Osteoporosis in children

Prof. Abdulmoein Al-Agha,

Pediatric Endocrinologist,

King AbdulAziz University Hospital, Jeddah

aagha.kau.edu.sa

- While many think of osteoporosis as something that happens only later in life especially to women !!
  - The fact is that the condition can attack younger women , young men & children
- Although osteoporosis is rare in children, when does occur it can cause significant pain & long term disabilities

- Skeleton is not static structure, but in continuous “ modeling - remodeling process”
- Bone is continually remodeled throughout life because bones sustain recurring micro-trauma
- The hallmark of osteoporosis is reduction in skeletal mass caused by imbalance between bone resorption & bone formation

- Bone tissue in skeleton increases until mid 20s
- Factors that influence bone accretion during childhood & determine the peak bone mass are:
  - Heredity “genetic potentials”
  - Ethnic origin
  - Gender
  - Diet such as calcium & vitamin D intake
  - Physical activity
  - Endocrine status
  - Sporadic risk factors such as cigarette smoking

Gene	Protein	Chromosome
AHSG	α2 HS-glycoprotein	3q27
VDR	VDR	12q12–q14
ESR1	ER 1 (α)	6q25.1
ESR2	ER 2 (ß)	14q23
COL1A1	Collagen, type 1,α 1	17q21.3–q22.1
COL1A2	Collagen, type 1,α 2	7q22.1
CALCR	Calcitonin receptor	7q21.3
TNFRGF5	TNF receptor	1p36.3–p36.2

- Gender
  - Bone density is generally higher in males than in females
  - Before puberty, boys & girls develop bone mass at similar rates
  - After puberty, boys tend to acquire greater bone mass than girls
- Race
  - for reasons still not well understood, BMD varies from various racial groups
  - African American girls tend to achieve higher peak bone mass than Caucasian girls
  - More research is needed to understand the differences in bone density between various racial & ethnic groups

Hormonal factors

Corticosteroid

Growth factors

Oestrogen

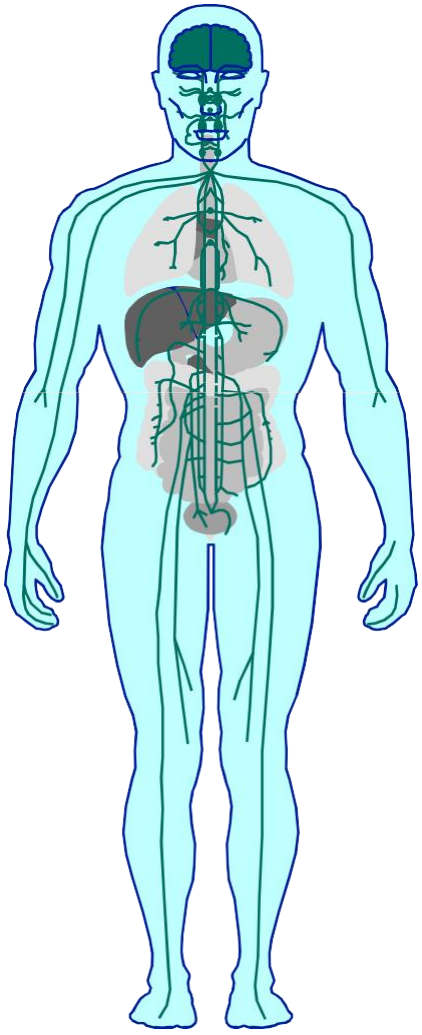
Pituitary hormones

PTH

Testosteron

Thyroxin

Vitamin Ds



- Nutritional status
  - Calcium is essential nutrient for bone health
  - A well-balanced diet including adequate amounts of vitamins & minerals such as magnesium, zinc & vitamin D are important for bone health
- Physical activity
  - important for building- up healthy bones
  - benefits of activity are most pronounced in weight - bearing areas:
    - hips during walking & running
    - arms during gymnastics
    - upper-body in weight-lifting

What is the definition of Osteoporosis in children ??

- WHO definitions of osteoporosis based on bone mass density measurements in adults as:
  - Normal - Bone density no lower than 1 standard deviation (SD) below the mean for young adult women (T-score above -1)
  - Low bone mass (osteopenia) - Bone density 1-2.5 SD below the mean for young adult women (T-score between -1 and -2.5)
  - Osteoporosis - Bone density 2.5 SD or more below the normal mean for young adult females (T-score at or below -2.5)

- The interpretation of densitometry data in the young is difficult because "normal" BMD values has to be corrected for:
  - gender, body size, pubertal stage, skeletal maturation & ethnicity
- No regional references in children in most countries
- In children, we cannot use T- score, only Z score

- The definition of childhood osteoporosis should include the presence of low trauma fractures with evidence of reduction of BMD Z score of > -2 SDs below the age matched mean “not adult matched” and has to be corrected for body size i.e. Volumetric BMD not Arial BMD

Causes of Osteoporosis In Children

- Primary osteoporosis in children & adolescents is relatively uncommon and usually secondary to identifiable causal factors

- Primary
  - Heritability of bone loss
    - Osteogenesis imperfecta
    - Idiopathic juvenile osteoporosis

Secondary Osteoporosis

- Endocrine disorder / Metabolic
  - Estrogen deficiency
  - Testosterone deficiency
  - Cushing's syndrome
  - Primary hyperparathyroidism
  - Thyrotoxicosis
  - GH deficiency
  - Gaucher's disease
- Malabsorption disorder
  - Gastrectomy
  - Celiac disease
  - Small bowel resection
  - Crohn's disease
  - Cystic fibrosis

Secondary Osteoporosis

- Malignancies
  - multiple Myeloma
- Autoimmune disorders
  - Rheumatoid arthritis, Lupus erythematosis
- Immobilization
  - CP/ Neuromuscular disorders
- Drugs
  - Corticosteroids
  - loop diuretics
  - Anticonvulsants (phenytoin)
  - GnRH agonist
  - Chemotherapy (Methotrexate)
  - Heparin

Secondary Osteoporosis

- Nutritional factors
  - Calcium
  - Vitamin D
  - Vitamin C
  - Protein
- Lifestyle
  - Physical activity Vs sedentary life style
- Smoking / Alcohol
- Pregnancy
- Anorexia nervosa

Osteogenesis imperfecta

- So far, 8distinct forms of OI representing extreme variation in severity from one person to another
  - Mild: Type 1.
  - Moderate: Type 4, 5, 6 and 7.
  - Severe or most severe: Type 2, 3, and 8.
- Inherited disorder of collagen 1 deficiency
- The most common features of OI include:
  - Bone that fracture easily
  - Family history usually present
  - Short stature common
  - Blue sclera common
  - Hearing loss
  - Dental problems
  - In mild form of the disease, with late onset, should be distinguished from “idiopathic Juvenile osteoporosis”

Corticosteroid-induced osteoporosis (CIO)

- Represents the most common form of secondary osteoporosis
- Has been associated with diseases such as asthma, rheumatoid arthritis, inflammatory bowel disease
- With long-term use, corticosteroids interfere both with bone formation and resorption, progressively decreasing bone mineral density and increasing the risk for fractures

Diagnosis of osteoporosis

- In addition to a thorough history and physical examination, the following should be performed:
  - Calcium, phosphorus, albumin, & liver enzymes
  - Bone-specific alkaline phosphatase
  - 25-hydroxyvitamin D
  - Intact parathyroid hormone (PTH)
  - Thyroid function test
  - 24–hour urinary calcium & creatinine values
  - ESR & CRP
  - LH / FSH & Sex hormones

Biochemical markers of bone turnover:

- **Formation (osteoblast products)**
  - Serum
    - Bone specific alkaline phosphatase (BSAP)
    - Osteocalcin (OC)
    - Carboxyterminal propeptide of type I collagen (PICP)
    - Aminoterminal propeptide of type I collagen (PINP)
- **Resorption (osteoclast products)**
  - Urine
    - Hydroxyproline
    - Free and total pyridinolines (Pyd) & deoxypyridinolines (Dpd)
    - Free and total *N*-telopeptide of collagen cross-links (NTx)
    - *C*-telopeptide of collagen cross-links (CTx)
  - Serum
    - Cross-linked *C*-telopeptide of type I collagen
    - *N*-telopeptide of collagen cross-links
    - *C*-telopeptide of collagen cross-links

Imaging Assessment of Bone Strength in Children

Techniques for Assessing Bone Mass

- A number of technologies can be used to assess mineral density including:
- Plain X-ray, especially of spine
- Assessment of bone mass
  - QCT (Quantitated Computer Tomography)
  - DPA (Dual Photon Absorptiometry)
  - DXA (Dual Energy X-ray Absorptiometry)
  - Ultrasound

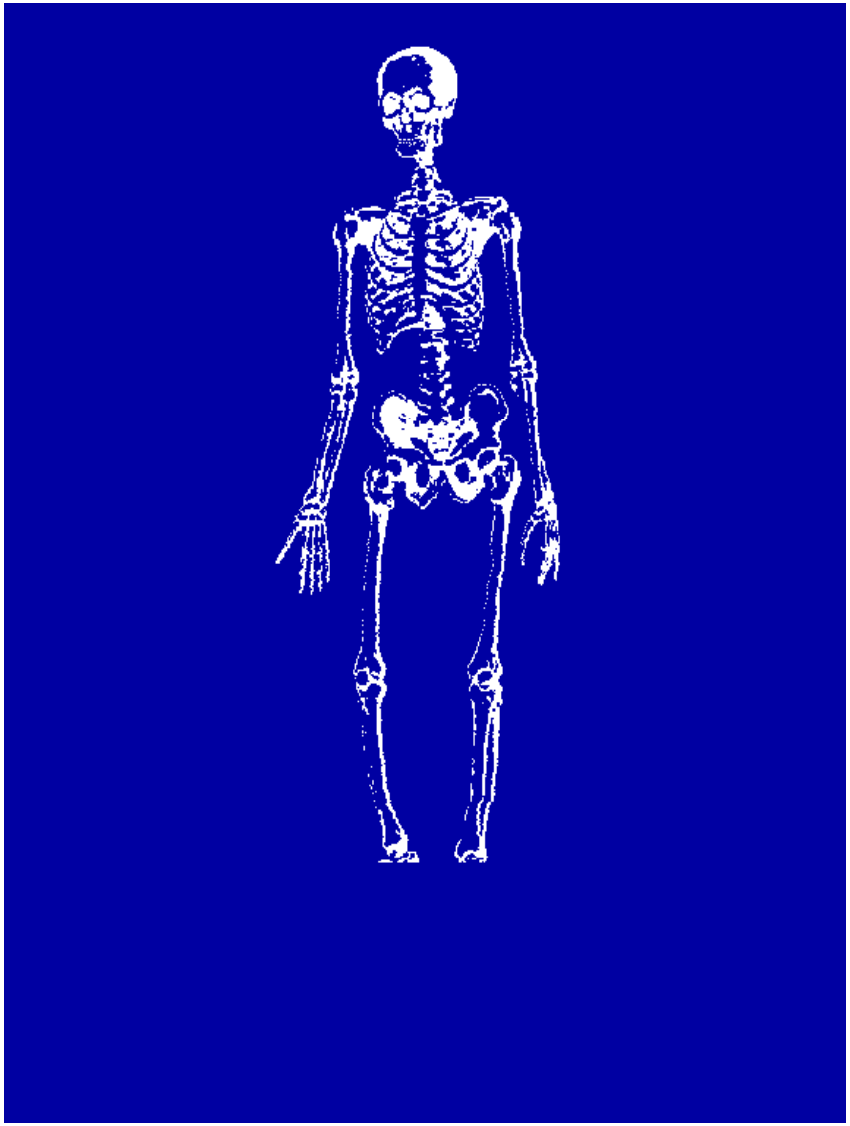
DXA software

total body

spine

femur

forearm



Assessment of bone mass by DXA

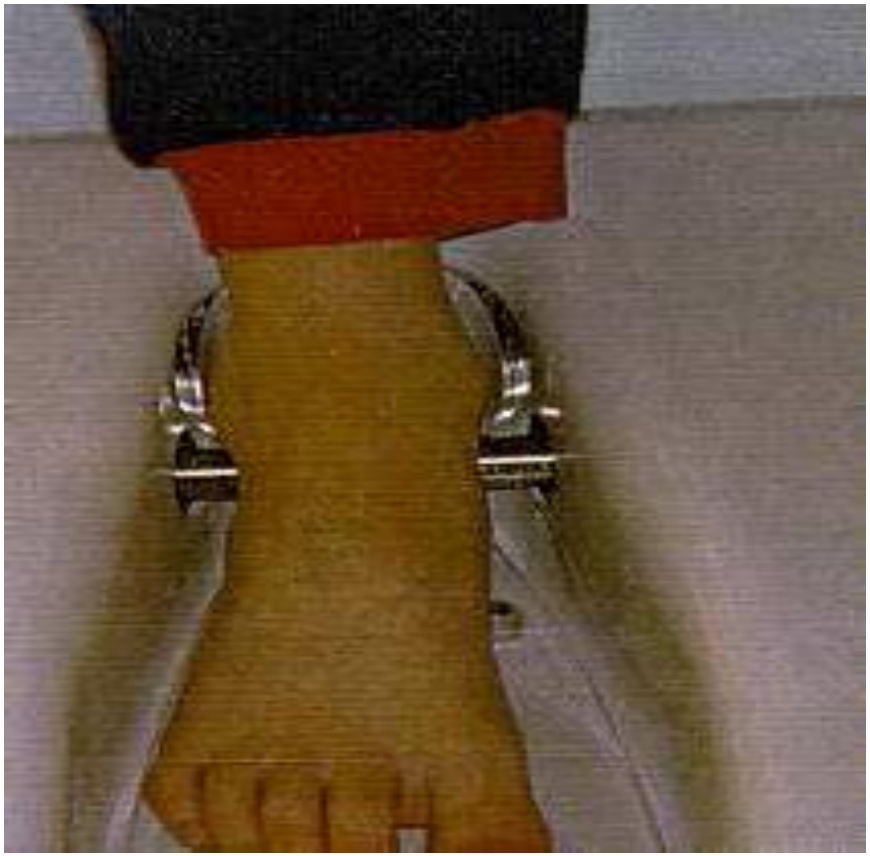
What is measured?

- Bone Mineral Content (BMC) in the volume of bone
- 2D projected area of bone

What form is the output?

- Areal bone density, g/cm^2 derived from BMC / projected bone area (not volume!)

Calcaneal Ultrasound Densitometry

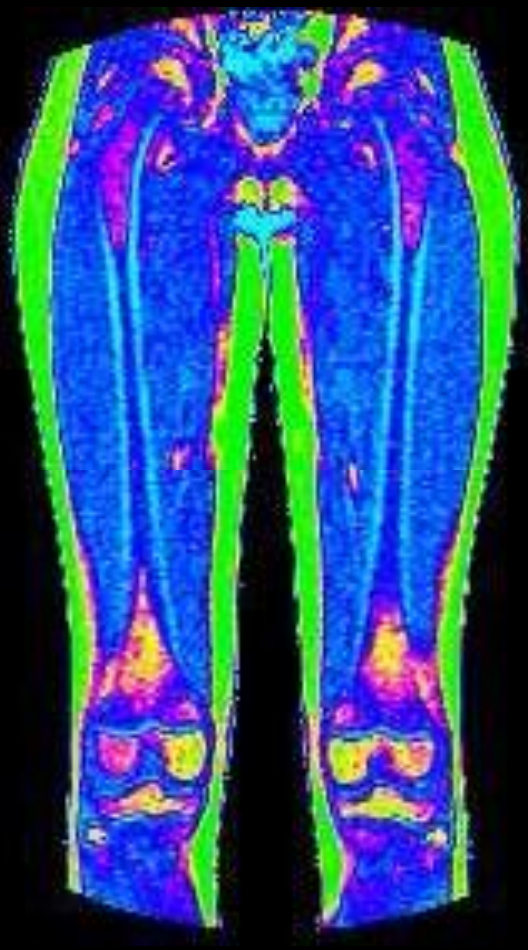


- Quantitative ultrasound (QUS) was also well tolerated and was technically easy to perform
- Speed of sound (SOS) shows a significant correlation with BMD as measured by DXA
- With the added advantage that it is free from radiation risk, further assessment of this potentially valuable tool for measuring bone status in children is warranted

- MRI - Geometry (mid-femoral shaft)
  - cortical width/ area /volume
  - medullary cavity width
  - shape
  - muscle parameters

- MRI can be useful in the assessment of metabolic bone disease
- MRI can be used to discriminate between acute and chronic fractures of the vertebrae and occult stress fractures of the proximal femur
- These osteoporotic fractures demonstrate characteristic changes in the bone marrow that distinguish them from other uninvolved parts of the skeleton and the adjacent vertebrae

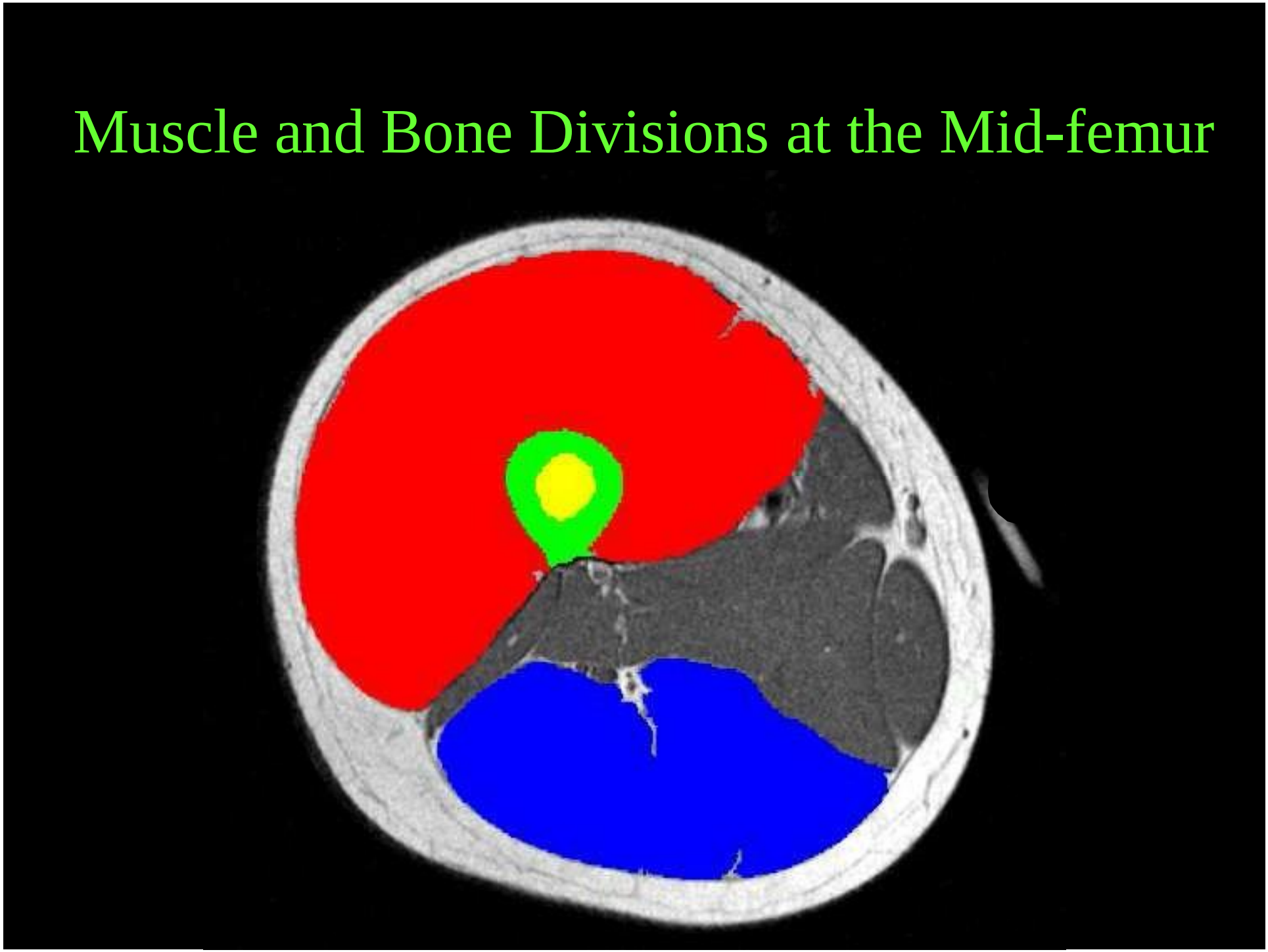
Geometry Assessment using MRI

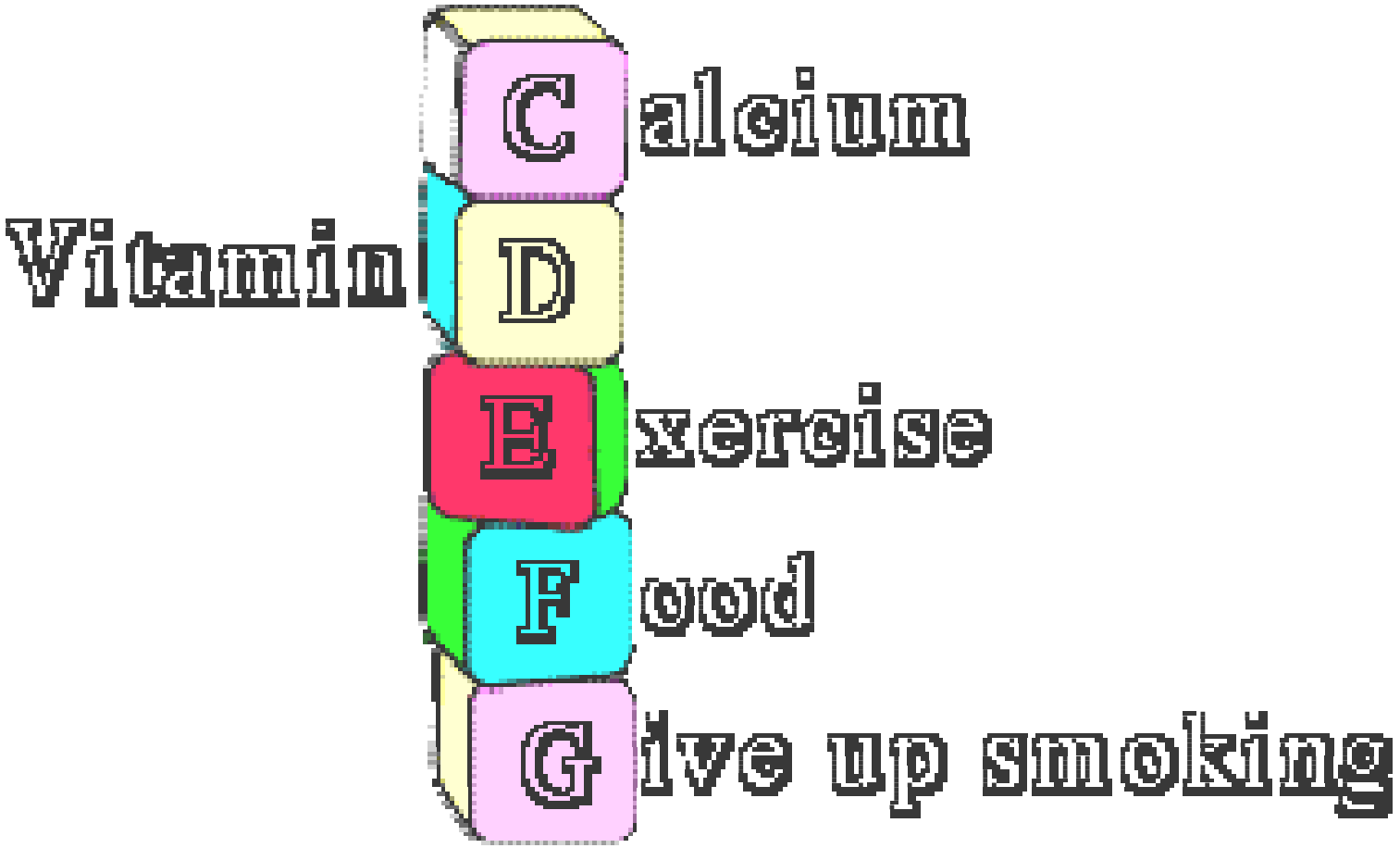


Scout Scan

Middle Slice of Mid-Third Region

Muscle and Bone Divisions at the Mid-femur




C alcium
Vitamin D
E xercise
F ood
G ive up smoking

- There is evidence that some children with rheumatic disease receiving corticosteroids would benefit from calcium & vitamin D supplementation
- During supplementation, of nine patients who completed all the BMD measurements, the mean spinal BMD increased to 11% over the baseline measures
- Eight patients had increased BMD and one had decreased BMD
- Seven patients had lower BMD values without supplementation, two had improved values

Treatment

Established treatment

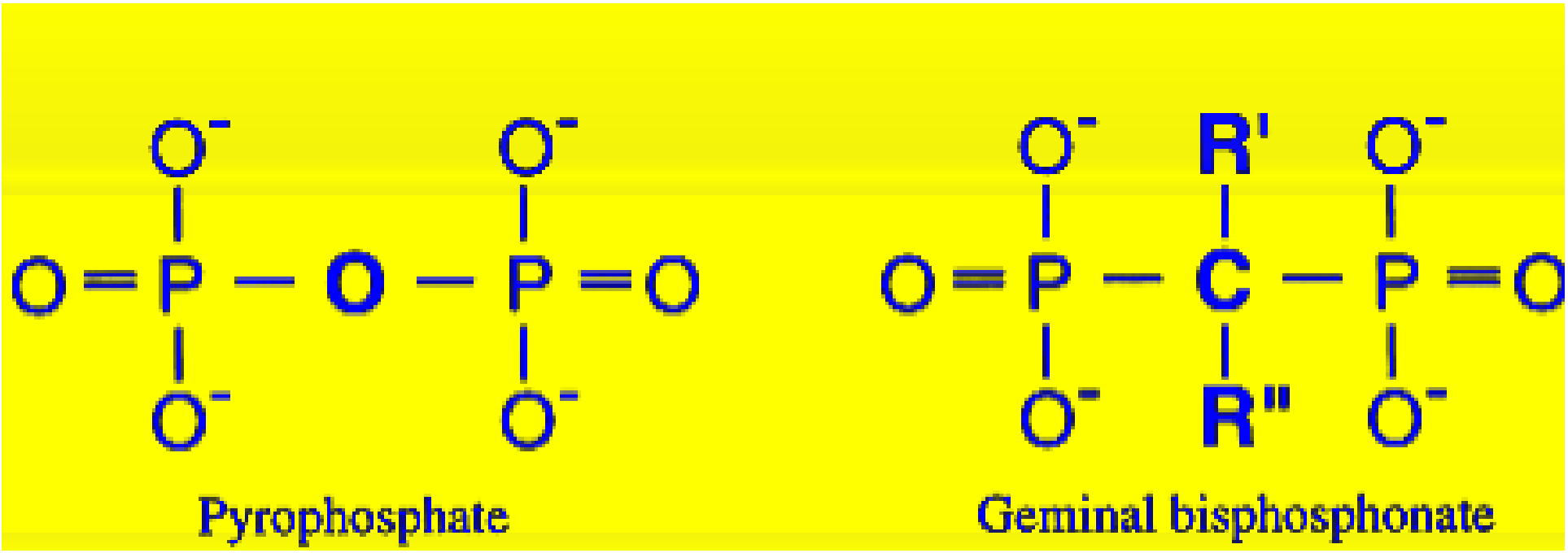
- calcium supplementation & vitamin D
- Calcitonin
- Bisphosphonates

Experimental treatment

- Combination therapy
- Thiazide
- Fluoride
- PTH
- GH

Bisphosphonates

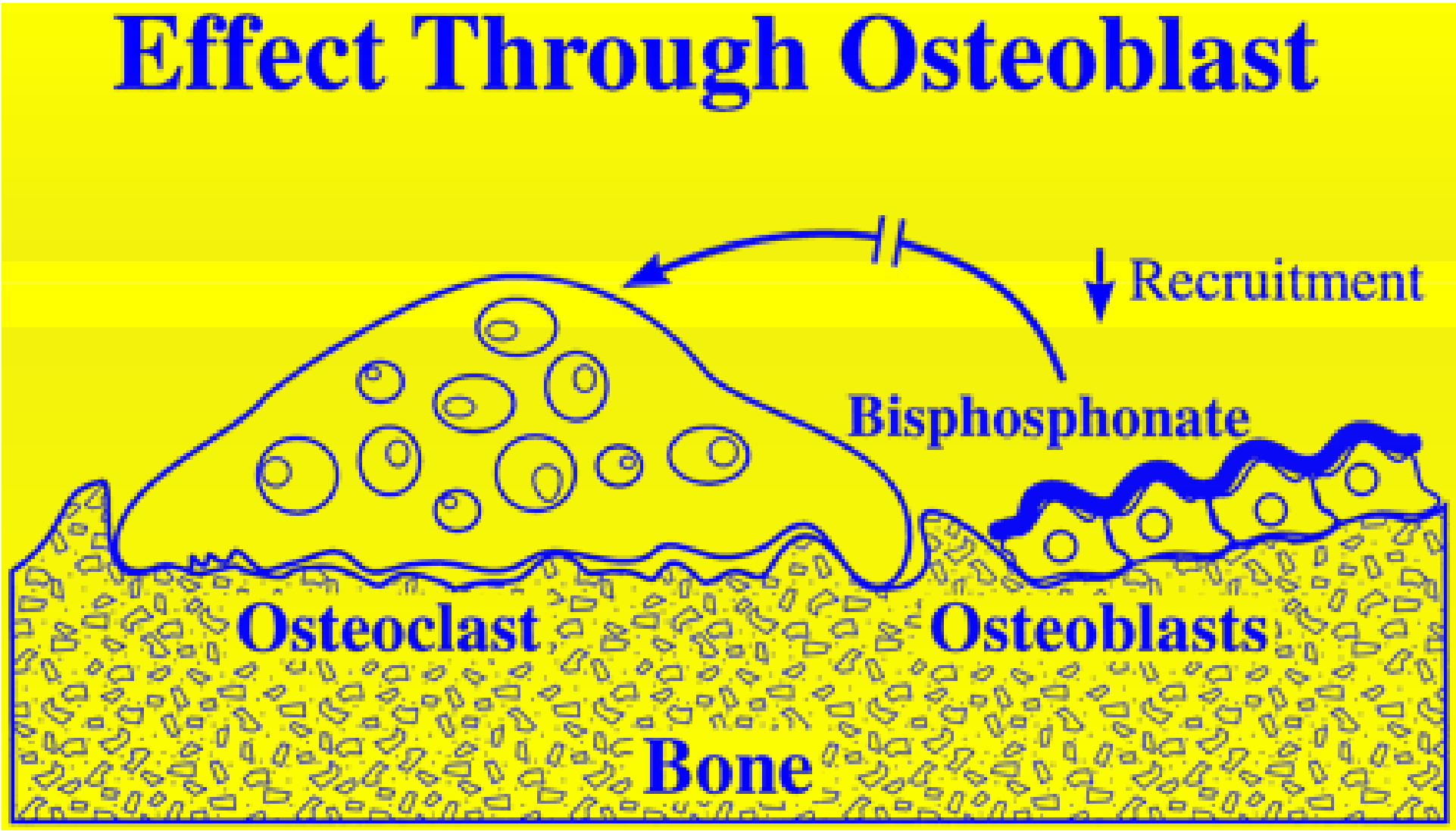
Chemical structure of pyrophosphate and bisphosphonates

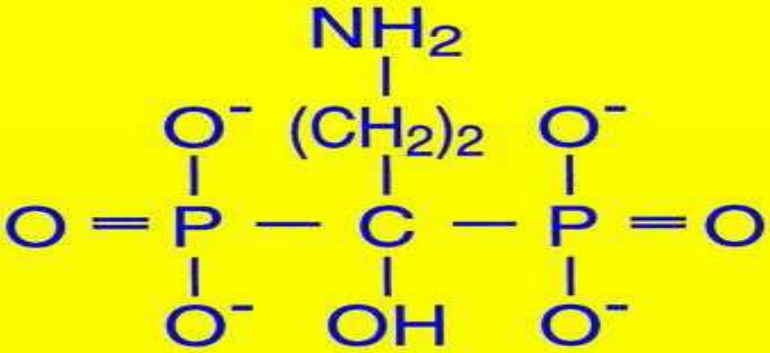


Bisphophonates

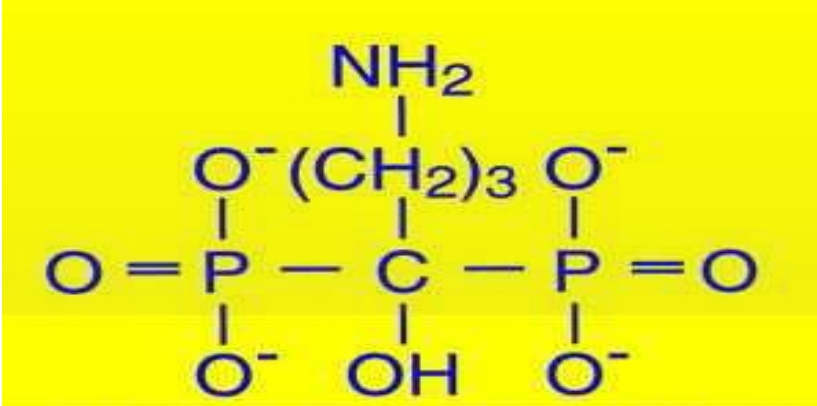
- Bisphosphonates are a class of medicines which mimic the structure of pyrophosphate, a natural component of normal bone
- Pamidronate or Zolodronate is selectively deposited in the skeleton
- The trials in children have all involved intravenous use
- It has turned out that intermittent use is particularly effective with children

Effect Through Osteoblast





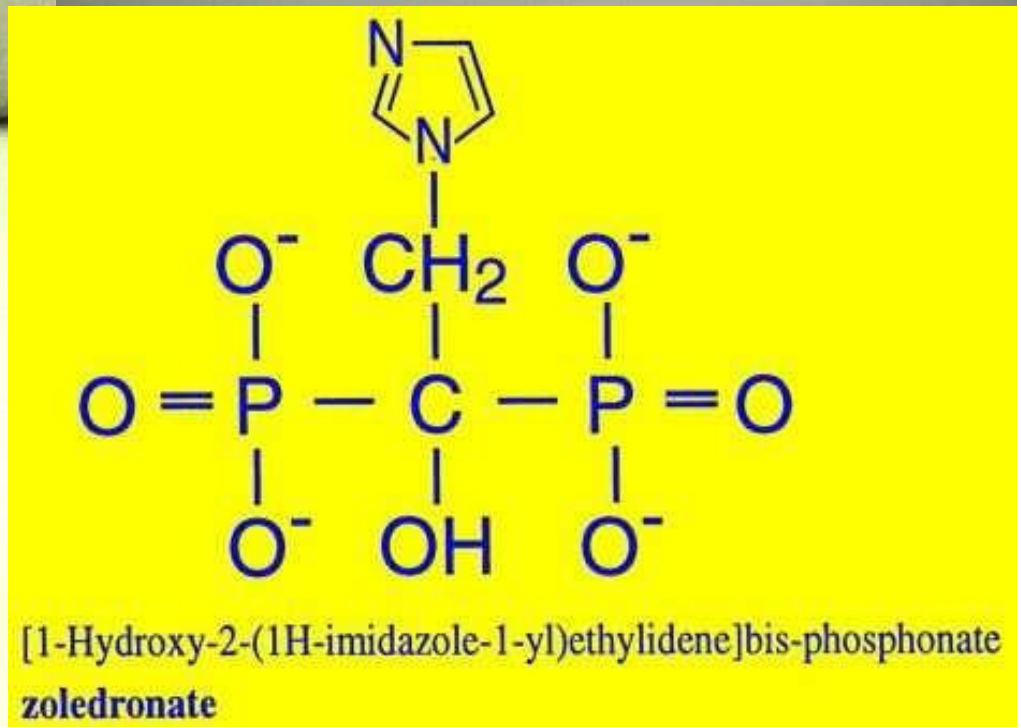
(3-Amino-1-hydroxypropylidene)bis-phosphonate
pamidronate*
Ciba-Geigy; Gador



(4-Amino-1-hydroxybutylidene)bis-phosphonate
alendronate*

[1-Hydroxy-2-(3-pyridinyl)-ethylidene]bis-phosphonate
risedronate

[1-Hydroxy-2-(1H-imidazole-1-yl)ethylidene]bis-phosphonate
zoledronate



[1-Hydroxy-2-(1H-imidazole-1-yl)ethylidene]bis-phosphonate

zoledronate

Zoledronate

- Zoledronate is the most potent of the clinically tested compounds
- Third-generation bisphosphonate
- 100-850 times more active than pamidronate in several in vivo and in vitro pharmacological test
- The new generation of bisphosphonates are likely to increase clinical options in terms of administration regimens, but their real advantage over those already available in terms of clinical efficacy remains uncertain.
- The effective doses (in adults) ranged from 2 to 4 mg

Bisphosphonates

Side effects

- long term safety uncertain

- Acute side effects include:
  - transient hypocalcemia (IV)
  - pyrexia (IV)
  - Myalgia & bone pain (IV)
  - GI disturbances (oral)
    - Esophagitis, GOR, oesophageal perforation

Conclusions

- Bone is continually remodeled throughout life because bones sustain recurring micro-trauma
- Bone tissue in skeleton increases until mid 20s
- Factors that influence bone accretion during childhood & determine the peak bone mass are:
  - Heredity “genetic potentials”
  - Ethnic origin
  - Gender
  - Diet such as calcium & vitamin D intake
  - Physical activity
  - Endocrine status
  - Sporadic risk factors such as cigarette smoking

Conclusions

- The definition of childhood osteoporosis should include the presence of low trauma fractures with evidence of reduction of BMD more than 2 SD below the age matched mean “not adult match” and has to be corrected for body size i.e. Volumetric BMD not Arial BMD

Conclusions

- Treatment of childhood osteoporosis includes:
  - calcium supplementation & vitamin D
  - Calcitonin
  - Bisphosphonates:
  - Bisphosphonates are a class of medicines which mimic the structure of pyrophosphate, a natural component of normal bone
  - The trials in children have all involved intravenous use It has turned out that intermittent use is particularly effective with children


THANKS