(Renal Physiology 9)

Acid-Base Balance 1

Basics of Acid Base

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Acid – Base Balance

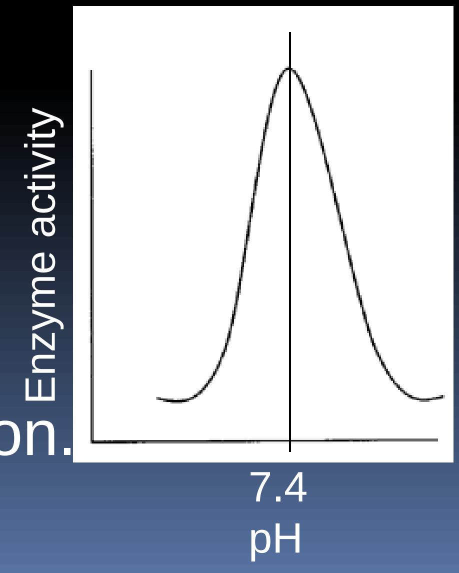
Why is control of $[H^+]$ so important?

- Highly reactive chemical species (protons).
  - combine easily with negatively charged ions and bases.

- Precise $[H^+]$ regulation is vital because activity of almost all enzyme systems / proteins (inc. ion channels) influenced by pH **(*e.g.* hydrogen bonding and charge on proteins altered by pH ∴ tertiary structure and function affected.)**

- Most enzymes function optimally at pH ~ 7.4 (except gastric enzymes).

- Acid-base imbalances can cause cardiac arrhythmias and abnormal neuronal excitation.



Acid – Base Balance

Definitions (Bronsted-Lowry)

- **ACIDS** – Molecules containing hydrogen atoms that can release (**DONATE**) H^+ into solution (*e.g.* $HCl \Leftrightarrow H^+ + Cl^-$).

- **STRONG** acids – all their H^+ is dissociated completely in H_2O.
- **WEAK** acids – dissociate partially in H_2O and are efficient at preventing pH changes.

- **BASES** (*a.k.a.* alkalis) – ions or molecules that can **ACCEPT** H^+ (*e.g.*, $HCO_3^- + H^+ \Leftrightarrow H_2CO_3$).

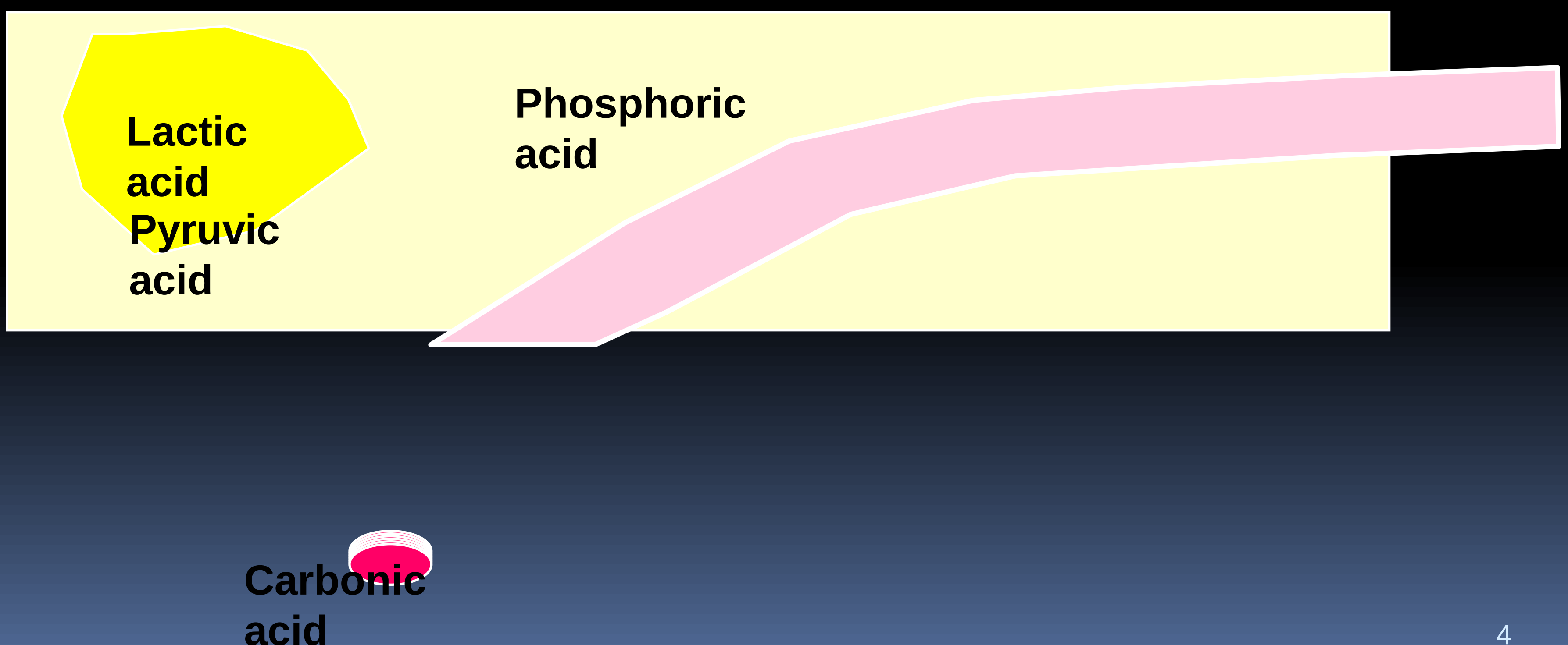
- **STRONG** bases – dissociate easily in H_2O and quickly bind H^+.
- **WEAK** bases – accept H^+ more slowly (*e.g.*, HCO_3^- and NH_3)

  Proteins in body function as weak bases as some constituent **AMINO ACIDS** have net negative charge and attract H^+ (*e.g.* **HAEMOGLOBIN**).

Physiologically important acids include:

- **Carbonic acid (H_2CO_3)**
- **Phosphoric acid (H_3PO_4)**
- **Pyruvic acid ($C_3H_4O_3$)**
- **Lactic acid ($C_3H_6O_3$)**

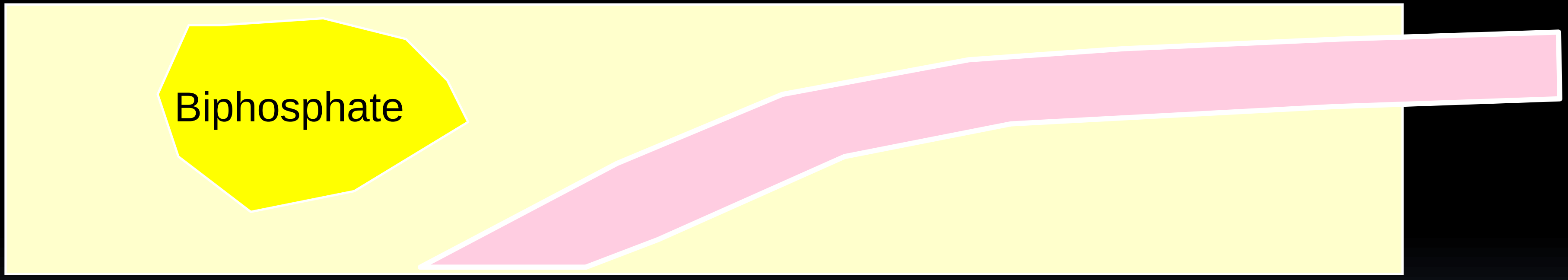
These acids are dissolved in body fluids



Physiologically important bases include:

Bicarbonate (HCO_3^-)

Biphosphate (HPO_4^{-2})

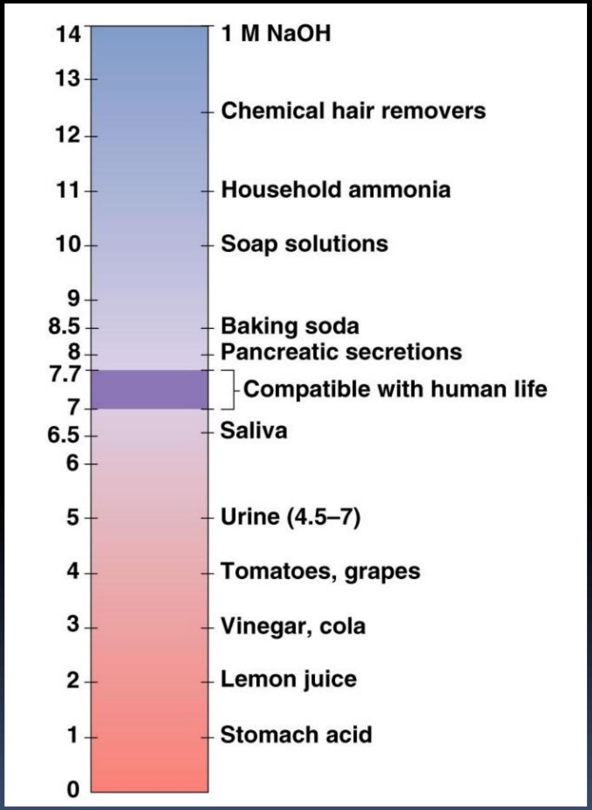


Bicarbonate

Acid – Base Balance

pH Scale (Sørensen, 1909)

- Relative to other ions, $[H^+]$ of body fluids kept **VERY LOW**
  e.g., ECF $[Na^+] \approx 145$ mM/L, ECF $[H^+] \approx 0.00004$ mM/L (40nM)
  (~ 3.5 million fold difference).



- Because $[H^+]$ so low, easier to express $[H^+]$ on a logarithmic scale $\Rightarrow$ pH units.

$$pH = \log \frac{1}{[H^+]} = -\log [H^+]$$

  - Normal pH = -log [0.00000004] M
    = 7.4

Acid – Base Balance

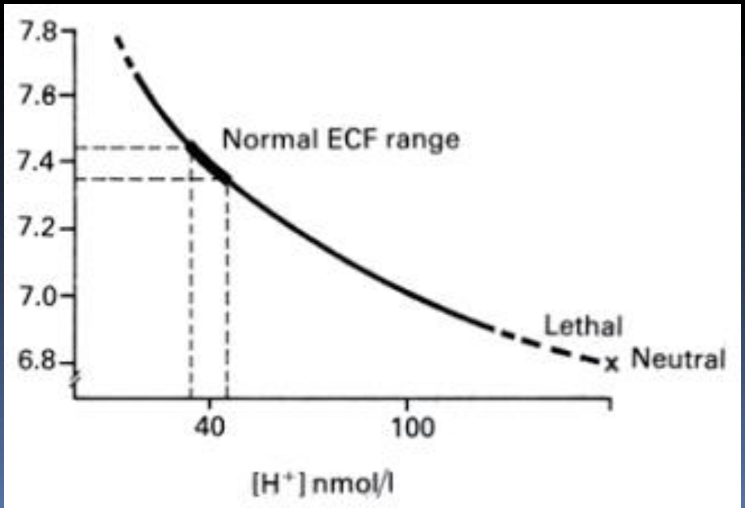
pH Scale (Sørensen, 1909)

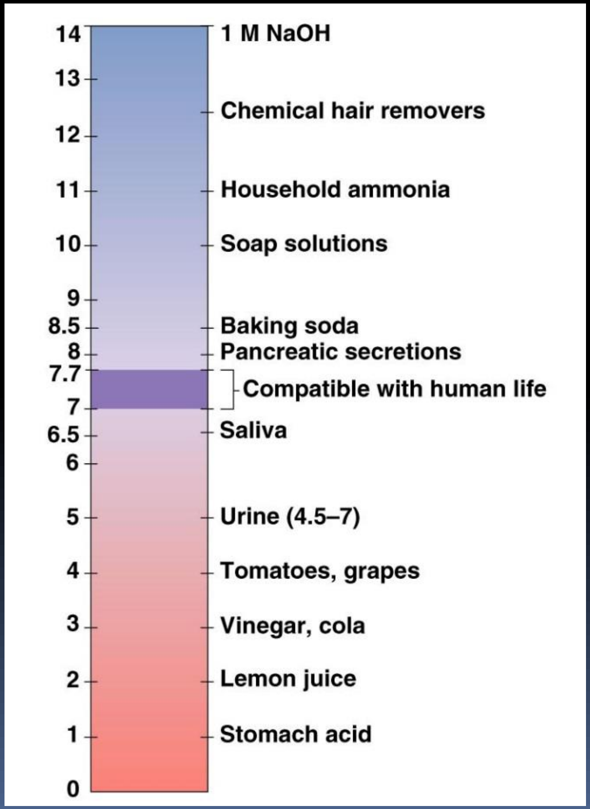
- pH **INVERSELY** related to $[H^+]$, *i.e.*

  as $[H^+]$ ↑, pH falls – acidosis (below 7.35)

  as $[H^+]$ ↓, pH increases – alkalosis (above 7.45)

- Normal **BLOOD** pH range for adults = **7.35 – 7.45** maintained by chemical buffer systems, kidneys and lungs.
  - **DEATH** likely if pH ↑7.8 or ↓6.8.





Sources of H^+

- <u>The body generally **PRODUCES** more acids than bases.</u>

1) Cellular aerobic metabolism produces **15,000 mmol** CO_2/day.

$$CO_2 + H_20 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

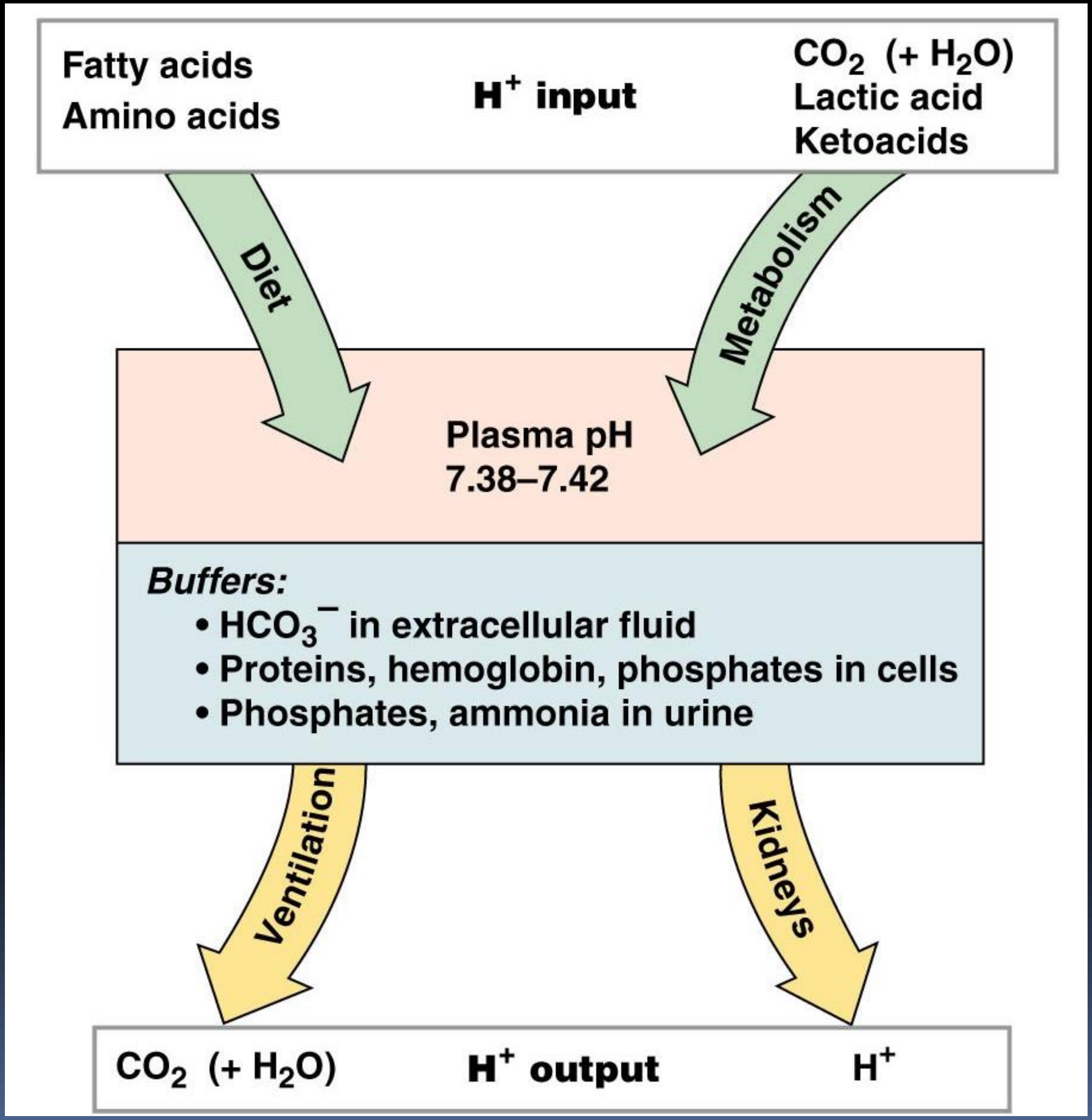
(volatile acid)

- Normally all volatile acid **<u>excreted by the lungs</u>**.

2) **DIET** – incomplete metabolism of carbohydrates (lactate) lipids (ketones) and proteins (H_2SO_4, H_3PO_4) generates **fixed (non-volatile) acids** – ~50 -100 mEq per day.

- In order to maintain balance, acids need to be **BUFFERED** and/or **EXCRETED**.

Hydrogen and pH Balance in the Body



Catabolism of sulphur containing AA gives H_2SO^4

Catabolism of phospholipids/ phosphoproteins give H_3PO^4

How is $[H^+]$ Controlled?

- Three systems involved;

  1) **BUFFERS** – first defence

     - second – to - second regulation of $[H^+]$

  2) Excretion of CO_2 ($\downarrow H_2CO_3$) by **LUNGS** (removal of volatile acid) – second defence

     - regulation in minutes - to - hours

  3) Excretion of H^+ ($\uparrow HCO_3^-$) by **KIDNEYS** (fixed acids)

     - third defence
     - regulation over several hours to days
     - slowest, but most **POWERFUL**, of body's acid-base regulatory systems.

- Relative concentrations of CO_2 and HCO_3^- in plasma / ECF determine pH (**HENDERSON-HASSELBALCH** equation) .

(show the relationship between pH, hydrogen ion conc. and the ratio of buffer membrane in a solution)

HENDERSON-HASSELBALCH equation

$$pH = pK' + \frac{\log [HCO_3^-]}{sPCO_2}$$

pH is the negative logarithm of H^+ in mol/L.
pK' is negative logarithm of overall dissociation constant for the reaction = 6.1 in health.
s is solubility of CO_2 in solution = 0.03 at 37ºC

$$pH = 6.1 + \frac{\log [HCO_3^-]}{0.03 \times PCO_2}$$

In health, $[HCO_3^-]$ = 24 mmol/L & PCO_2 = 40 mm Hg

7.4 = 6.1 + 1.3

What happen to the pH using H-H

In case if the HCO_3 in Plasma remains normal

- If Pco_2 increased, the ratio of $[HCO_3]P/ 0.03\ Pco_2$ will decrease which lead to acidosis.

- If Pco_2 decrease, the ratio will increase and pH will increase causing alkalosis.

In case the Pco_2 remains normal

- Increase bicarbonate in plasma causes an increase in the ratio which leads to alkalosis.

- Decrease in bicarbonate in plasma causes a decrease in the ratio which leads to acidosis.

Control of $[H^+]$ - Buffers

- Buffer is substance that stabilises (limits the change of) $[H^+]$ when H^+ ions are added or removed from a solution.

- They <u>do not</u> eliminate H^+ from body – **REVERSIBLY** bind H^+ until balance is re-established.

- General form of buffering reaction usually in form of conjugate acid-base pair:

$$HA \rightleftharpoons H^+ + A^-$$

HA = undissociated acid
A^- = conjugate base (any anion)

- Reaction direction (& dissociation rate) dependent on effective concentration of each chemical species.

- If $[H^+]\uparrow$ then equation moves leftwards and *vice versa* if $[H^+]\downarrow$ - ***minimises changes in $[H^+]$.***

First line of defense against pH shift

- **Chemical buffer system**
  - **Bicarbonate buffer system**
  - **Phosphate buffer system**
  - **Protein buffer system**

Second line of defense against pH shift

- **Physiological buffers**
  - **Respiratory mechanism (CO_2 excretion)**
  - **Renal mechanism (H^+ excretion)**

Control of [H^+] - Buffers

What buffer systems exist in the body?

1) Bicarbonate buffer system

- Most important buffering system. Works by acting as proton acceptor for carbonic acid.

$$\underset{}{CO_2 + H_2O} \overset{CA}{\rightleftharpoons} \underset{\text{carbonic acid}}{H_2CO_3} \rightleftharpoons H^+ + \underset{\text{bicarbonate}}{HCO_3^-}$$

- [H_2CO_3] **very low** (6800 x less than HCO_3^-)
- To maintain pH of **7.4**, HCO_3^- : H_2CO_3 = **20:1** – if ratio changes, so too will pH.
- When enough [H^+] added to halve [HCO_3^-], pH would drop to 6.0, **BUT**, $H_2CO_3 \Leftrightarrow H_2O + CO_2 \rightarrow$ ventilation↑ and CO_2 is removed.
- ∴ buffering means that **pH only drops to ~ 7.2**.

Control of [H^+] - Buffers

2) Phosphate Buffering System

- Phosphate buffer system not important as extracellular fluid buffer (concentration too low).
- However, major **INTRACELLULAR** buffer and important in **RENAL TUBULAR FLUID**.
- Main components are HPO_4^{2-} and $H_2PO_4^-$

$$H^+ + HPO_4^{2-} \leftrightarrow H_2PO_4^-$$

(Strong acid converted to weak acid ∴ less effect on pH)

$$OH^- + H_2PO_4^- \leftrightarrow H_2O + HPO_4^{2-}$$

(Strong base converted to weak base ∴ less effect on pH)

Control of [H^+] - Buffers

3) Protein Buffers

- Proteins among most plentiful buffers in body, particularly highly concentrated **INTRACELLULARLY.**

- ~ 60 - 70% of total chemical buffering of body fluids is located intracellularly, mostly due to intracellular proteins.

- Carboxyl and amino groups on plasma proteins are effective buffers;

$$RCOOH \leftrightarrow RCOO^- + H^+$$

$$RNH_3^+ \leftrightarrow RNH_2 + H^+$$

Control of $[H^+]$ - Buffers

3) Protein Buffers

- Most important non-bicarbonate buffering proteins are titratable groups on **HAEMOGLOBIN**
  (Hb also important for buffering CO_2).

$$CO_2 + H_2O \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + HCO_3^-$$

$$\downarrow$$

(DeoxyHb a better buffer than OxyHb)

$$H^+ + Hb^- \Leftrightarrow HHb$$

- pH of cells changes in proportion to pH of extracellular fluid – CO_2 can rapidly traverse cell membrane.

Control of $[H^+]$ - Buffers

4) Bone

- Probably involved in providing a degree of buffering (by ionic exchange) in most acid-base disorders.

- However, important source of buffer in **CHRONIC** metabolic acidosis (*i.e.* renal tubular acidosis & uraemic acidosis).

- $CaCO_3$ (base) is most important buffer released from bone during metabolic acidosis.

- Results in major depletion of skeletal mineral content (*e.g.* Chronic metabolic acidosis that occurs with renal tubule acidosis (RTA) can lead to development of Rickets / osteomalacia).

Control of $[H^+]$ - Buffers

- Remember that all of these buffer systems work in **TANDEM**, *NOT* in isolation.

- Buffers can only ***LIMIT CHANGES*** in pH, they cannot **REVERSE** them.

- Once arterial pH has deviated from normal value, can only be returned to normal by **RESPIRATORY** or **RENAL COMPENSATION**.