{Na}^+ - (\text{Cl}^- + \text{CO}_2)$

• Normal AG calculated without K$^+$ is about 12.4mEq/L;
• Anion Gap exists because not all Electrolytes are routinely measured;
• Normally there is electrochemical balance in cells; thus the sum of all Anions equals the sum of all Cations;
• However, several Anions are not measured routinely, leading to the Anion Gap;
• Anion Gap is thus an artifact of measurement, and not a Physiologic reality;