PBL
Application of Biochemistry in dental prctice

Talib A. Najjar , DMD, MDS, PhD
Professor Oral & Maxillofacial Surgery
Rutgers University

Biochemistry Interaction with Oral & Systemic Diseases

Periodontal disease
Jaw Bone Necrosis
due to Bisphosphonate

Paget`s Disease
Osteoporosis

pathogenesis of Patient Condition presented with:

Osteonecrosis of the jaw bone due to Bisphosphonate

Patient's Data

- 54 year old male presented with sever **periodontal** disease ,type 2 diabetes ,lung **cancer** treated with **Bisphosphonate**

Progress of Dental Treatment

Patient referred to his Dentist for oral evaluation during cancer therapy.

Dentist referred him to Periodontist to evaluate periodontal condition.

Periodontist referred him to Oral Surgeon. Oral Surgeon performed for full mouth extractions due to sever periodontal condition.

This leads to sever **osteonecrosis** of the maxillary and mandibular alveolar ridges

Biochemistry Knowledge Provide Better Understanding of this patient

Osteonecrosis of jaw bone due to **Bisphosphonate**

Why Bisphosphonate causes such a sever Osteonecrosis & Why it was used ?

Why Bisphosphonate was given to this patient ?

- **Bisphosphonate (Aredia or Zometa®) are used to control**

Bone metastases from lung cancer

Hypercalcemia due to bone metastasis

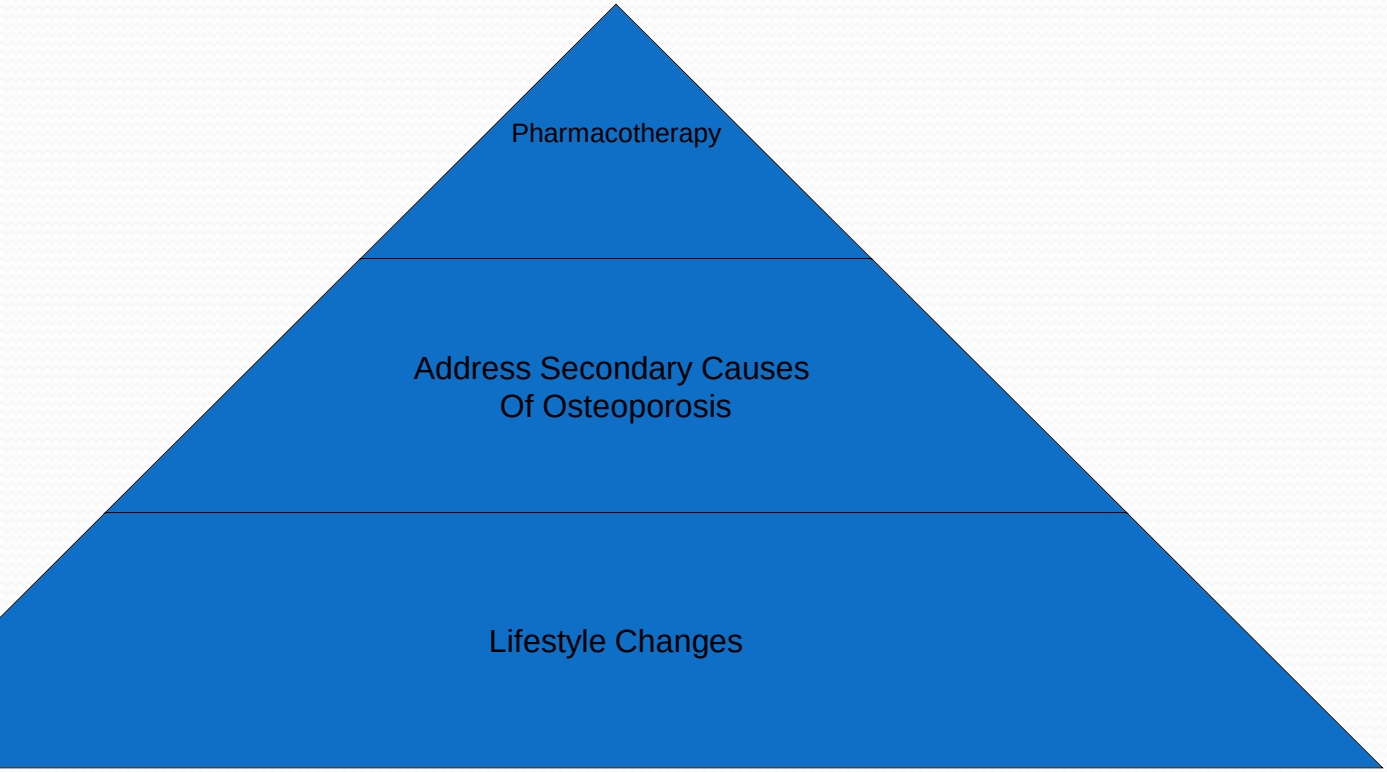
Common uses of Bisphosphonate

Oral Forms	• Prevention and treatment of osteoporosis in postmenopausal women • Increase bone mass in men with osteoporosis • Glucocorticoid-induced osteoporosis • Paget's disease of bone • osteogenesis imperfecta
Intra-venous Forms	• Hypercalcemia of malignancy • Bone metastases of solid tumors • Breast and prostate carcinoma; other solid tumors • Osteolytic lesions of multiple myeloma

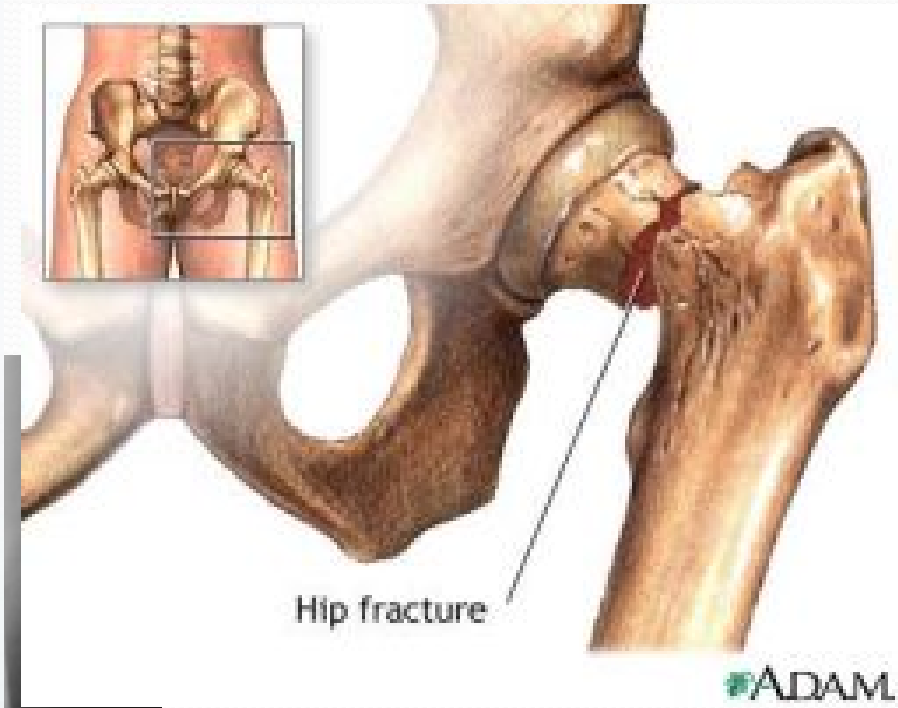
Relative Potency & Effect of Bisphosphonates

• Etidronate (Didronel)	1
• Tiludronate (Skelide)	10
• Pamidronate (Aredia)	100
• Alendronate (Fosamax)	1,000
• Risedronate (Actonel)	10,000
• Ibandronate (Boniva)	10,000
• Zolendronic acid (Zometa)	>100,000

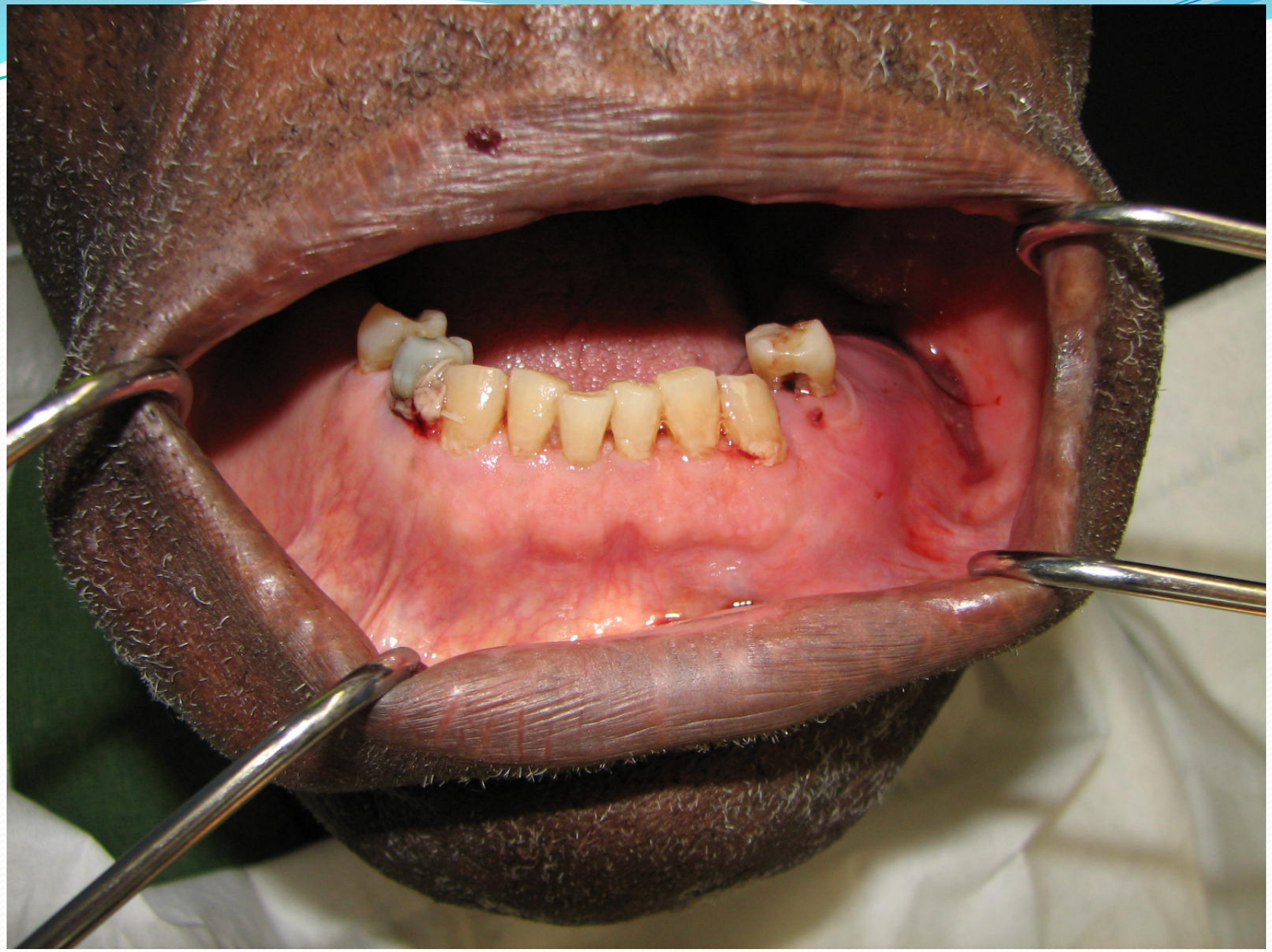
US Surgeon General Report recommends a pyramidal approach to osteoporosis treatment



Osteoporosis & Fracture Risk



Paget's Disease

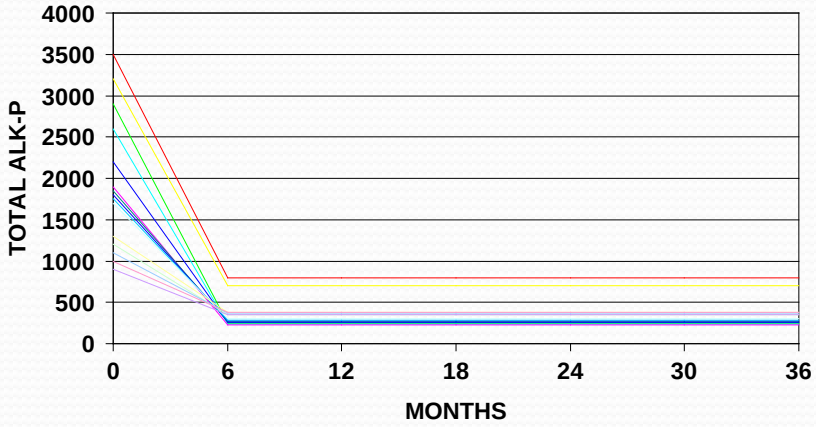


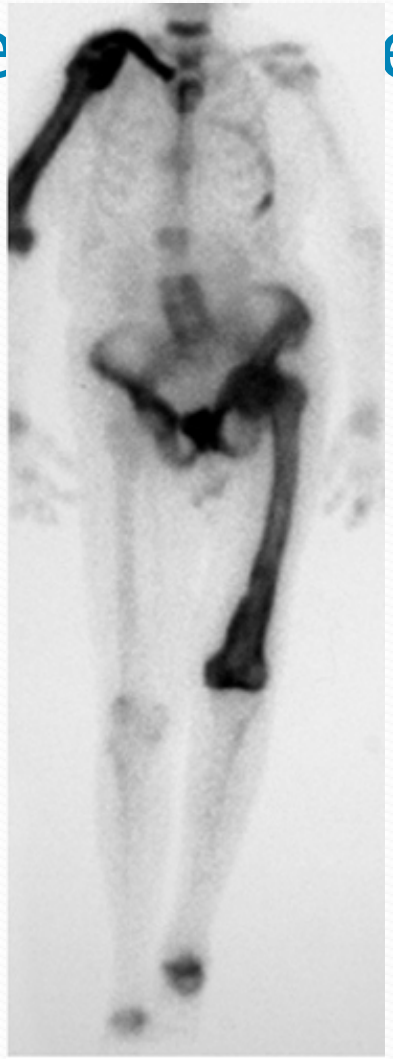
Paget's Disease

Paget's Diseases

- Characterizes by increased bone mass & density
- Abnormal bone remodeling
- Enlarged head and jaw bones
- Patient frequently change hat ,eyeglasses and dentures
- Cotton-wool appearance in the radiograph
- Loss of sight and hearing
- High Alkaline Phosphatase

Bisphosphonate therapy for Page e





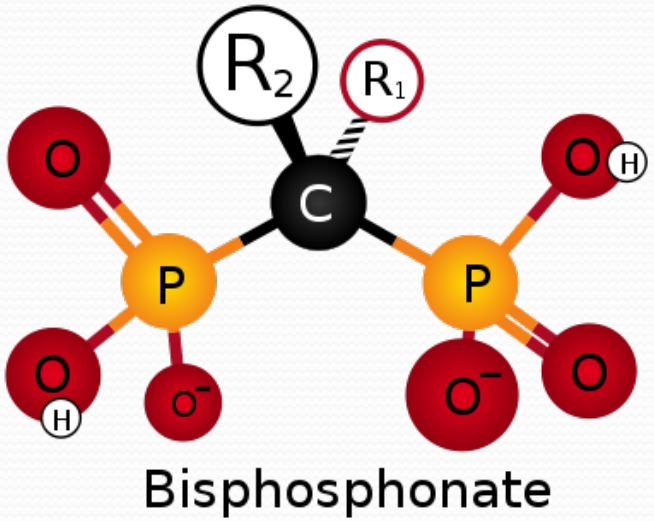
- Rendina et al. NEJM 353:24, 2005

Bisphosphonate
Basic Chemical Composition

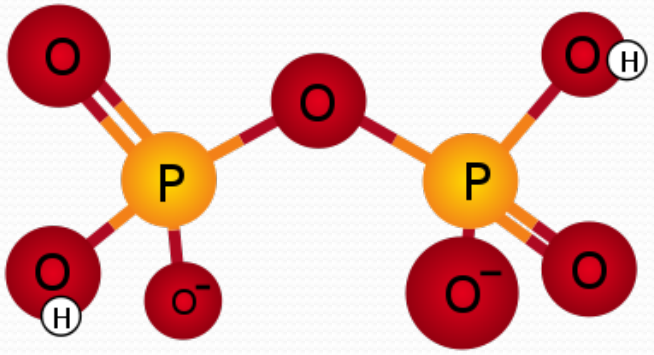
- Pyrophosphate compound
  Essential for normal cellular functioning as it incorporate in ATP

- Substitution of Carbon for Oxygen
  - Resistance to hydrolysis
  - Bone matrix accumulation
  - Extremely long half-life

- Nitrogen-containing side chain
  - Increases potency, toxicity
  - Direct link to BIONJ cases



Bisphosphonate

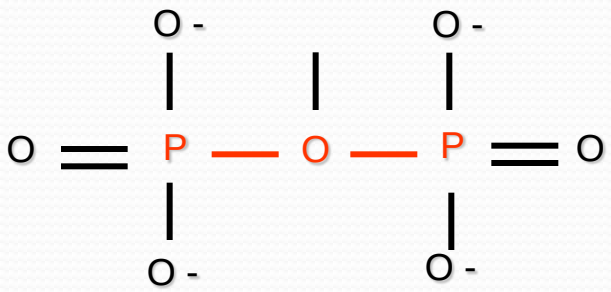


Pyrophosphate

Chemical Structure

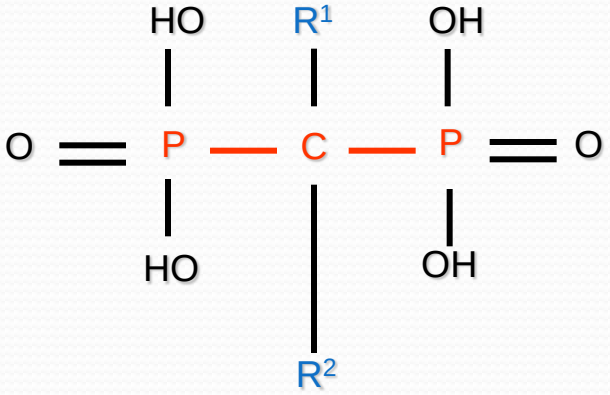
Pyrophosphate (PPi)

(ATP = AMP + PPi)

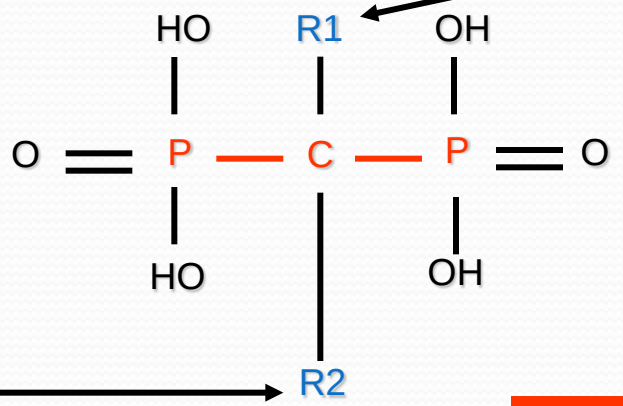


Bisphosphonate

(P-C-P)



P-C-P acts as ‘bone hook’ and is essential for binding to hydroxyapatite



When R^1 is an OH group binding to hydroxyapatite is enhanced

The R2 side chain determines potency

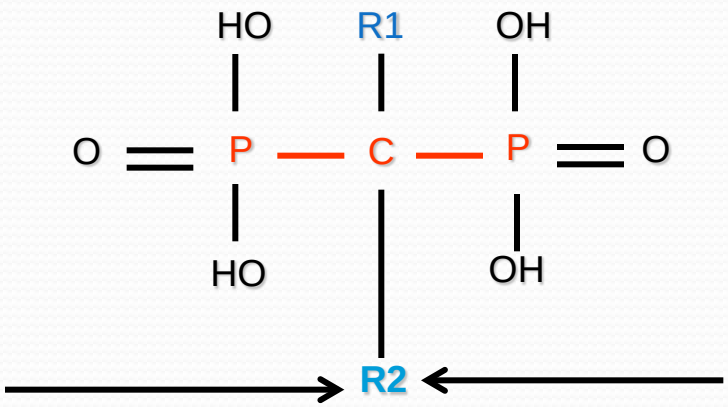
The P-C-P group is essential for biological activity

Bisphosphonate Structure

Bisphosphonate Structure

Nitrogen Side Chain

- Alendronate (Fosamax)
- Risedronate (Actonel)
- Ibandronate (Bonviva)
- Zolendronate (Zometa)
- Pamidronate (Aredia)

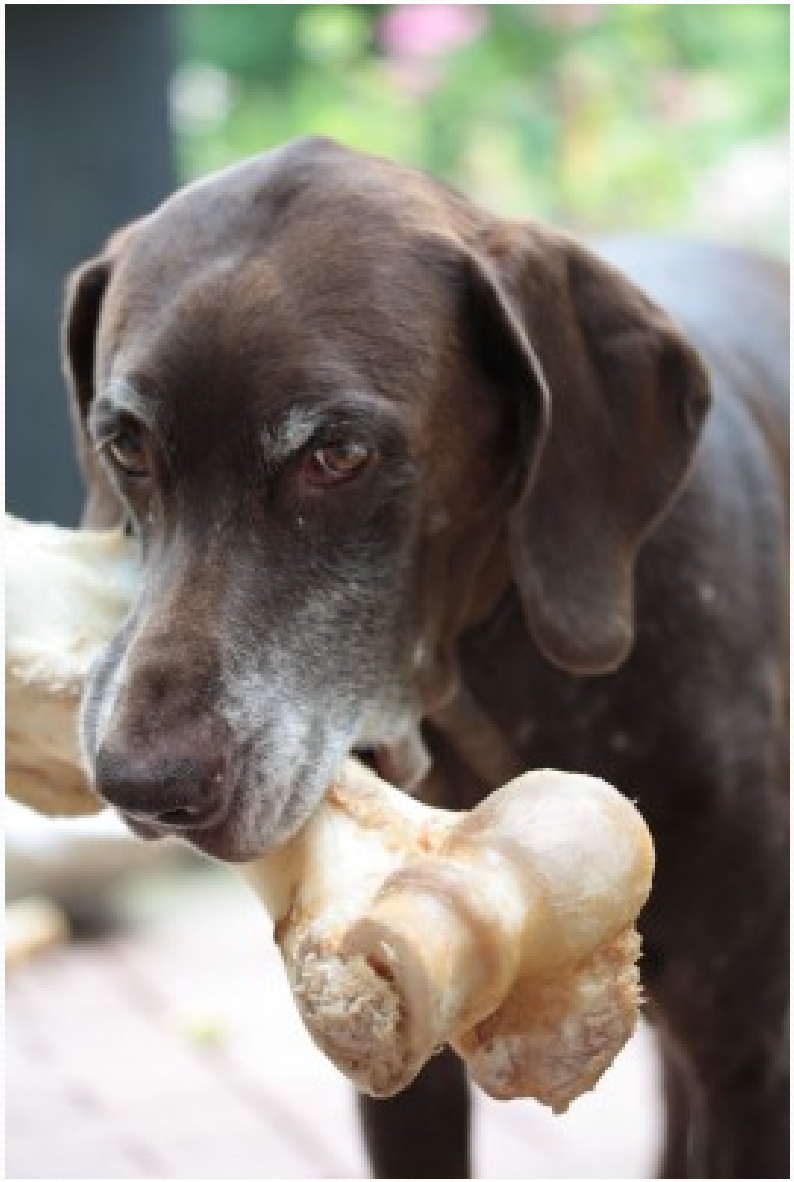


Non Nitrogen Side Chain

- Etidronate (Didronel)
- Clondronate (Bonefos)
- Tiludronate (Skelid)

Understanding Pathogenesis of Bone Necrosis

Understanding the pathophysiology of Bone Remodeling



Bone remodeling as Tissue Organ & System

Tissue

Haversian (osteons) which are aligned to withstand biofunctional challenges

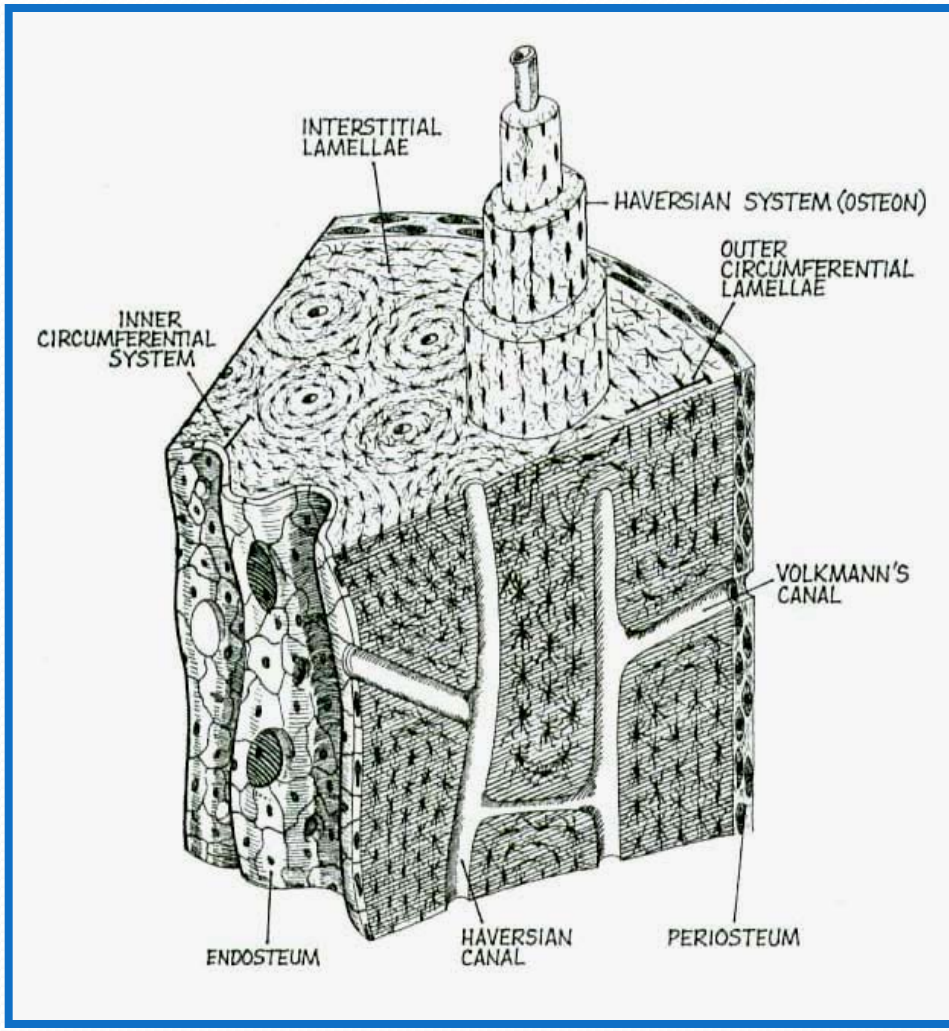
Organ

Mandible

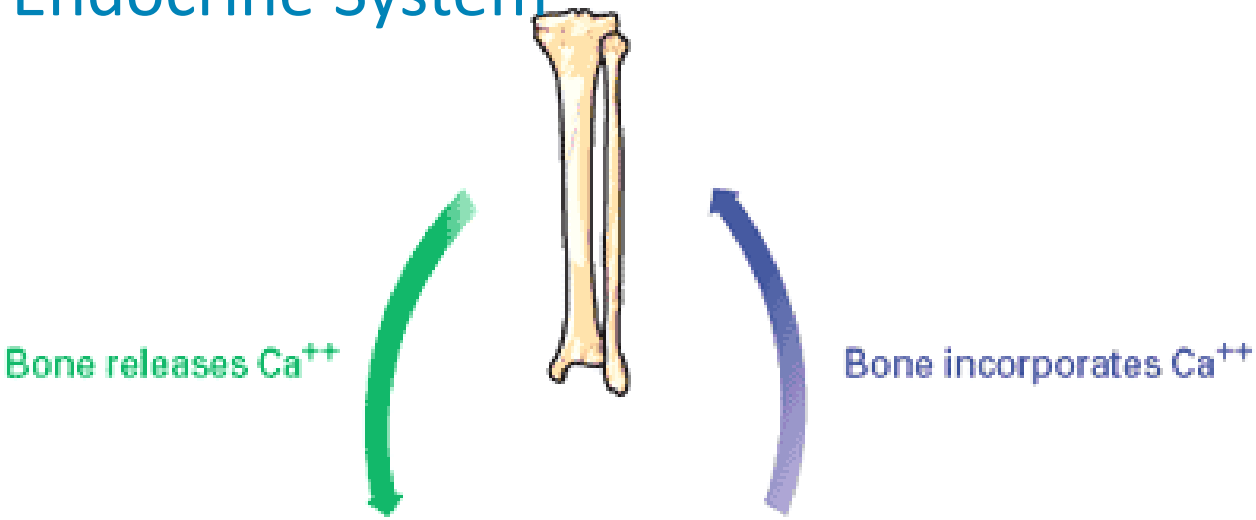
Tibia

System

Interacate with endocrine, renal ,vascular & GI systems



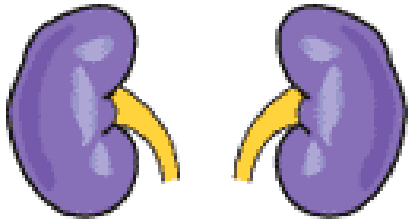
Effects of other systems in Bone Remodeling
Endocrine System



Bloodstream maintains a constant concentration of Ca^{++}

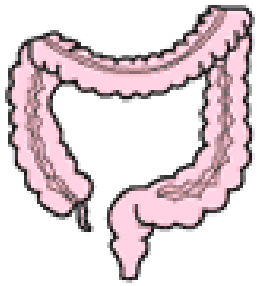
Ca^{++}

Kidneys conserve Ca^{++}



Ca^{++}

Intestine absorbs Ca^{++} from diet



Understanding Pathogenesis of Bone Necrosis

Biochemistry of Bisphosphona

Inhibition of farnesyl diphosphate synthase **in the osteoclasts**

Metabolized to toxic **analogue of ATP (non-nitrogen containing Bisphosphonate)**

Bisphosphonate Causes The Following

1. Disruption of normal bone turnover
2. Compromised bone blood flow
3. Antiangiogenic
4. Mucosal toxicity
5. Local Enviermentsof the Oral Cavity

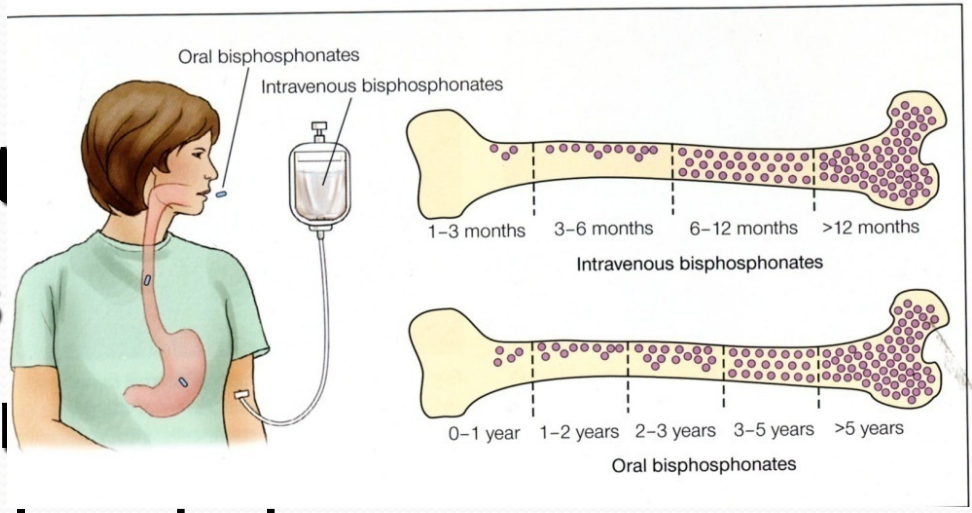
Bisphosphonate

Pharmacokinetics

Rapid accumulation in sit

of increased bone depos

Not metabolized (nitroge

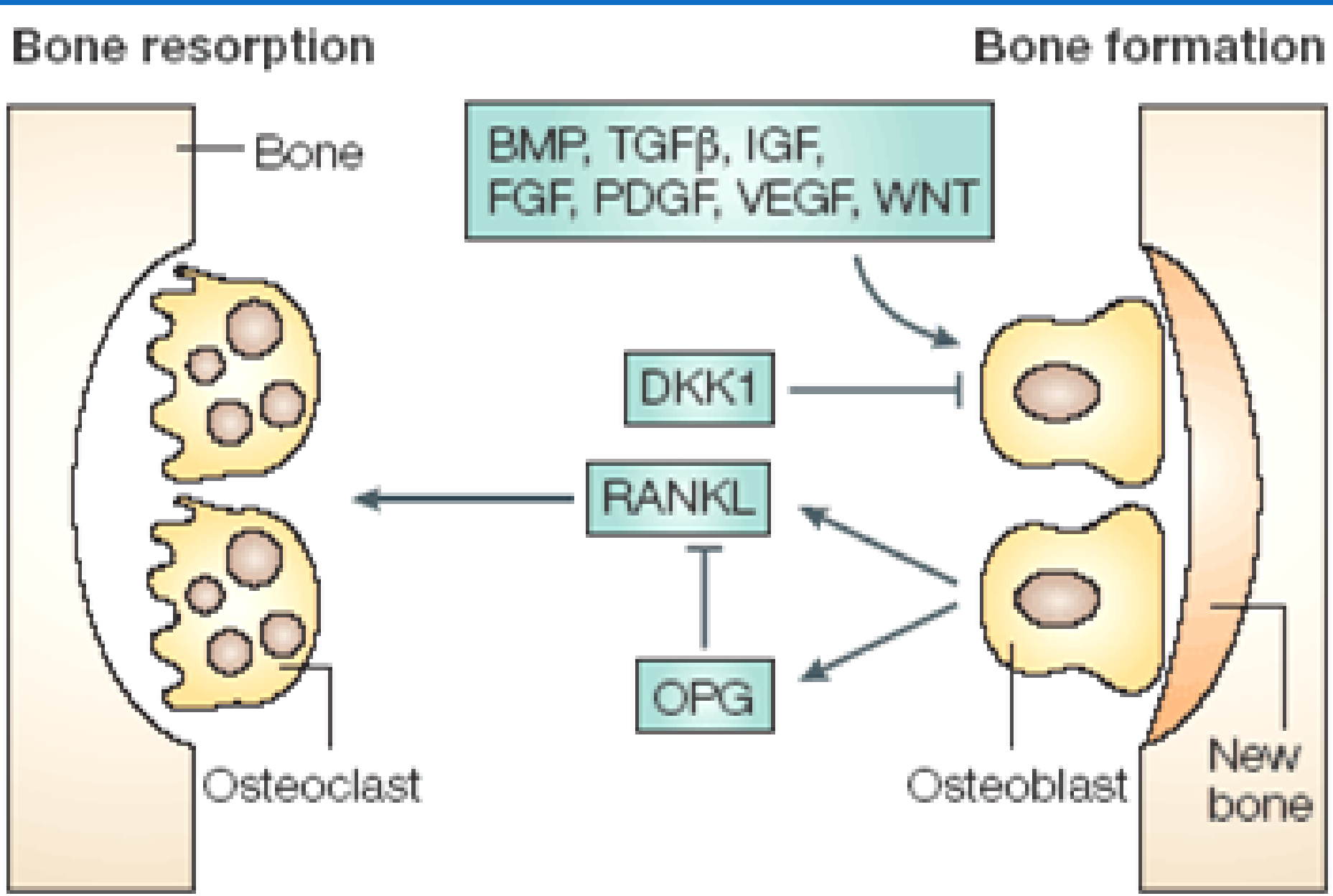


Repeated doses accumulate in bone

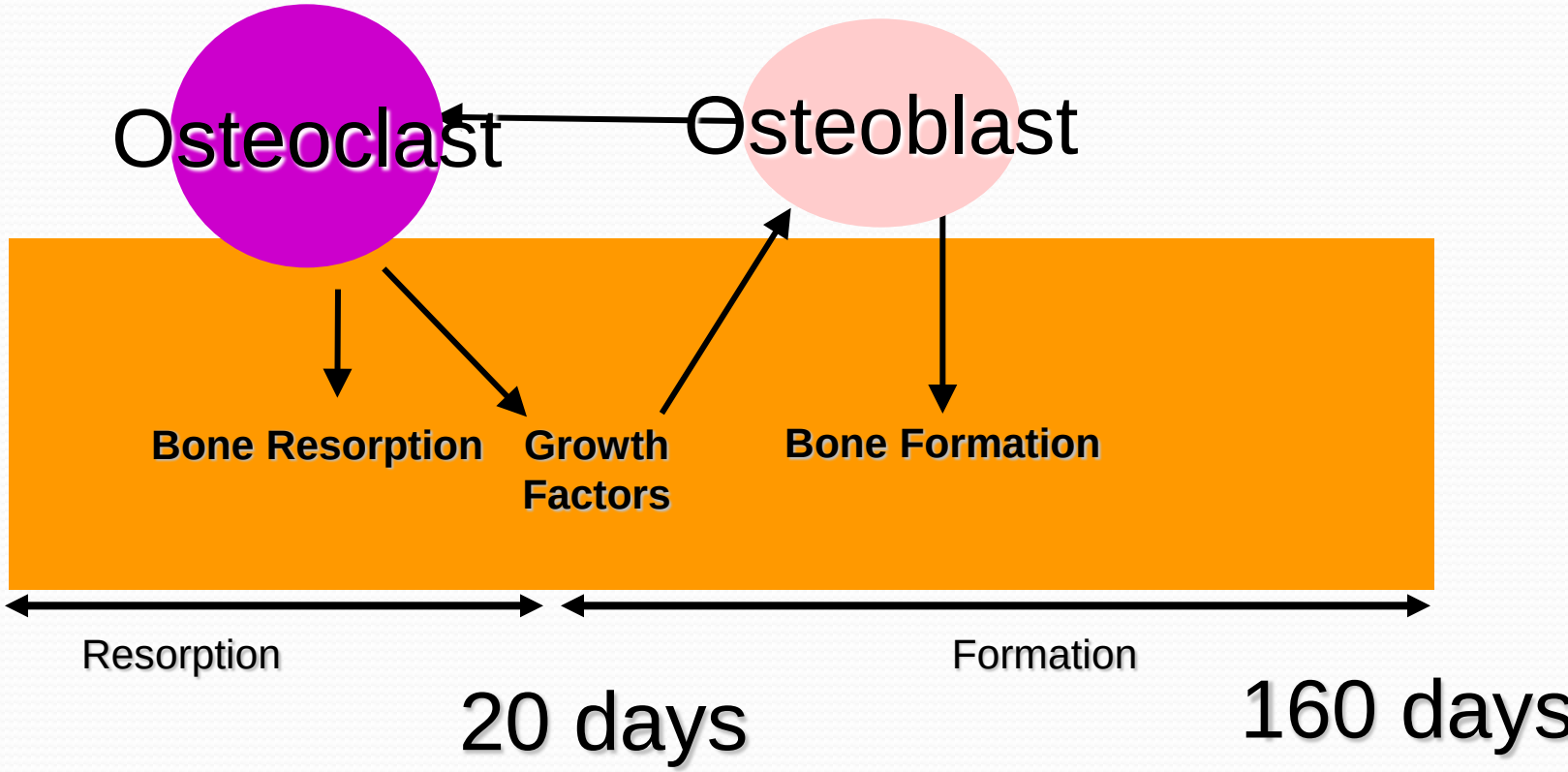
Bone ½ life of "years" – maybe a lifetime..

Removed only by osteoclast-mediated resorption

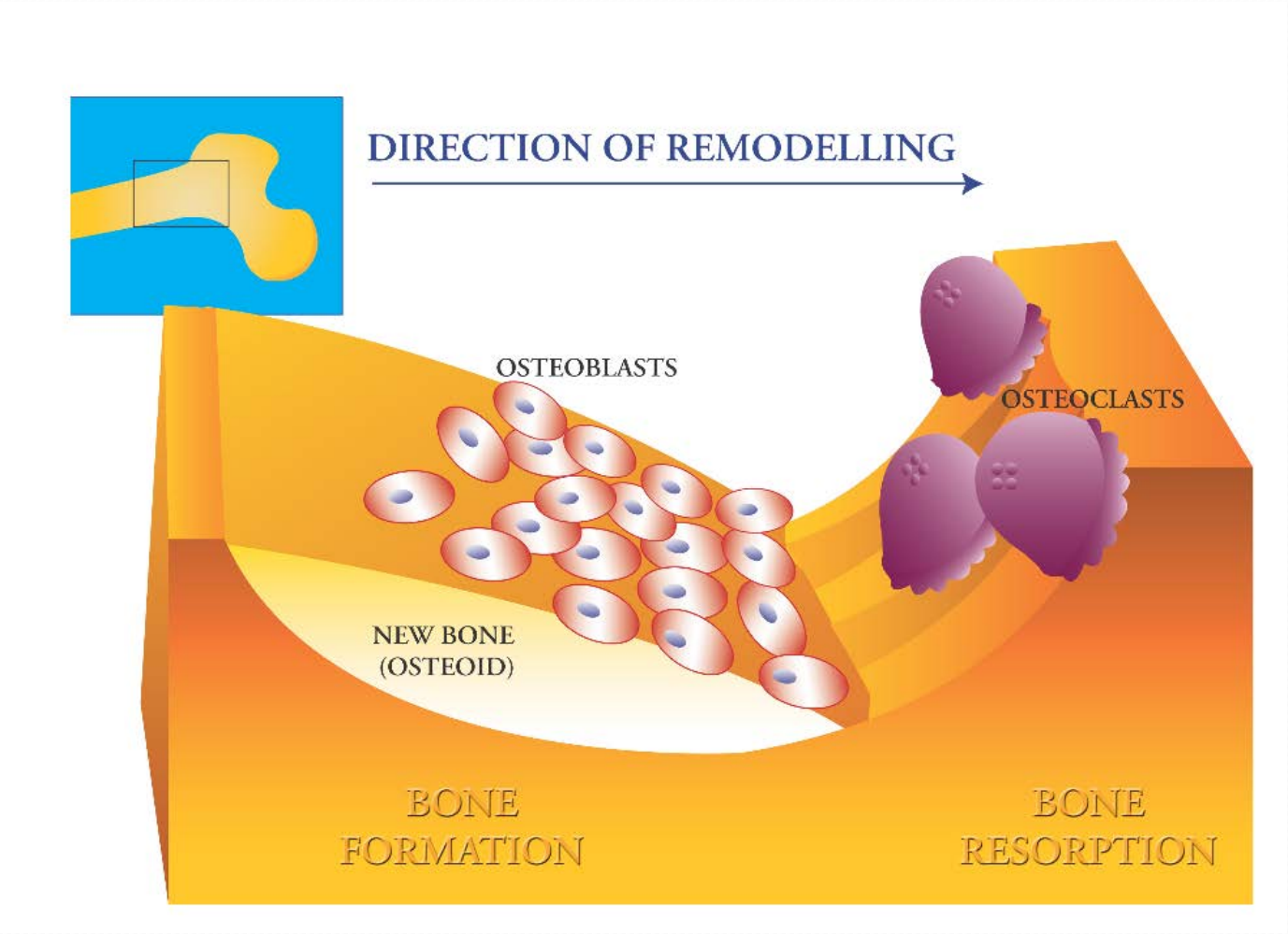
"Biologic Catch 22"


Bone resorption
Bone formation
Bone
BMP, TGFβ, IGF,
FGF, PDGF, VEGF, WNT
DKK1
RANKL
OPG
Osteoclast
Osteoblast
New
bone

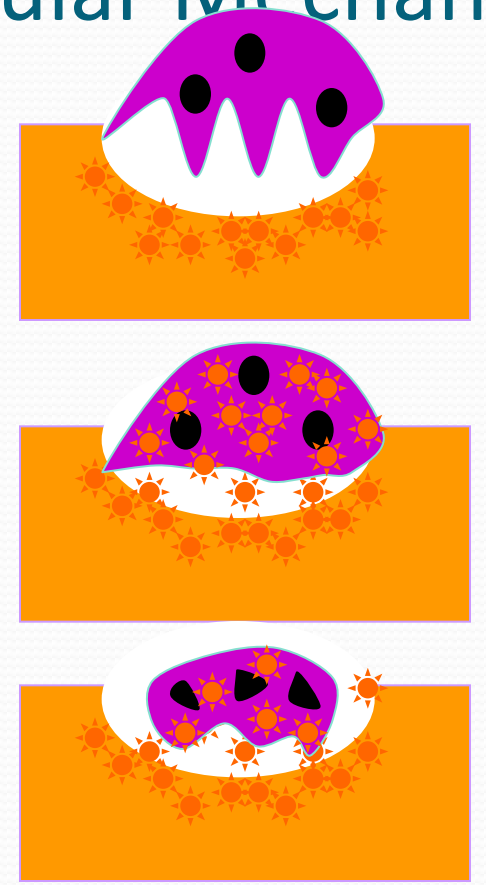
Normal Bone Remodelling



Bc


DIRECTION OF REMODELLING
OSTEOBLASTS
OSTEOCLASTS
NEW BONE
(OSTEOID)
BONE
FORMATION
BONE
RESORPTION

Cellular Mechanism of Action



1. Osteoclast actively reabsorbs bone matrix
2. BISPHOSPHONATE (☼) binds to bone mineral surface
3. BISPHOSPHONATE is taken up by the osteoclast
4. Osteoclast is inactivated
5. Osteoclast becomes apoptotic (‘suicidal’) and dies

Biologic Action of Bisphosphonates

- Osteoclastic toxicity

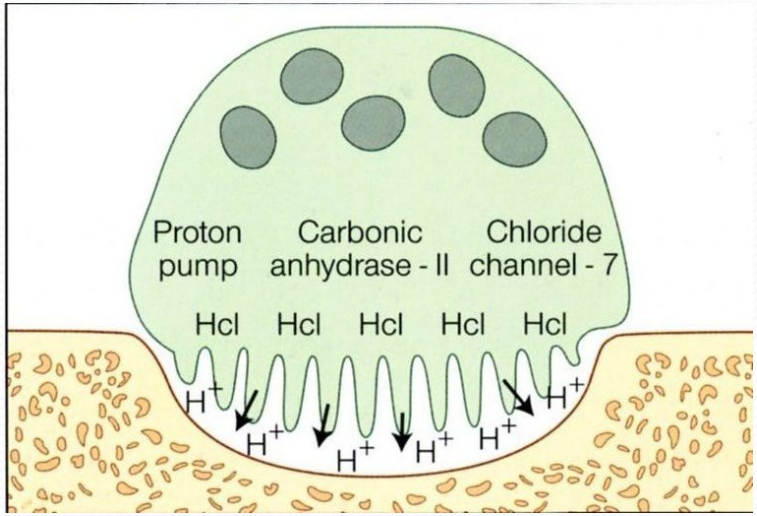
  Apoptosis
  Inhibited release of bone induction proteins

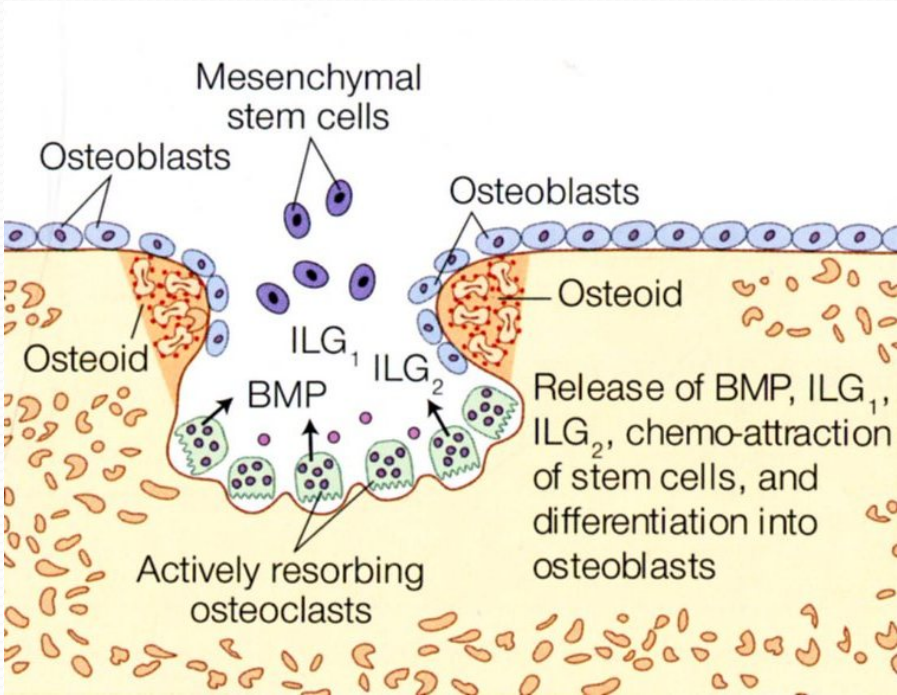
  BMP, ILG1, ILG2

  Reduced bone turnover, resorption
  Reduced serum calcium*

  Hypermineralization
  *

  "sclerotic" changes in lamina dura of alveolar bone



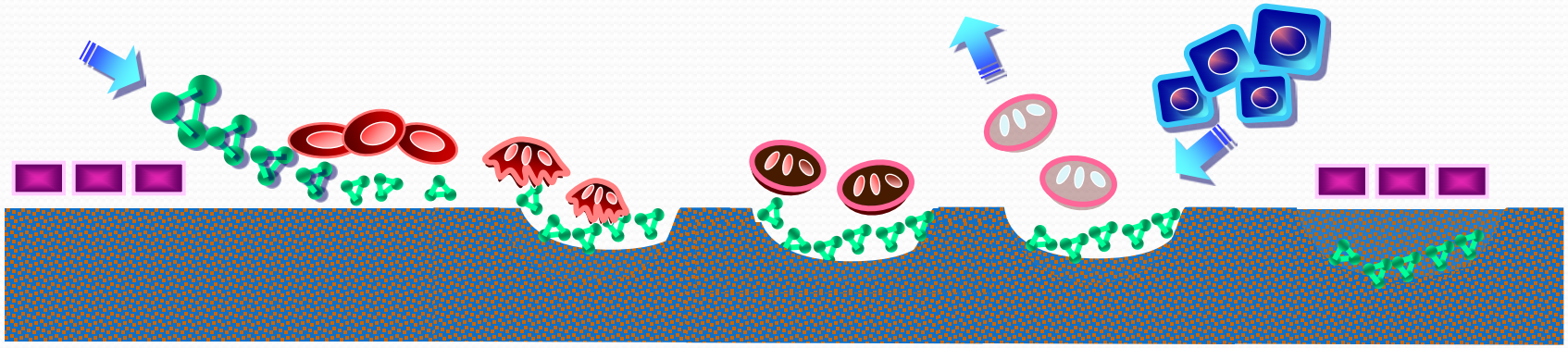


Bisphosphonates Effects on Osteoclasts

Bisphosphonate attaches to exposed bone mineral surfaces

Osteoclast takes up bisphosphonate → loss of ruffled border, inactivation, detachment

New bone formation by osteoblasts renders bisphosphonate inert, inaccessible



Lining cells

Bisphosphonate

Osteoclast precursors

Osteoclast

Inactivated osteoclast

Osteoblast

1. Sato M et al. *J Clin Invest.* 1991;88:2095–2105.
2. Rodan G et al. *Curr Med Res Opin.* 2004;20:1291–1300.

contributes to his sever osteonecrosis ?

- Does hyperglycemia (increased blood sugar) alone influenced his osteonecrosis ?
- Does abnormal metabolic changes in the glucose and ultimately protein and lipid metabolisms influenced his osteonecrosis ?

Conclusion

- **In this patient the combination of hyperglycemia , ketoacidosis , Steroid , Bisphosphonate ,chemotherapy and his lung cancer resulted in reduce blood supply ,impaired tissue function and reduced vascularity which resulted in sever periodontal disease . Osteonecrosis subsequent to teeth extractions were due to IV bisphosphonate use.**