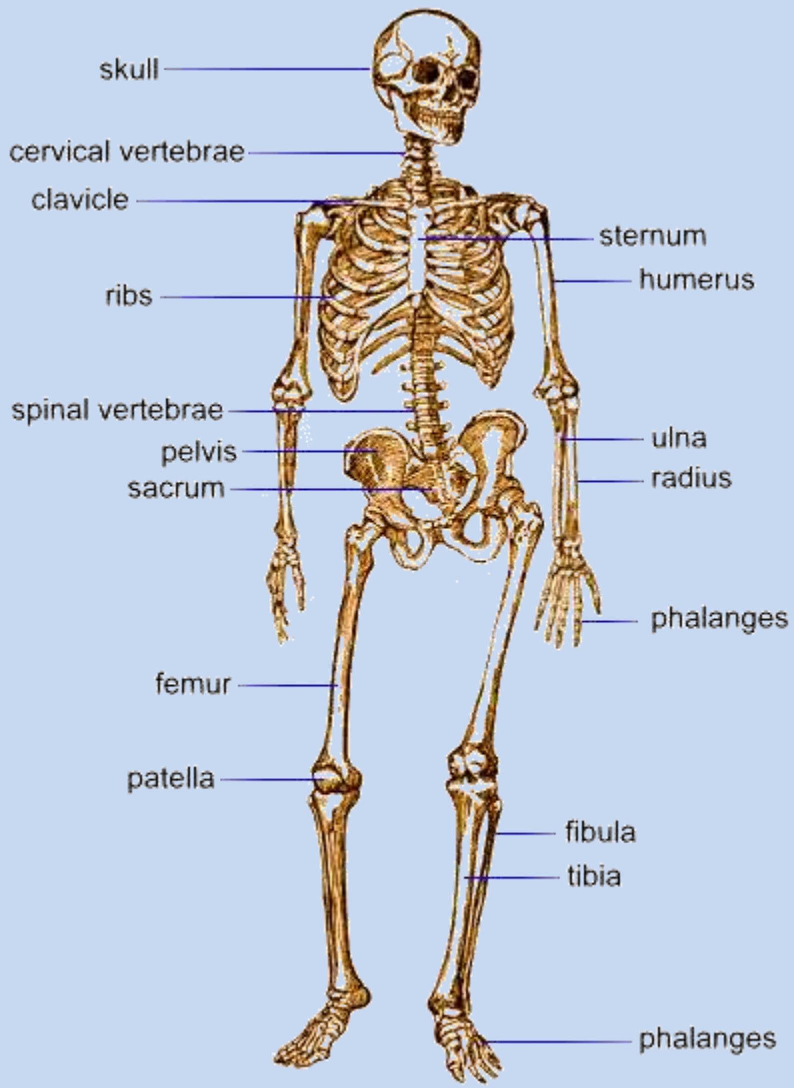
BIOCHEMISTRY OF BONES



Bones

Bones are rigid organs that constitute part of the endoskeleton of vertebrates. They support and protect the various organs of the body, produce red and white blood cells and store minerals.

Functions

A- Mechanical function

1- Protection — Bones Can Serve To Protect Internal Organs, Such As The Skull Protecting The Brain Or The Ribs Protecting The Heart And Lungs.
2- Structure — Bones Provide A Frame To Keep The Body Supported.
3-Movement — Bones, Skeletal Muscles, Tendons, Ligaments And Joints Function Together To Generate And Transfer Forces So That Individual Body Parts Or The Whole Body Can Be Manipulated In Three-dimensional Space.

B- Synthetic function

Blood Production — The Marrow, Located Within The Medullary Cavity Of Long Bones Produces Blood Cells In A Process Called Hematopoiesis.

C- Metabolic function

1-Minerals Storage — Bones Act As Reserves Of Minerals Important For The Body (e.g. Calcium And Phosphorus).

2-Growth Factor Storage — Mineralized Bone Matrix Stores Important Growth Factors Such As Insulin-like Growth Factors, Transforming Growth Factor, Bone Morphogenetic Proteins And Others.

3-Fat Storage — The Yellow Bone Marrow Acts As A Storage Reserve Of Fatty Acids.

4-Acid-base Balance — Bone Buffers The Blood Against Excessive pH Changes By Absorbing Or Releasing Alkaline Salts.

5-Detoxification — Bone Tissues Can Also Store Heavy Metals And Other Foreign Elements, Removing Them From The Blood And Reducing Their Effects On Other Tissues. These Can Later Be Gradually Released For Excretion.

6-Endocrine Organ — Bone Controls Phosphate Metabolism By Releasing Fibroblast Growth Factor – 23 (FGF-23), Which Acts On Kidneys To Reduce Phosphate Reabsorption.

-Bone Cells Also Release A Hormone Called Osteocalcin, Which Contributes To The Regulation Of Blood Sugar (Glucose) And Fat Deposition.

Bone matrix

- Bones contain both organic and inorganic materials.
- **The organic material** is mainly protein
- Type – I collagen, comprising 90-95% of organic material.
- Type – V collagen is also present in small amounts, as are number of non-collagen proteins.

-Both type I and V Are Synthesized Intracellularly As Tropocollagen And Then Exported, Forming Fibrils.

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- The Organic Part Is Also Composed Of Various Growth Factors Include Glycosaminoglycans, Osteocalcin, Osteonectin, Bone Sialo Protein, Osteopontin And Cell Attachment Factor.

One Of The Main Things That Distinguishes The Matrix Of A Bone From That Of Another Cell Is That The Matrix In Bone Is Hard.

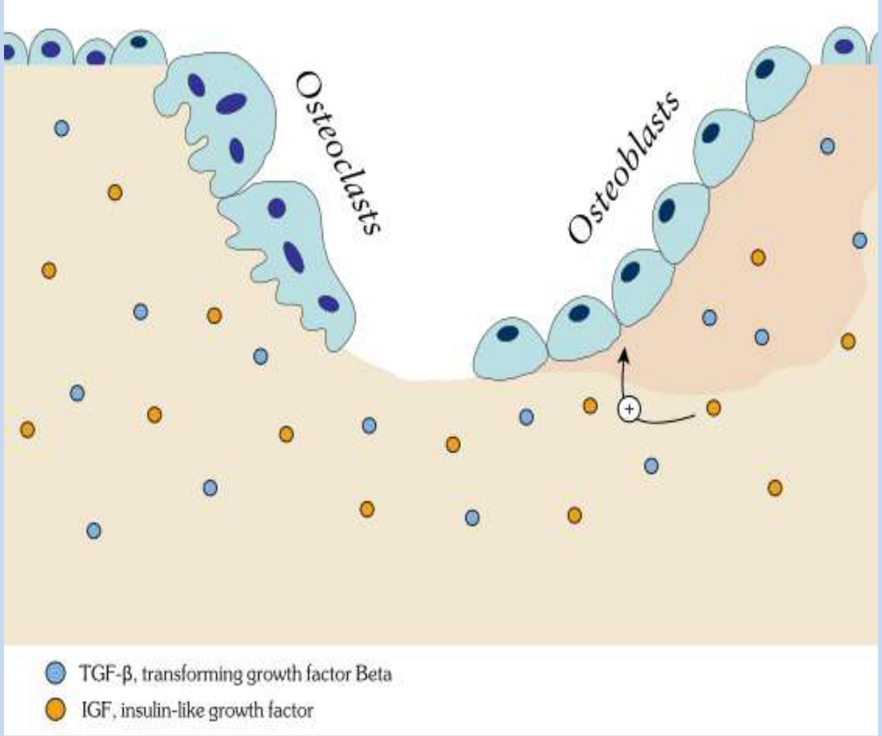
- **The inorganic component** is mainly crystalline hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ along with sodium, magnesium, carbonate and fluoride.
- Approximately 99% of body calcium is contained in bones.
- Bone is a dynamic structure that under goes continuing cycles of remodeling, consisting of resorption followed by deposition of new bone tissues.

Bone Remodeling

- Bone remodeling is a continuous process of bone resorption and bone formation for the purpose of maintaining normal bone mass:
- Bone Deposition is the apposition or formation of new bone as a normal physiological process (specialized cells called osteoblasts)
- Bone Resorption is a process involving the breakdown of bone by specialized cells known as osteoclasts

These processes also control the reshaping or replacement of bone following injuries like fractures but also micro-damage, which occurs during normal activity.

Remodeling responds also to functional demands of the mechanical loading.



Bone tissue is removed by osteoclasts, and then new bone tissue is formed by osteoblasts.

Purpose of bone remodeling

The purpose of remodeling is to regulate calcium homeostasis, repair micro-damaged bones and also to shape and sculpt the skeleton during growth.

Calcium balance

The process of bone resorption by the osteoclasts releases stored calcium into the systemic circulation and is an important process in regulating calcium balance.

Bone is a dynamic structure in a continuous state of remodeling by two types of cells (osteoblasts and osteoclasts).

Osteoblasts

Are mononucleated cells that are responsible for bone formation

- **Osteoblasts synthesize most of proteins found in bone as well as various growth factors & cytokines.**
- **They are responsible for the deposition of new bone matrix ; Osteoid (is the unmineralized, organic portion of the bone matrix that forms prior to the maturation of bone tissue) and its subsequent mineralization.**
- **Osteoblasts control mineralization by regulating the passage of calcium & phosphate ions across their surface membranes.**

Osteoclasts

is a type of bone cell that removes bone tissue by removing its mineralized matrix and breaking up the organic bone (organic dry weight is 90% collagen). This process is known as bone resorption

- **Osteoclasts are multinucleated cells.**

• mechanism

- **A proton translocating ATPase expels protons across the ruffled border into resorption area.**
- **This Lowers the Local PH to 4.0 or less, thus increasing the solubility of hydroxyapatite & allowing demineralization to occur.**

- **Lysosomal acid proteases are released that digest the new accessible matrix proteins.**

Regulation

Osteoclasts are regulated by several hormones, including parathyroid hormone (PTH) from the parathyroid gland, and calcitonin from the thyroid gland.

Role of Parathyroid Hormone

Parathyroid hormone (PTH) is secreted by the chief cells of the parathyroid glands as a polypeptide containing 84 amino acids. It acts to increase the concentration of calcium (Ca^{2+}) in the blood.

- **PTH half-life is approximately 4 minutes. It has a molecular mass of 9.4 kDa.**
- **It is synthesized as part of larger molecule containing 115 amino acid residues (pre-pro-PTH).**
- **Upon entry of pre-pro-PTH into <u>endoplasmic reticulum</u>, leader sequence is removed from the amino terminal to form the 90 amino acids polypeptide pro-PTH.**
- **Six additional amino acids residues are removed from the amino terminal of pro PTH in the <u>golgi apparatus</u> and the 84 a.a polypeptide PTH is packaged in secretory granules and released as the main secretory product of the chief cells.**

•PTH acts to increase the concentration of calcium in the blood by acting upon the parathyroid hormone 1 receptor (high levels in bone and kidney) and the parathyroid hormone 2 receptor (high levels in the central nervous system, pancreas, testis, and placenta).

Actions of Parathyroid Hormone:

Parathyroid hormone accomplishes its job by stimulating at least three processes:

1-Mobilization of calcium from bone: Although the mechanisms remain obscure, a well-documented effect of parathyroid hormone is to stimulate osteoclasts to reabsorb bone mineral, liberating calcium into blood.

2-Enhancing absorption of calcium from the small intestine: Facilitating calcium absorption from the small intestine would clearly serve to elevate blood levels of calcium. Parathyroid hormone stimulates this process, but indirectly by stimulating production of the active form of vitamin D in the kidney. Vitamin D induces synthesis of a calcium-binding protein in intestinal epithelial cells that facilitates efficient absorption of calcium into blood.

3-Suppression of calcium loss in urine: In addition to stimulating fluxes of calcium into blood from bone and intestine, parathyroid hormone puts a brake on excretion of calcium in urine, thus conserving calcium in blood.

Regulation of secretion:

- Circulating ionized calcium acts directly on the parathyroid gland in a negative feedback fashion to regulate the secretion of PTH.

- The key to this regulation is a cell membrane Ca^{2+} receptor.

- When the plasma Ca^{2+} level is high ,PTH secretion is inhibited and the Ca^{2+} is deposited in bones. When Ca^{2+} level is low, secretion of PTH is increased and Ca^{2+} is mobilized from the bones .

- **1,25-dihydroxycholecalciferol** acts directly on the parathyroid gland to decrease prepro PTH mRNA.

- **Magnesium** is required to maintain normal parathyroid secretory response .

PTH

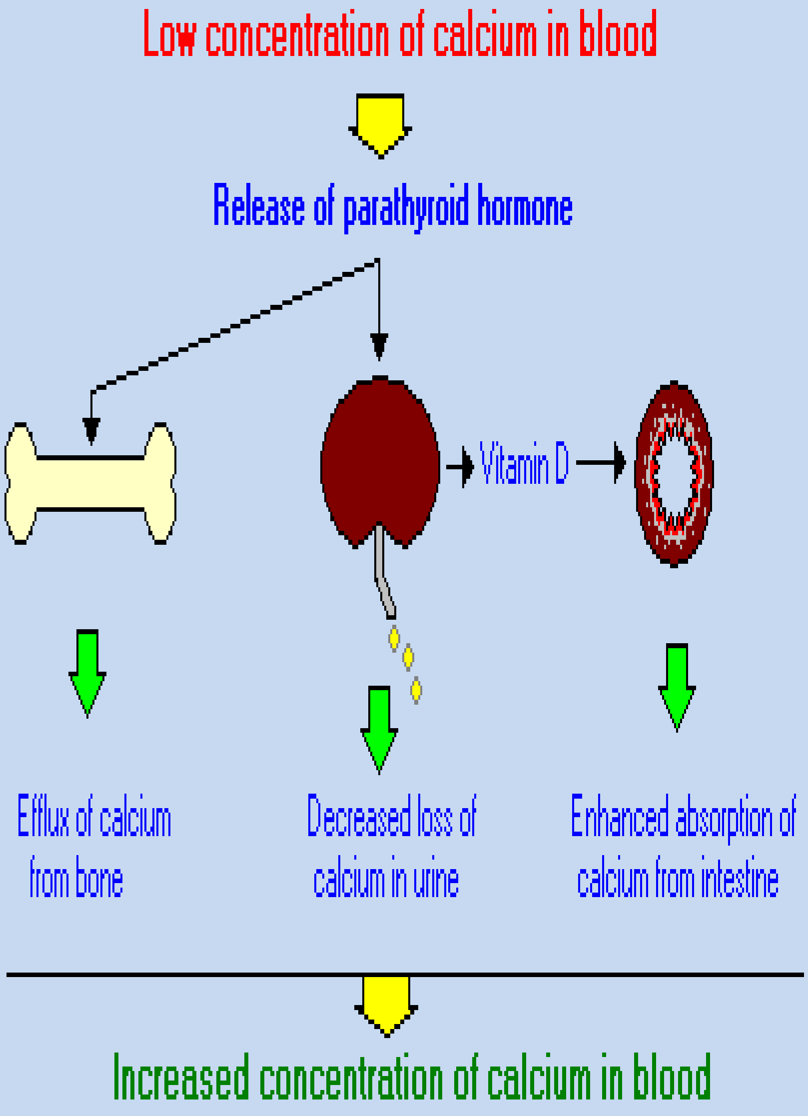
- Production related to plasma calcium levels
- Control of calcium levels
  - target organs
    - **Bone**

    - increased Ca/PO4 release

    - **Kidneys**
      - increased reabsorption of Ca

    - **Gut**

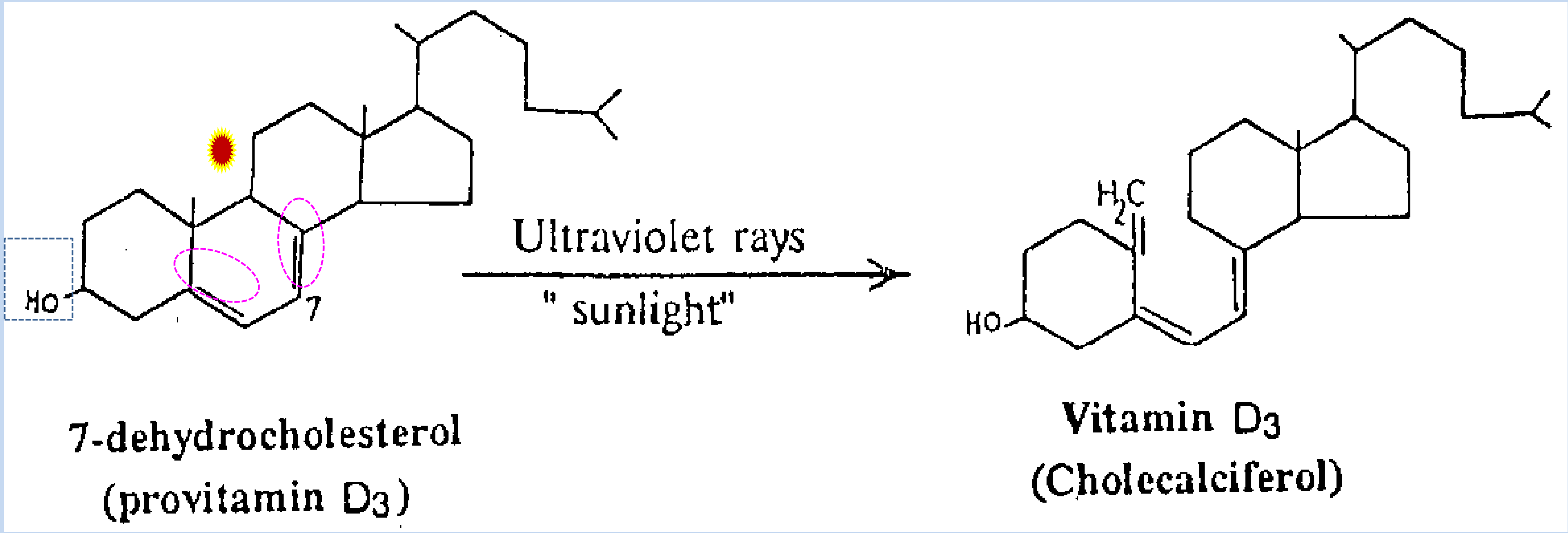
    - indirect increase in calcium reabsorption by stimulating activation of vitamin D metabolism



7-dehydrocholesterol (pro-vitamin D3)

- **7-dehydrocholesterol is stored under the skin, and by the effect of ultraviolet rays(in sunlight) it is transformed to cholecalciferol (vit. D_3 .)**

Insufficient sunlight can lead to a deficiency of vitamin D_3, interfering with Ca^{2+} transport and bone development.



Cholecalciferol (vitamin D3)

It is structurally similar to steroids such as testosterone, cholesterol, and cortisol.

Vitamin D_3 has several forms:

1-Cholecalciferol, is an inactive, unhydroxylated form of vitamin D_3.

2-Calcifediol (also called calcidiol, hydroxycholecalciferol, 25-hydroxyvitamin D_3. and abbreviated 25(OH)D is one of the forms measured in the blood to assess vitamin D status.

3-Calcitriol (also called 1,25-dihydroxyvitamin D_3) is the active form of vitamin D_3

Role of Vitamin D3

- **The active transport of Ca^{2+} & PO_4 from intestine is increased by metabolite of vitamin D.**
- **Vitamin D3 which is also called cholecalciferol is produced in skin from 7-dehydrocholesterol by action of sunlight.**
- **In liver vitamin D3 is converted to 25-hydroxycholecaciferol(25-OH D3).**
- **It is then converted to 1,25-dihydroxycholecalciferol (calcitriol) in the proximal tubules of kidney.**

Actions of Vitamin D3

•In addition to increasing Ca^{2+} absorption from the intestine, it also facilitates Ca^{2+} reabsorption in the kidneys.

Mechanism of actions:

•The formation of 1,25-dihydroxycholicalciferol in the kidneys (which is catalyzed by 1-alpha- hydroxylase) is regulated in feed back fashion by plasma Ca^{2+} & PO_4.

•Its formation is facilitated by PTH and when the plasma Ca^{2+} level is low, PTH secretion is increase.

•When the plasma Ca^{2+} level is high ,little 1,25-dihydroxycholicalciferol is produced .

•The production of 1,25-dihydroxycholecalciferol is also increased by low and inhibited by high plasma PO_4 levels, by the direct inhibitory effect of PO_4 on alpha hydroxylase .

Bone Health

One of the best known and long-established benefits of Vitamin D3 is its ability to improve bone health and the health of the musculoskeletal system.

It is well documented that Vitamin D3 deficiency causes osteopenia, precipitates and exacerbates osteoporosis, causes a painful bone disease known as osteomalacia, and exacerbates muscle weakness, which increases the risk of falls and fractures.

Vitamin D3 insufficiency may alter the regulatory mechanisms of parathyroid hormone (PTH) and cause a secondary hyperparathyroidism that increases the risk of osteoporosis and fractures.

Human calcitonin

is a 32-amino acid polypeptide hormone that is produced in humans primarily by the parafollicular cells (also known as C-cells) of the thyroid.
It acts to reduce blood calcium (Ca^{2+}), opposing the effects of parathyroid hormone (PTH)

Secretion of calcitonin is stimulated by

1-An increase in serum calcium
2-Gastrin (a peptide hormone that stimulates secretion of gastric acid (HCl)) and pentagastrin (stimulates the secretion of gastric acid, pepsin, and intrinsic factor, and has been used as a diagnostic acid as the pentagastrin-stimulated calcitonin test.)

Actions of calcitonin

Serpentine receptors for calcitonin are found in bones and the kidneys.
Calcitonin lowers the circulating calcium and phosphate levels.
It exerts its calcium lowering effect by inhibiting bone resorption.
This action is direct, and calcitonin inhibits the activity of osteoclasts.
It also increases Ca^{2+} excretion in Urine.

Gonadal steroids:

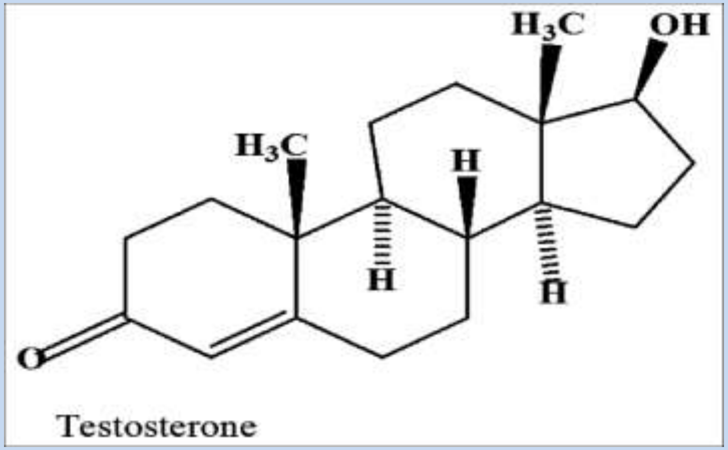
- Gonadal steroids are very important in maintaining bone balance.
They are also important in normal growth and development and in the development of peak bone mass.
The mechanism of action is unclear but receptors for estrogen and Androgen are found in bone

1- Estrogens:

* are the principal circulating sex steroids in females.
* help to regulate the rates of bone formation and bone resorption.
* estrogen decrease after menopause, could contribute in development of osteoporosis.

2- Androgens (such as testosterone):

* Are necessary for bone strength in males.



Growth hormone

-Growth Hormone (GH) is a growth promoting hormone produced by the pituitary gland.

-**It is "anabolic", which means it stimulates bone formation. Growth hormone also:**

* stimulates the production of insulin-like growth factor 1 (IGF-1)
* is important in stimulating longitudinal growth.
* Can increase bone mass when given to adults.

Thyroid hormone

Thyroid hormone is produced by the thyroid gland.

Bone cells have receptors for thyroid.

This hormone also:

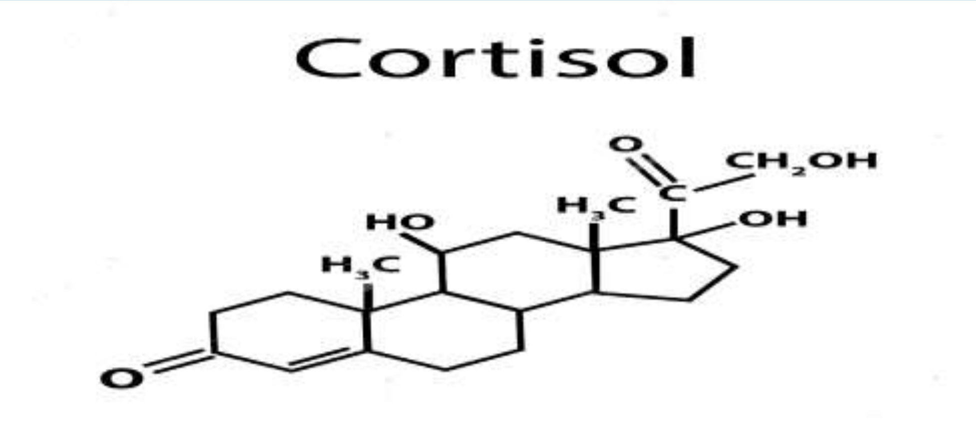
* is necessary for growth and maturation of the skeleton.
* causes increased osteoclastic bone resorption and osteoporosis when levels are too high.

Glucocorticoids

Glucocorticoid (eg. cortisol) is produced by the adrenal gland.
Bone cells have receptors for glucocorticoid.

This hormone is absolutely essential for life, but excess levels cause multiple deleterious effects on the skeleton.

This steroid hormone:
*** decreases calcium absorption from the intestines.**
*** inhibits bone formation.**
*** increases bone resorption.**
*** increases renal calcium excretion.**
*** decreases sex steroid production.**



Calcium metabolism

- **What is the recommended daily intake?**
- **1000mg**
- **What is the plasma concentration?**
- **2.2-2.6 mmol/L**
- **How is calcium excreted?**
- **Kidneys - 2.5-10 mmol/24 hrs**
- **How are calcium levels regulated?**
- **PTH and vitamin D (+others)**

Phosphate metabolism

- **Normal plasma concentration?**
- **0.9-1.3 mmol/L**
- **Absorption and excretion?**
- **Gut and kidneys**
- **Regulation**
- **Not as closely regulated as calcium but PTH most important**