REVIEW RENAL FUNCTION

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PBL MBBS IV

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What are some of the functions of the kidneys?

- **Regulation of water / fluid balance**:
  - Arginine Vasopressin (AVP) stimulates formation of Aqua-porins 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 D_3) 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)**:

$$\mathbf{GFR = CC = (U \times V)/P}$$

- Where **U** = Urine concentration of Creatinine (mmol/L);
- **P** = Concentration of Creatinine in Plasma or Serum (mmol/L; μmol/L)
- **V** = Urine Flow Rate (ml/minute);

How is GFR or CC calculated using Cockcroft and Gault equation?

- $$\textbf{CC (ml/min)} = \frac{(140 - \text{Age in yrs}) \times \text{Weight (Kg)}}{0.814 \times \text{Serum Creatinine (umol/L)}}$$

- 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

- **CC (ml/min)** = $\dfrac{(140 - \text{Age in yrs}) \times \text{Weight (Kg)}}{72 \times \text{Serum Creatinine (umol/L)}}$

- 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 β_2-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) {$H_2N\text{-}CO\text{-}NH_2$ }

- **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 (**HCO_3^-**)
  - Secretion of Hydrogen ions (**H^+**)
- Both processes depend on formation of HCO_3^- and H^+ ions from CO_2 and H_2O within Renal Tubular cells:

Carbonic Anhydrase

$$CO_2 + H_2O \Leftarrow\!=\!=\!=\!=\!=\!=\Rightarrow H_2CO_3 \Leftarrow\!=\!=\!=\!=\!=\Rightarrow H^+ + HCO_3^-$$

- 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

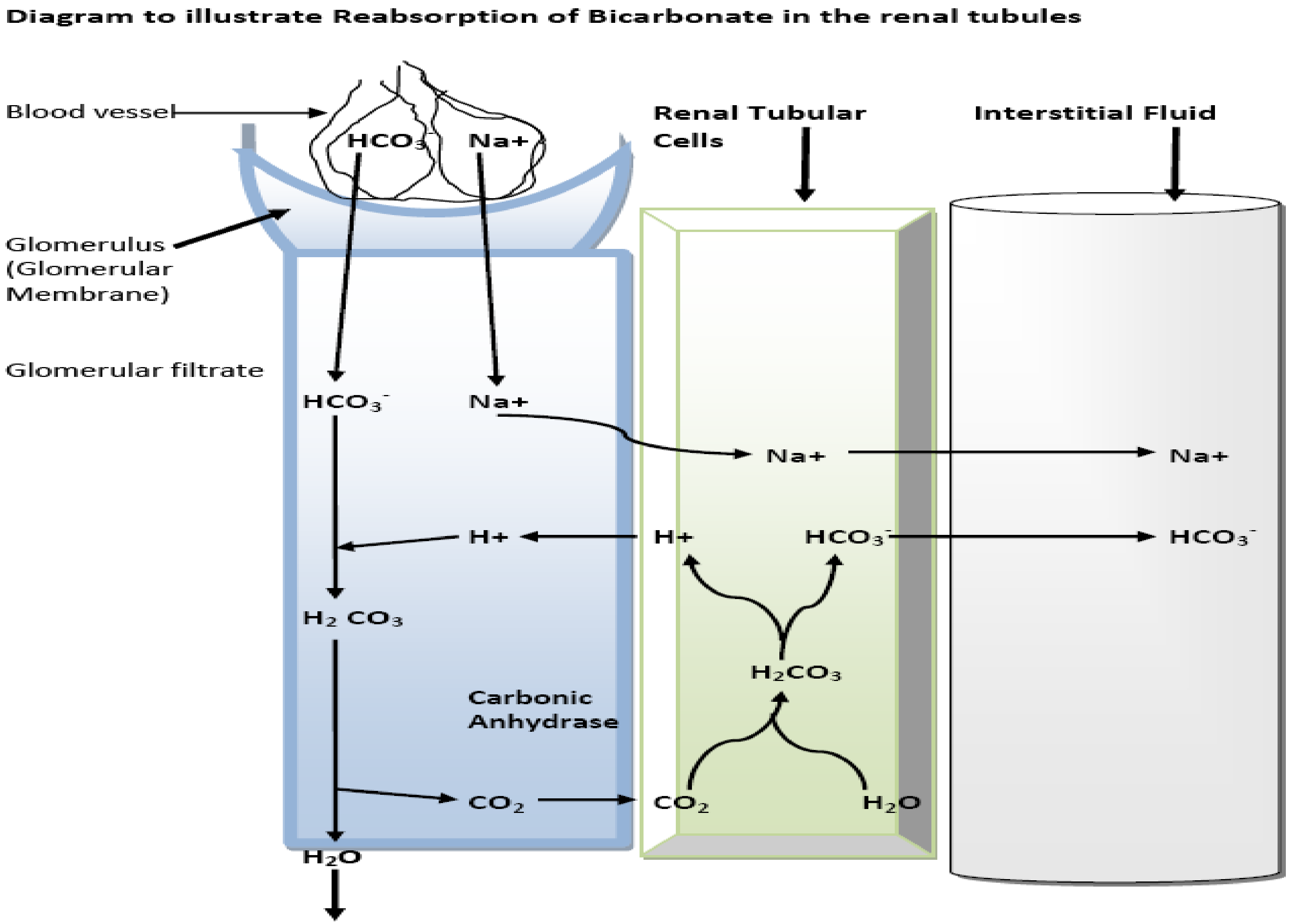


Fig. 2: Regeneration of Bicarbonate ions by Renal Tubules

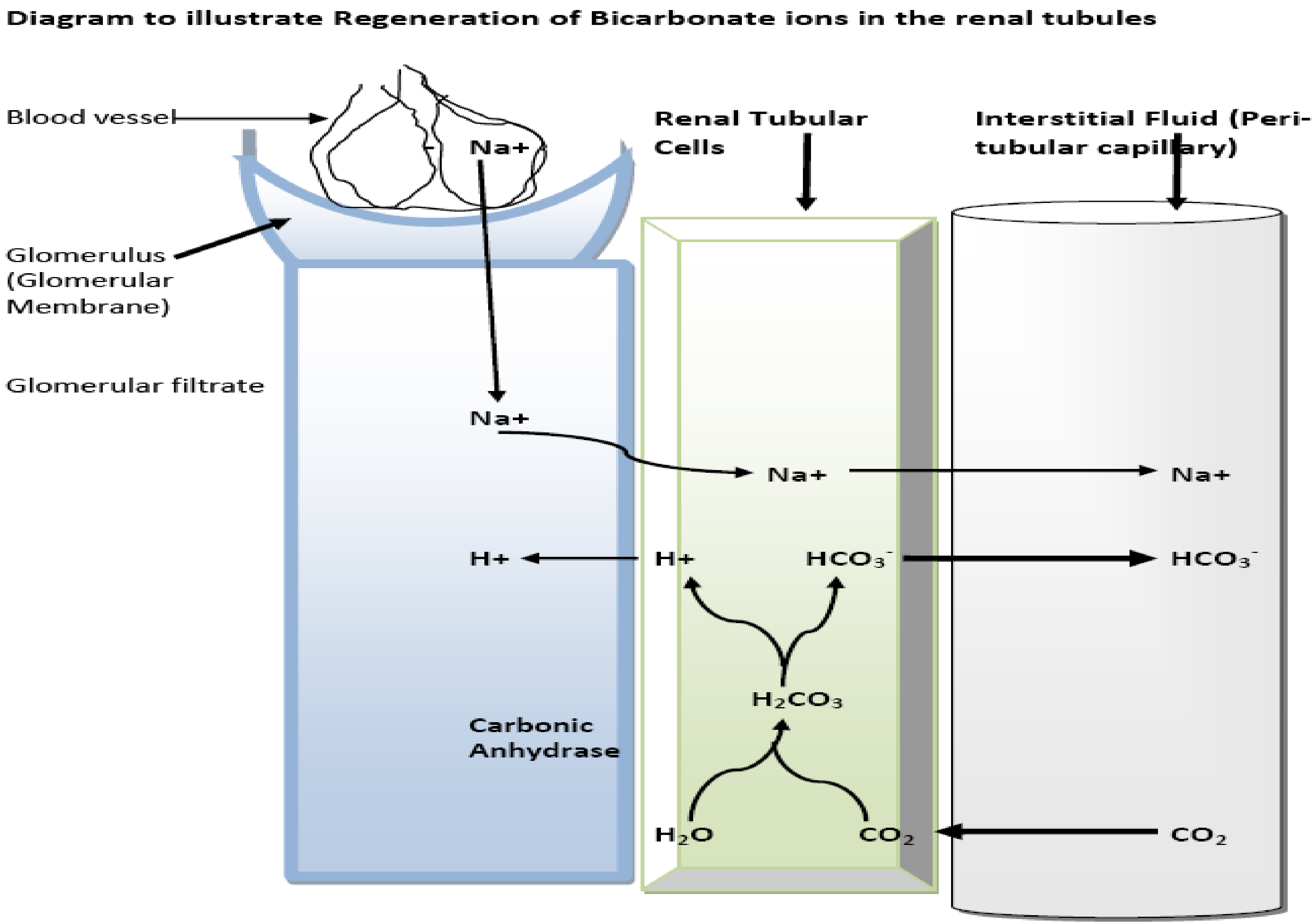


Fig. 3: Formation of Phosphate Buffer in Renal Tubules

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

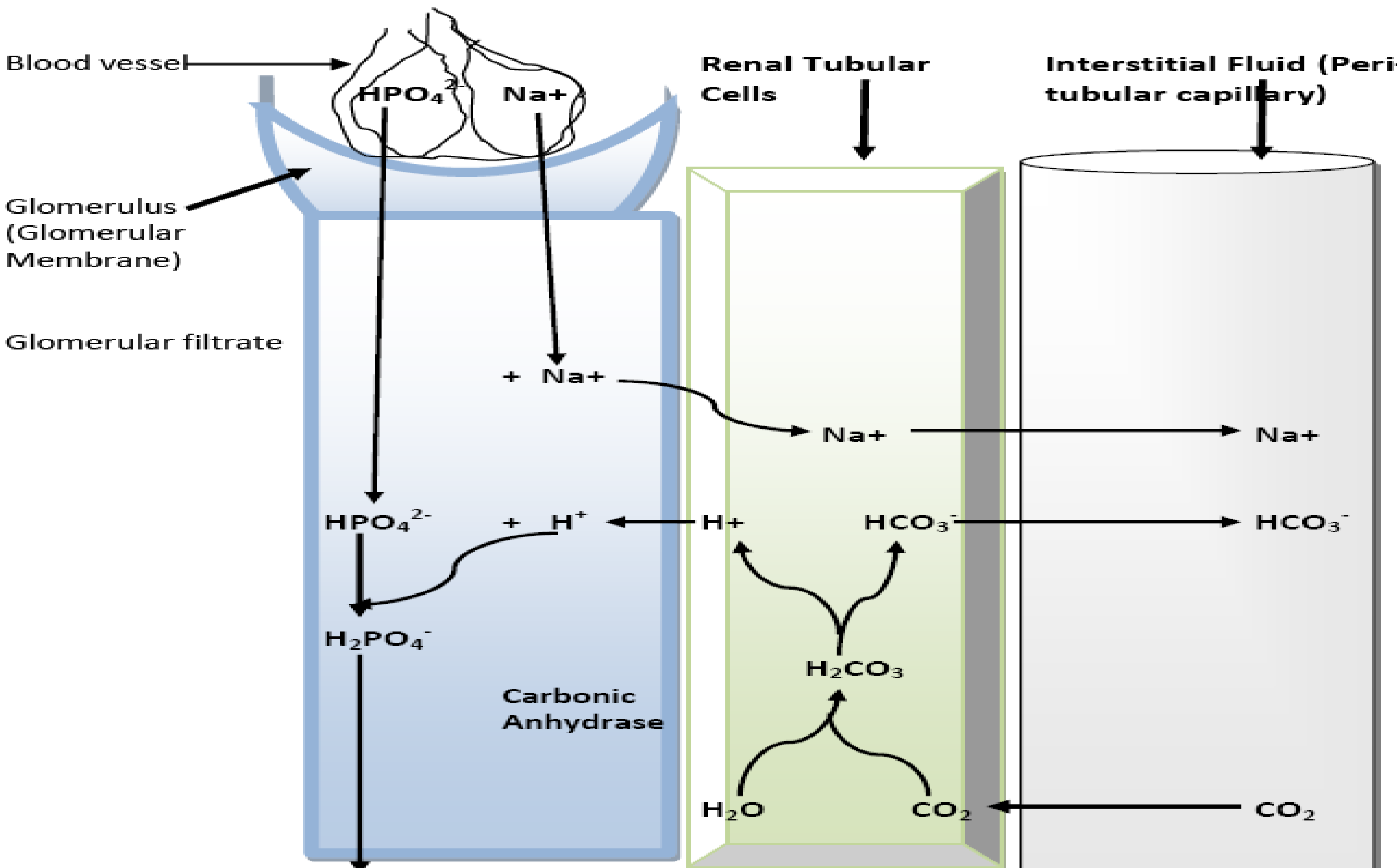
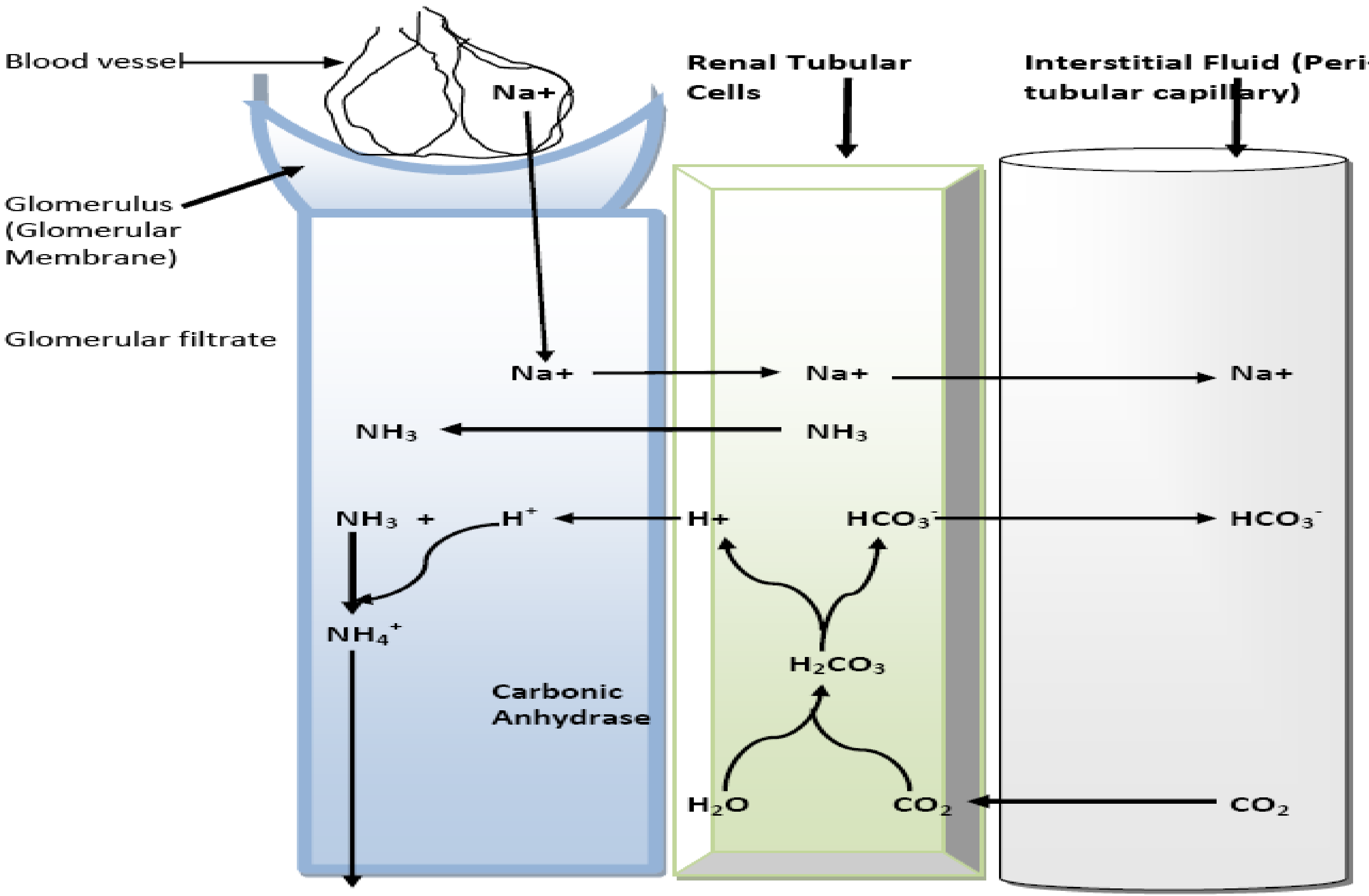


Fig. 4: Formation of Ammonium Buffer in Renal Tubules

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:

$$\textbf{Anion Gap} = (Na^{+} + K^{+}) – (Cl^{-} + HCO_3^{-})$$

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

$$\textbf{Anion Gap} = Na^{+} - (Cl^{-} + HCO_3^{-})$$

- 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: **$AG = Na^+ - (Cl^- + CO_2)$**

- 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;