RENAL TUBULAR ACIDOSIS – An Overview

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What is Renal Tubular Acidosis (RTA)?

Two simple definition of RTA:

• **RTA**: group of disorders of Renal Tubules that result in Normal Anion Gap Hyperchloremic Metabolic Acidosis in the presence of Normal Glomerular Function;

• **RTA**: group of disorders in which there is Metabolic Acidosis due to defect in Renal Tubular Acidification Mechanism used to maintain normal Plasma Bicarbonate (HCO$_3^-$ ions) concentration and blood pH
IMPORTANT TO NOTE

• Control of pH is needed for normal metabolism,

• Large quantities of **Anions** (Sulphate, Phosphate, Lactate) are produced during metabolism,

• They are collectively called “Unmeasured Anions”
  • Accumulation of Anions causes increase in Plasma Anion gap,

• Renal Tubules play major role in:
  • Elimination of the unmeasured anions,
  • Regulation of H⁺ ions,
  • Control of pH in body fluids;

• Failure of Renal tubules to regulate H⁺ ions may cause metabolic acidosis,
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⁻ & H⁺ ions from CO₂ and H₂O within Renal Tubular cells:

  \[
  \text{Carbonic Anhydrase} \\
  \text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^- \\
  \]

• H⁺ ions formed are actively secreted into Tubule fluid in exchange for Na⁺
What mechanisms are used by renal tubules for regulation of Acids Base Balance?

- Renal acidification mechanisms keep the blood pH within a narrow range of 7.35 – 7.45 that is vital for normal function of cellular and tissue metabolism,

- Renal Tubules regulate Acid Base Balance by the following mechanisms:
  
  **Re-absorption** of Sodium Bicarbonate (\(\text{NaHCO}_3\)) by Proximal Renal Tubules, *(Fig. 1)*,
  
  - Proximal Tubule reabsorbs about 85 to 90% of filtered Bicarbonate ions (\(\text{HCO}_3^-\)),
    
    - Failure of this process leads to reduction of \(\text{HCO}_3^-\) ions in the systemic blood,
    
    - Resulting in Metabolic Acidosis;
Fig. 1: Reabsorption of Bicarbonate by Renal Tubules

Diagram to illustrate Reabsorption of Bicarbonate in the renal tubules

Blood vessel → HCO₃⁻, Na⁺ → Renal Tubular Cells

Glomerulus (Glomerular Membrane)

Glomerular filtrate → HCO₃⁻, Na⁺ → Interstitial Fluid

H⁺ → H₂CO₃ → CO₂, H₂O

Carbonic Anhydrase

HCO₃⁻ → H₂CO₃ → H₂O, CO₂
• **Regeneration** of HCO$_3^-$ ions by Distal Tubules:
  • Distal tubule reabsorbs the remaining filtered HCO$_3^-$ ion,
  • However, after all the HCO$_3^-$ ions have been reabsorbed, any **deficit that occurs** is **regenerated** by Distal Tubules (Fig. 2);
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

Na+

Renal Tubular Cells

Na+

H+

H+

HCO$_3^-$

H$_2$CO$_3$

H$_2$O

CO$_2$

Interstitial Fluid (Peritubular capillary)

Na+

HCO$_3^-$

CO$_2$
• **Secretion of H\(^+\) ions and Buffering of the H\(^+\) ions by Ammonium and Phosphate buffers by Distal Tubule;**

• These processes include the following:
  
  • 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)*,
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 $\rightarrow$ Glomerulus (Glomerular Membrane) $\rightarrow$ Glomerular filtrate $\rightarrow$ Renal Tubular Cells $\rightarrow$ Interstitial Fluid (Peritubular capillary)

- $HPO_4^{2-}$ $\rightarrow$ $HPO_4^{2-}$ $\rightarrow$ $H_2PO_4^-$ $\rightarrow$ Carbonic Anhydrase
- $H^+$ $\rightarrow$ $HCO_3^-$ $\rightarrow$ $H_2CO_3$ $\rightarrow$ $CO_2$ $\rightarrow$ $H_2O$ $\rightarrow$ $CO_2$
Fig. 4: Formation of Ammonium Buffer in Renal Tubules

Diagram to illustrate excretion of H⁺ ions by Ammonium buffer in the renal tubules.
What are the major conditions that impair handling of HCO$_3^-$ by Kidneys?

- The major conditions include:
  - Renal Failure,
  - Renal Tubular Acidosis,
- Both involve defect in Renal Tubules,
- HCO$_3^-$ ions reabsorption and regeneration are tubular functions;
- It is Tubular defect that causes Metabolic Acidosis,
- **Important to note**: Renal Failure also involves marked defect in Glomerular Filtration,
What are some of the possible causes of RTA in children?

- RTA in children in majority of cases is Congenital;
  - Can be Inherited as Recessive or Dominant trait,
  - Can be associated with Genetic disorders like Salt Loosing Congenital Adrenal Hyperplasia,
- Sickle cell disease,
- Carbonic Anhydrase II deficiency,
- Some cases are acquired, may be due to use of drugs like outdated Tetracycline, or by Heavy metals, etc,
- Withdrawal of the causative agent can result in cure,
What are some of the signs and symptoms of RTA in infants?

• When other disease conditions are excluded (e.g. Diarrhoea) a number of signs and symptoms can be considered, when due to no apparent cause a child:
  • Fails to put on weight or loses weight,
  • Becomes Dehydrated,
  • Excessive urine output (Polyuria),
  • Excessive Thirst,
  • Weakness,
  • Poor appetite,
  • Vomiting,
  • Constipation,
• Muscle weakness, which may be severe enough to cause Paralysis of respiratory muscles due to Low Serum Potassium levels (Hypokalemia),
• Breathlessness with air hunger type of breathing due to Acidosis may be seen in severe cases,
• Rickets & Bony Deformities occur late in the disease,
• Skeletal deformities due to RTA occur because Calcium from the bones is mobilized to buffer excess H⁺ ions and bones become Demineralised, Deformed, Bowed and can sustain fractures;
• In clinically suspected cases, Arterial Blood Gas estimation will reveal Low Serum $\text{HCO}_3^-$ /$p\text{CO}_2$ level with Low blood pH and Normal Anion Gap,

• Urinary pH may be inappropriately high (>5.5) for the level of Acidosis in distal RTA,
What is Anion Gap?

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

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

- However, because \( K^+ \) 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 $\text{HCO}_3^-$ 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 $\text{K}^+$ is about $12.4\text{mEq/L}$;
What causes Anion Gap?

• Anion Gap exists because not all Electrolytes are routinely measured;
• Normally there is electrochemical balance in cells; thus
  Total Anions = Total 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;
How can Distal RTA (Type I RTA) be characterised?

Distal RTA (Type I RTA):

• Reduced capacity of Distal Tubule to lower pH in Luminal fluid,

• Defect may be due to:
  • Failure to eliminate $H^+$ ions,
  • Failure in $H^+$ ions secretion, or
  • Retention of $H^+$ ions in the renal tubular lumen,
Consequences of Distal RTA

• High Urinary pH (above 5.5),
• Reduced Excretion of Titrable Acid and Ammonium ions,
• Mild Bicarbonaturia (HCO$_3^-$ ions in urine), because a small amount of HCO$_3^-$ is reabsorbed distally,
• Plasma [HCO$_3^-$] is often below 10mmol/L,
  • Severe Hypobicarbonatemia,
• Plasma [K$^+$] usually low, but may be normal,
• GFR relatively normal,
• Subdivisions of Type I RTA:
  • Related to difficulties in maintaining a secretory H$^+$ ion gradient in Distal Tubule,
How can Proximal RTA (Type II RTA) be characterised?

**Proximal (Type II) RTA:**

- Relative decrease in ability of Proximal Tubule to reabsorb filtered $\text{HCO}_3^-$ ions causing metabolic acidosis,
  - Associated with loss or failure to reabsorb $\text{HCO}_3^-$
- Decreased Ammonium excretion into Tubule lumen,
- Type II RTA is often part of Fanconi syndrome:
  - Proximal Tubule loss of Glucose, Calcium, Phosphate, other Electrolytes, and Organic Acids,
- Inhibitors of Carbonic Anhydrase cause Type II RTA,
Consequences of Type II RTA

• Clinically associated with failure to thrive,
• Urine pH above 5.5 as Acidosis develops,
• Urine pH below 5.5 when Acidosis is fully established,
• Plasma $\left[ \text{HCO}_3^- \right]$ typically 15 – 20mmol/L,
  • Moderate Hypobicarbonatemia;
• Plasma $\left[ \text{K}^+ \right]$ usually low, but may be normal,
• Substantial Bicarbonaturia (high $\text{HCO}_3^-$ in urine),
• GFR relatively normal,
How can Type IV RTA be characterized?

**Type IV:** Hyperaldosteronism, Aldosterone resistance, Hyperkalemic RTA):

- Typically diagnosed when RTA is associated with Hyperkalemia,

- Causative defect is decreased Aldosterone Secretion, often secondary to Low Renal Renin secretion (“Hyporeninemic Hypoaldosteronism”),
  - Acidosis Inhibiting production of NH$_4^+$ ion,
• Defect in Distal Tubule Aldosterone Receptor ("Aldosterone Resistance") may be present,
• In some case, a receptor defect is the sole cause,
• Type IV RTA can result from numerous causes:
  • Decreased Aldosterone,
  • Increased Renal Resistance to Aldosterone,
  • Presence of Aldosterone Antagonist, example: Spironolactone,
Consequences of Type IV RTA

- Associated with Increased Renin Activity,
- Hyponatraemia,
- Hyperkalemia and Volume Depletion,
- Urine pH usually below 5.5,
- Plasma $[\text{HCO}_3^-]$ typically 15 – 20mmol/L,
  - Moderate Hypobicarbonatemia,
- Plasma $[\text{K}^+]$ High,
Some Laboratory Tests Useful in Diagnosis of RTA

Urine pH:

- Urine pH greater than 5.5 in the presence of Acidosis is diagnostic of Type I RTA (Distal RTA) if the following conditions are excluded:
  - Urea-splitting UTI (which raises urine pH),
  - Hypokalemia (which stimulates NH₃ production, buffering free protons),
  - Avid salt retentive state,
- Other lab tests include:
  - Net Acid Excretion; Urine Acidification Tests;
  - Na₂ SO₄ administration;
  - Fractional Excretion of HCO₃⁻ (Fe₉HCO₃⁻);
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