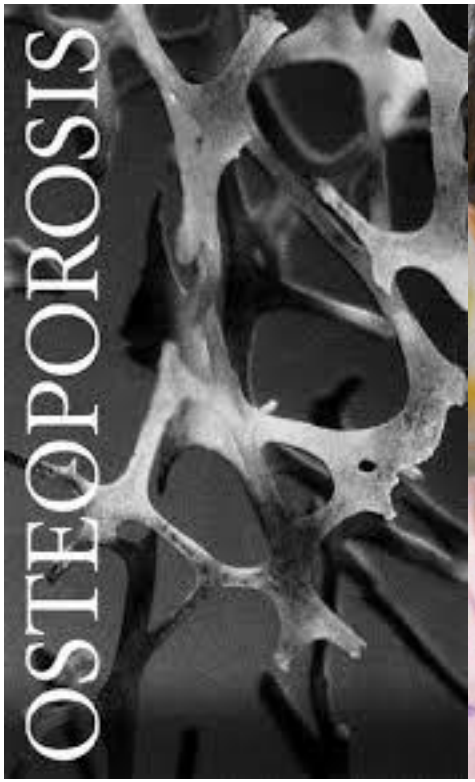
OSTEOGENESIS IMPERFECTA & THE EFFICACY/ SAFETY OF INTRAVENOUS ZOLEDRONIC ACID TREATMENT OF PEDIATRIC OSTEOPOROSIS



Prof. Abdulmoein Al-Agha, FRCPCH (UK)

aagha@kau.edu.sa

OBJECTIVES

- Basics of Bone physiology
- What happens in osteoporosis!!
- Different causes of Pediatric Osteoporosis
- Presentation ,diagnosis & management of patients with OI
- Importance of making the right diagnosis
- Local published Data on usage & Safety of Zoledronic acid therapy in cases of Pediatric Osteoporosis over 13- year follow up

MECHANISM OF BONE FORMATION AND BREAKDOWN

Key words

Osteoblasts : cells that synthesize bone matrix

Osteoid : Unmineralized bone matrix

Osteoclasts: cells that resorb bone.

Modeling : formation of bone

Remodeling: breakdown and renewal of bone.

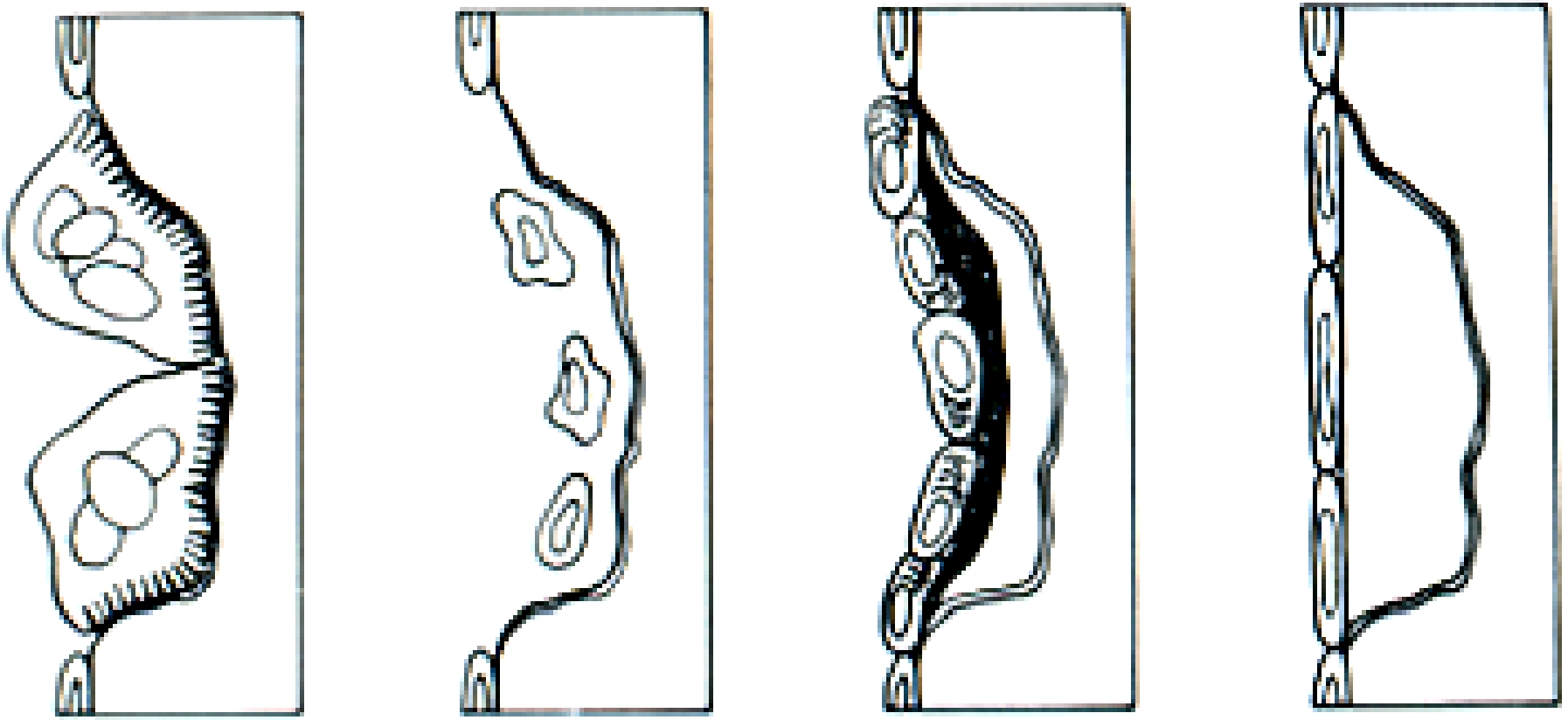
Calcidiol : 25 (OH)2 D

Calcitriol : 1, 25 (OH)2 D

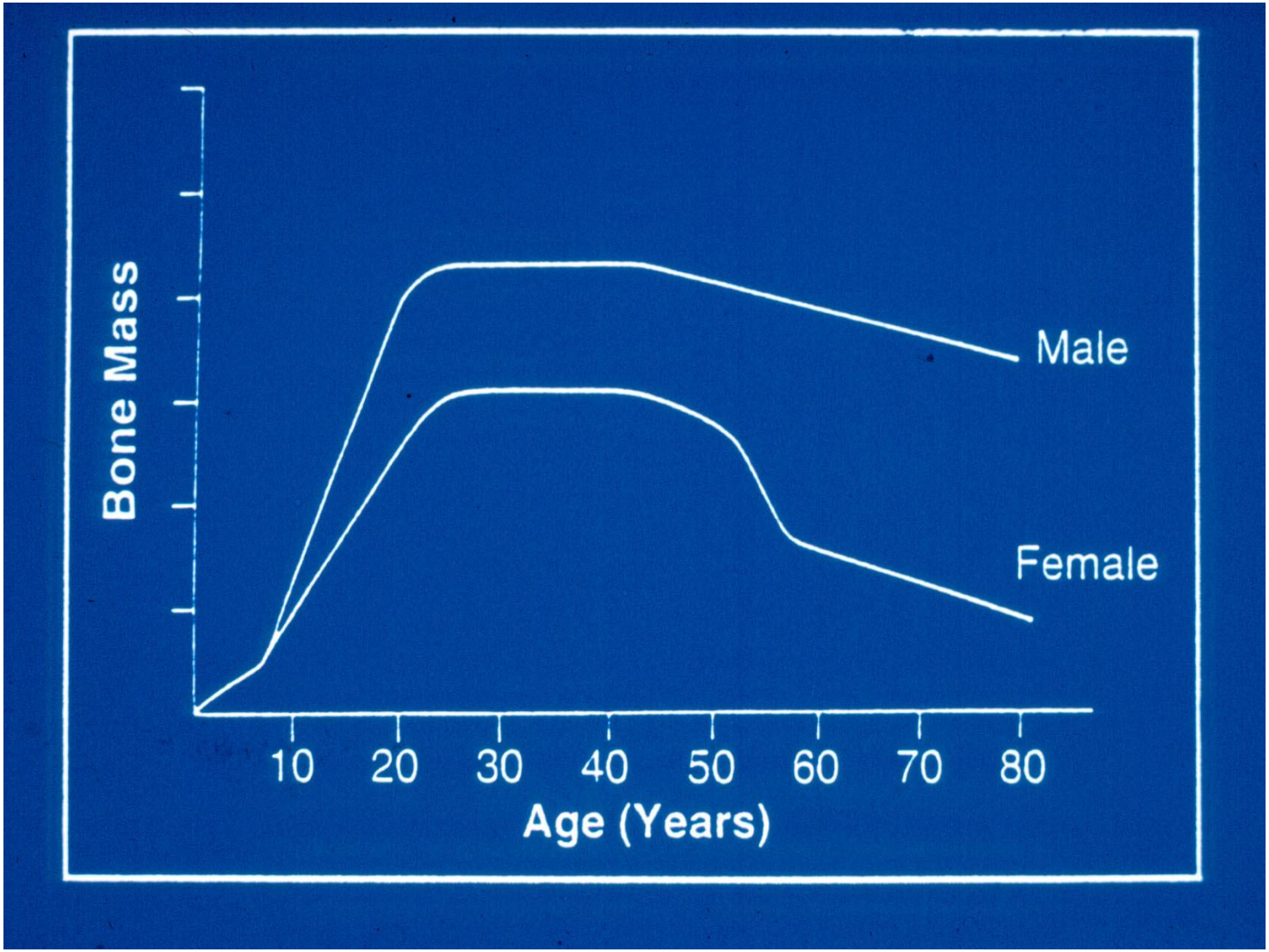
COMPONENTS OF BONE

- **Calcified matrix (90%)**
  - composed of collagen fibers (type-1),
  - Glycosaaminoglycan containing spindle shaped crystals of hydroxyapatite
- **Mineral Element**
  - Crystals of Calcium and Phosphate are arranged either amorphously or as Hydroxyapatite Ca_{10} $(PO4)_6$ $(OH)_2$ on or within the collagen fibers.
  - Na, Zn, Mg, Cu and fluoride
- **Non Collagenous Components (Proteins)**
  - Osteocalcin: protein produced by the Osteoblasts
  - α2 HS- glycoprotein: produced by the liver and absorbed by the bone matrix
  - Amino Acids: about one fourth of amino acids present in collagen are proline and hydroxproline.

Normal Bone Remodelling



Peak bone mass: accrued during adolescence



BONE TURNOVER CYCLE – HORMONAL BALANCE ENABLES APPROPRIATE ACTIVITY OF OSTEOBLASTS VS OSTEOCLASTS

Bone Formation

Bone Resorption

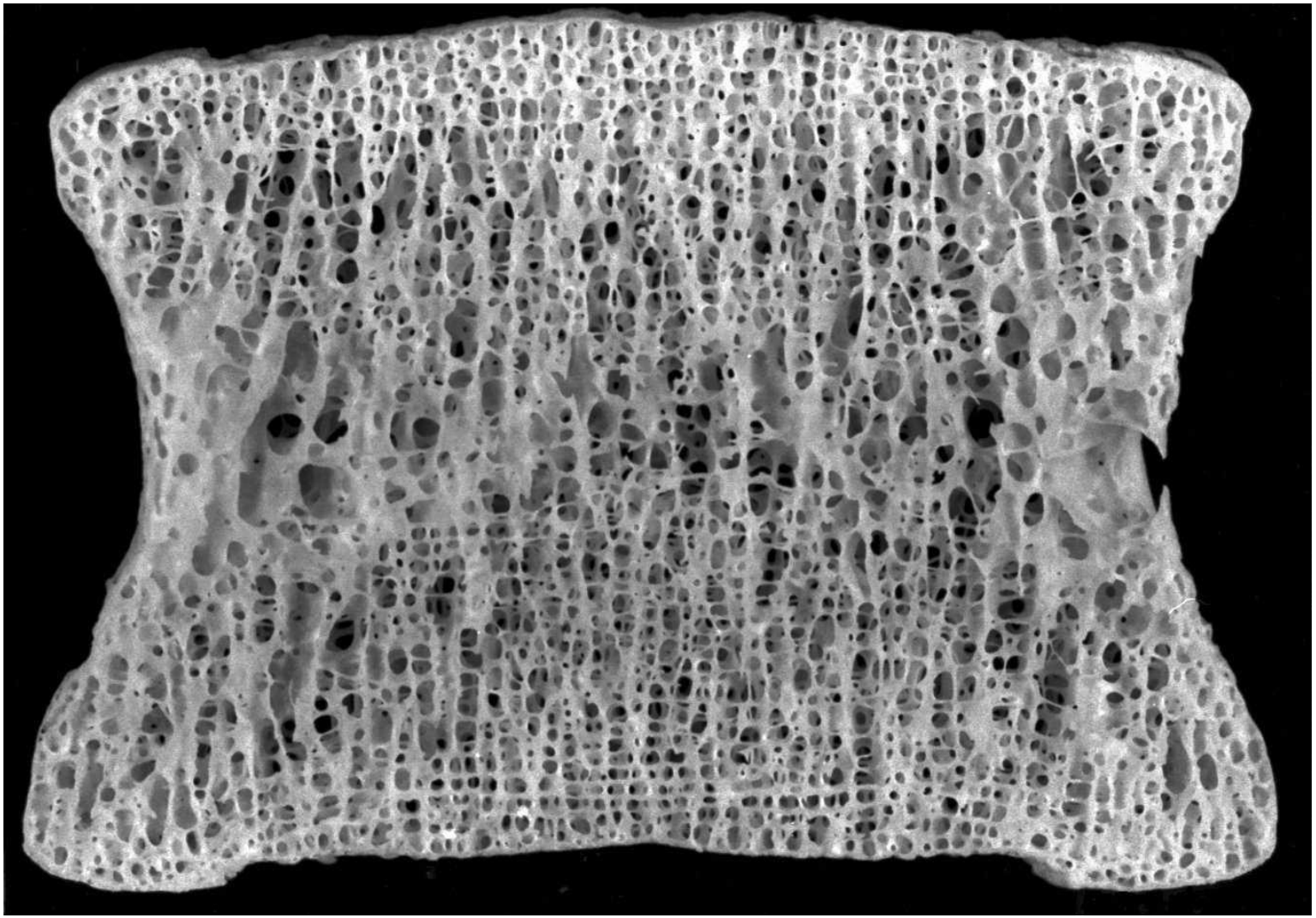
GH
IGF-1
DHEA
Androgens

Estrogen
PTH
Cortisol

OSTEOPOROSIS

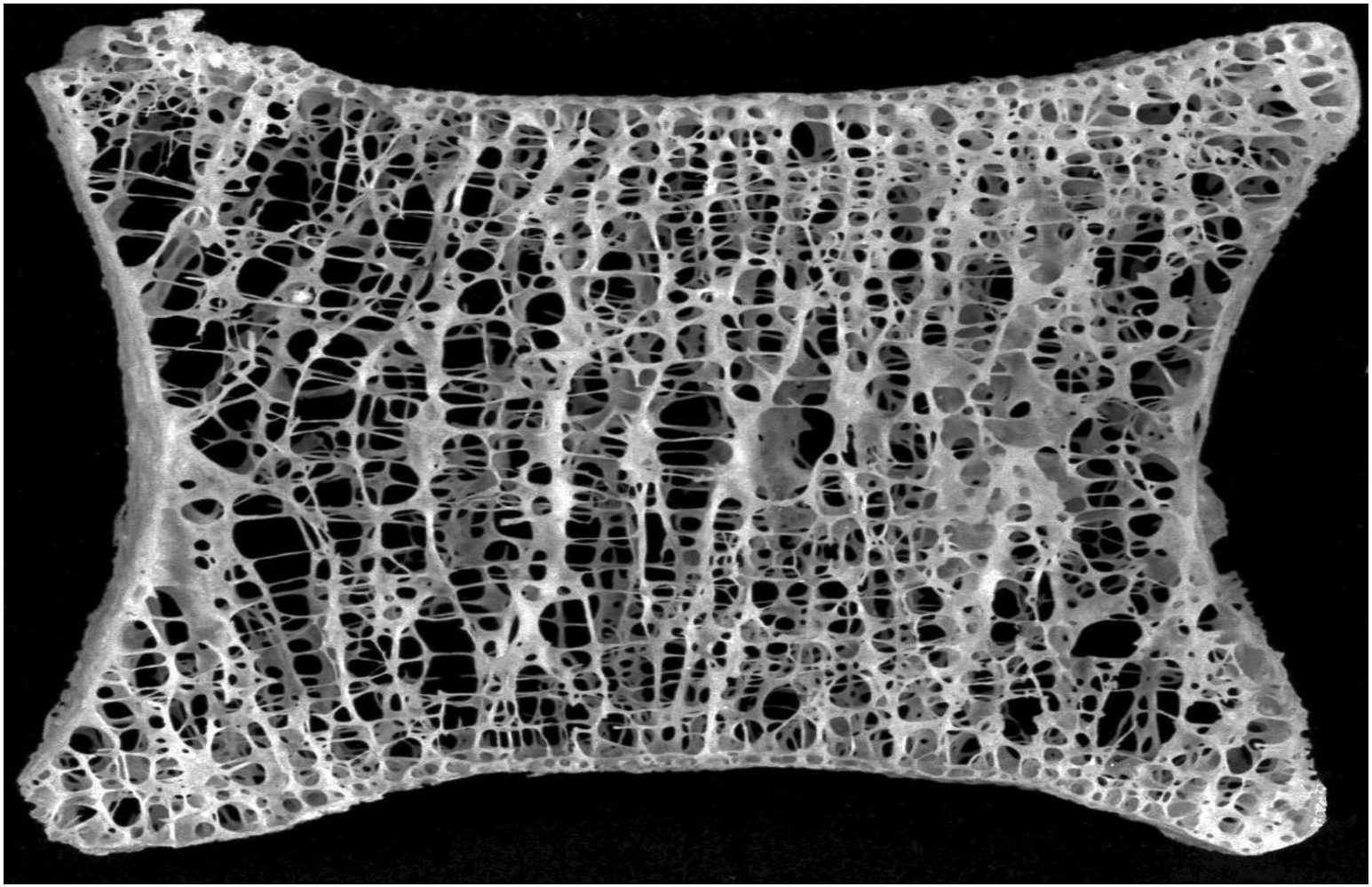
- preventable disease
- no cure
- new interest in childhood and adolescence as critical years for bone acquisition

NORMAL BONE



Female, age 30 years

Osteoporosis



Female, age 88 years

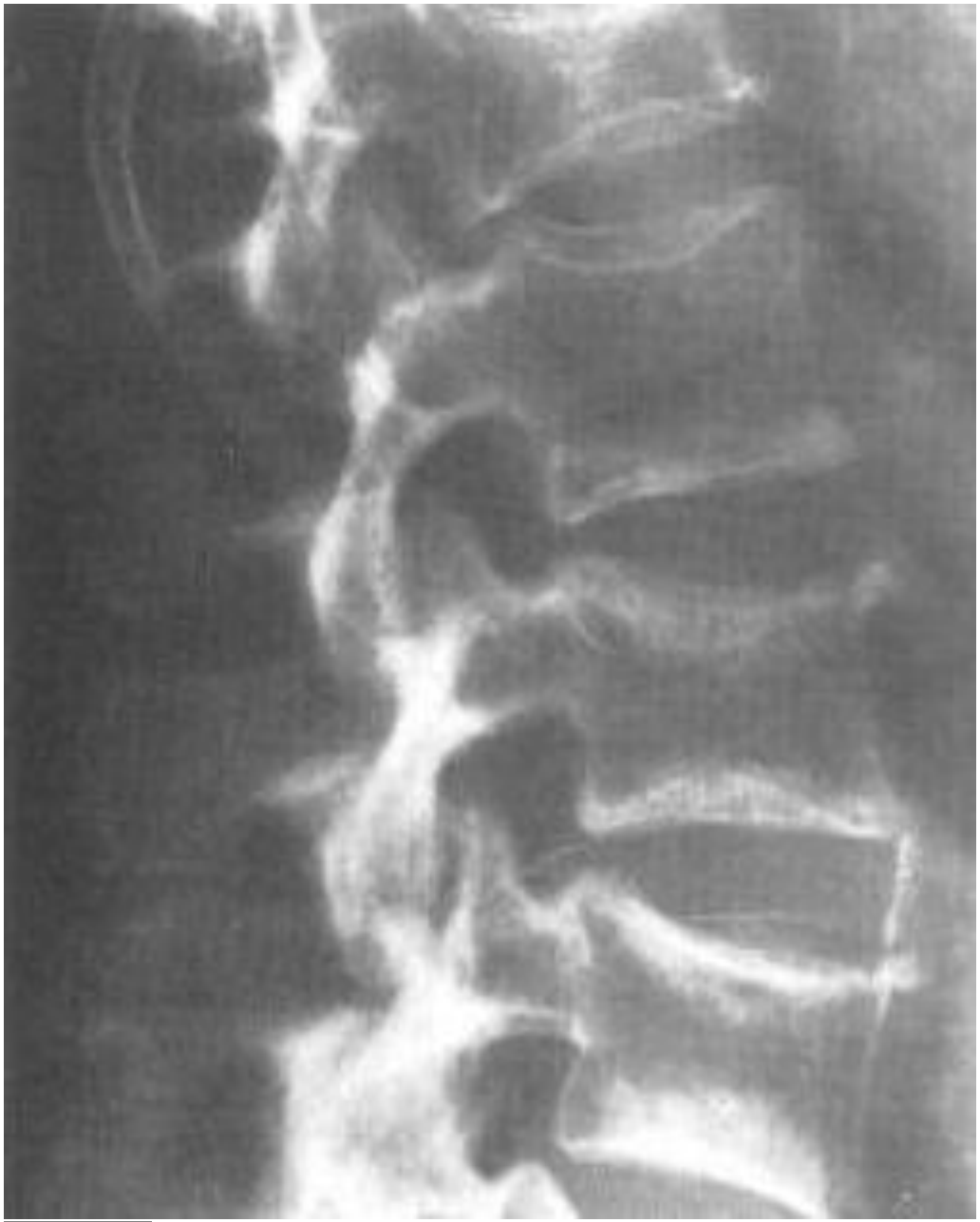
DEFINITION OF "OSTEOPOROSIS" IN CHILDREN

- **No WHO definitions in children and teens**
- **Concern for low bone mass**
  - BMD Z-score by DXA ≤ -2.0 SD
  - Slightly low if Z-score between -1.0 and -2.0
- **"Diagnosis of osteoporosis in children and adolescents should NOT be made on the basis of BMD alone."**

Int'l Soc Clinical Densitometry 2007

OSTEOPOROSIS: CLINICAL MANIFESTATIONS

- Early osteoporosis is asymptomatic
- As skeletal integrity declines, fractures occur, often with minimal trauma
- Vertebral compression fractures are most common, hip and wrist fractures also are major problems
- End stage disease associated with marked dorsal kyphosis



DETERMINANTS OF BONE MASS

Extrinsic

- **Diet**
- **Body mass/habitus**
- **Hormonal milieu**
- **Illnesses**
- **Exercise**
- **Lifestyle choices**

Intrinsic

- **Gender**
- **Family History**
- **Ethnicity**
- **Genetic factors**

GENETIC FACTORS

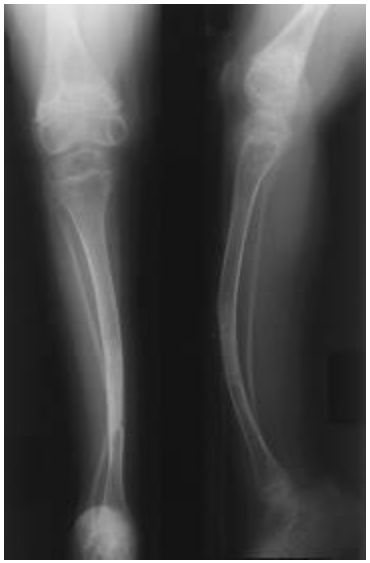
- **Striking patterns within families**
- **Candidate genes:**
  - Vitamin D receptor
  - Estrogen receptor
  - IGF-I receptor
  - TGF-β
  - Alleles involved in collagen synthesis :COL -1

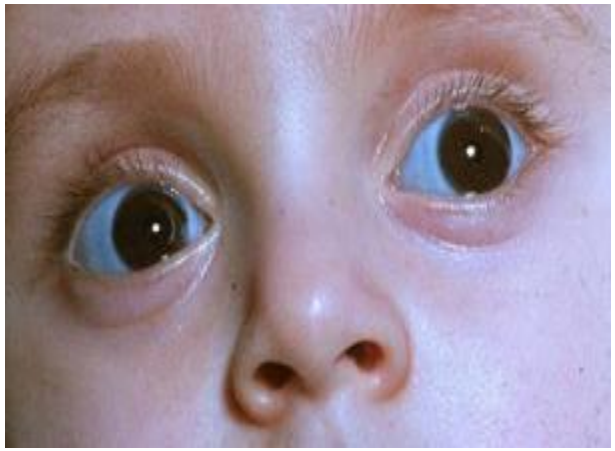
AT-RISK CHILDREN AND ADOLESCENTS

- ***Obesity**
- ***Poor diet/little sun exposure**
- **Anorexia nervosa/chronic amenorrhea/delayed puberty**
- **Turner syndrome**
- **Growth hormone deficiency**
- **Medications: glucocorticoids, anticonvulsants, depot medroxyprogesterone, GnRH agonists**
- **Gastrointestinal disease (IBD)**
- **Cerebral palsy/neuromuscular diseases**
- **Rheumatologic diseases: SLE, JRA, dermatomyositis**
- **Cystic fibrosis**
- **Celiac disease**
- **Renal failure**
- **Diabetes mellitus**
- **Hemoglobinopathies (sickle cell, thalassemia) + hemophilia**
- **Immobilized patients**
- **HIV**
- **Hyperprolactinemia**

OSTEOGENESIS IMPERFECTA

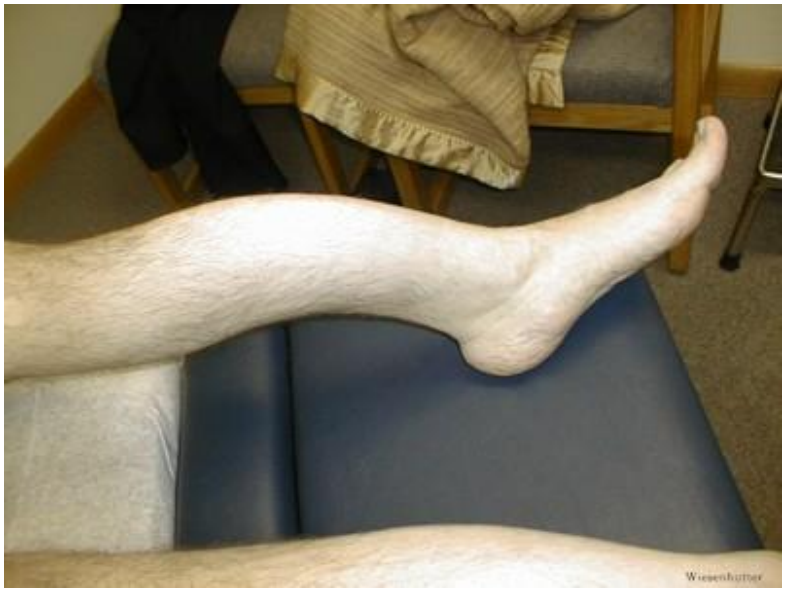
- Manifest itself with 1 or more of the following findings:
- Blue sclerae
- Triangular facies
- Macrocephaly
- Hearing loss
- Defective dentition
- Barrel chest
- Scoliosis
- Limb deformities
- Fractures
- Joint laxity
- Growth retardation
- Constipation and sweating





OSTEOGENESIS IMPERFECTA

- Pathologic changes seen in all tissues in which type 1 collagen is an important constituent (e.g., bone, ligament, dentin, and sclera)
- Basic defect : qualitative or quantitative reduction in type 1 collagen
- Mutations in genes encoding type 1 collagen affect the coding of 1 of the 2 genes
- Mutations are either genetically inherited or new
- Inherited mutations : recurrence risk in subsequent pregnancies of 50% if a parent is affected
- New mutations unpredictable recurrence risk



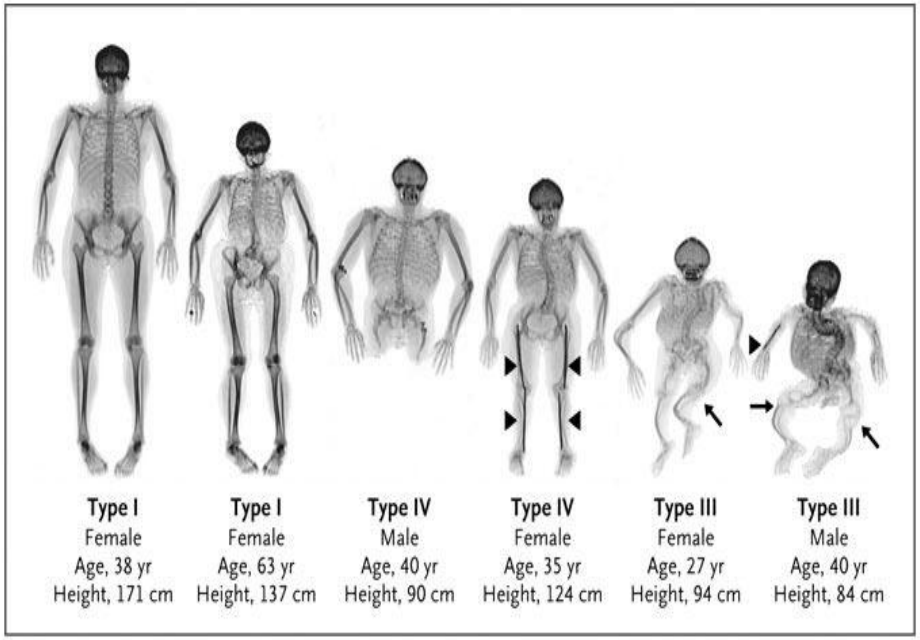

1x

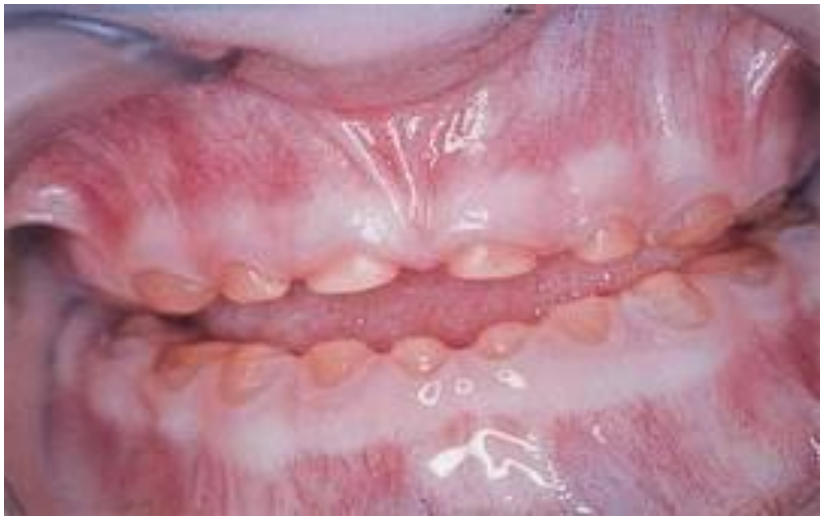
OSTEOGENESIS IMPERFECTA

- Incidence : 1 case for every 20,000 live births
- Equally common in males and females
- Described in every human population in which skeletal dysplasias have been studied
- No predilection for a particular race
- Family history , but most cases due to new mutations
- Commonly present with fractures after minor trauma

OSTEOGENESIS IMPERFECTA

- Clinical presentation depends on phenotype
- Sillence classificatiom : 4 types on basis of clinical and radiologic features
- Dentinogenesis imperfecta denoted as subtype B, whereas OI without dentinogenesis imperfecta is denoted as subtype A





TYPES OF OI

- 8 types described so far
- OI types range from a mild form with no deformity, normal stature and few fractures to a form that is lethal during the perinatal period (prior to and after birth).
- Medical problems a person will depend on the type of OI
- OI varies greatly from person to person, even among people with the same type of OI, even within the same family

TYPE I

- mildest and most common form
- 50% of the total OI population
- mild bone fragility
- relatively few fractures
- minimal limb deformities
- child might not fracture until he or she is learning to walk
- Some children have few obvious signs of OI or fractures while others experience multiple fractures of the long bones, compression fractures of the vertebrae, and chronic pain.
- Appear healthy yet need to accommodate for bone fragility

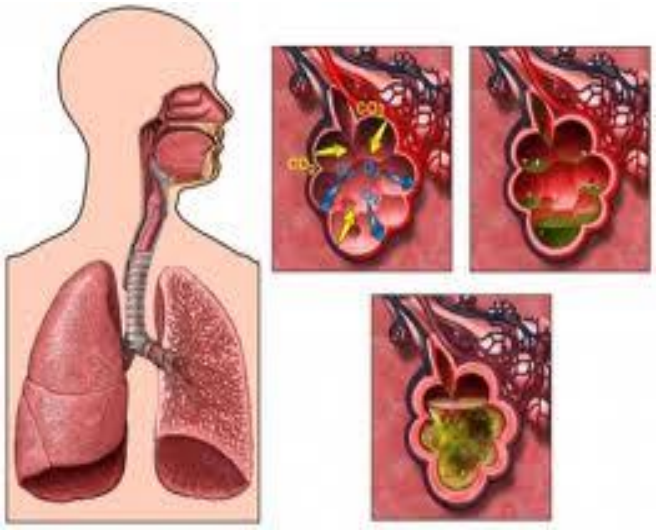
Table. Adapted Sillence Classification of Osteogenesis Imperfecta

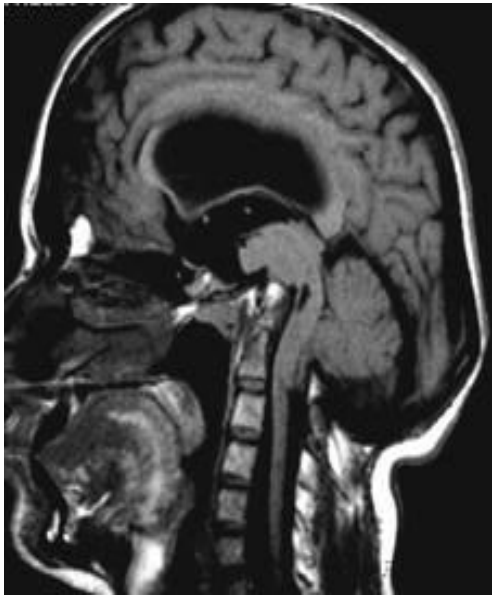
Type	Genetic	Teeth	Bone Fragility	Bone Deformity	Sclera	Spine	Skull	Prognosis
IA	AD*	Normal	Variable but less severe than other types	Moderate	Blue	20% scoliosis and kyphosis	Wormian bones	Fair
IB	AD	Dentinogenesis imperfecta	NA	NA	NA	NA	NA	NA
II	AD	Unknown	Very severe	Multiple fractures	Blue	NA	Wormian bones with absence of ossification	Perinatal death
III	AD	Dentinogenesis imperfecta	Severe	Progressive bowing of long bones and spine	Bluish at birth but white in adults	Kyphoscoliosis	Hypoplastic wormian bones	Wheelchair-bound, not ambulatory
IVA	AD	Normal	Moderate	Moderate	White	Kyphoscoliosis	Hypoplastic wormian bones	Fair
IVB	AD	Dentinogenesis imperfecta	NA	NA	NA	NA	NA	NA

* AD = autosomal dominant; NA = not applicable.

COMPLICATIONS

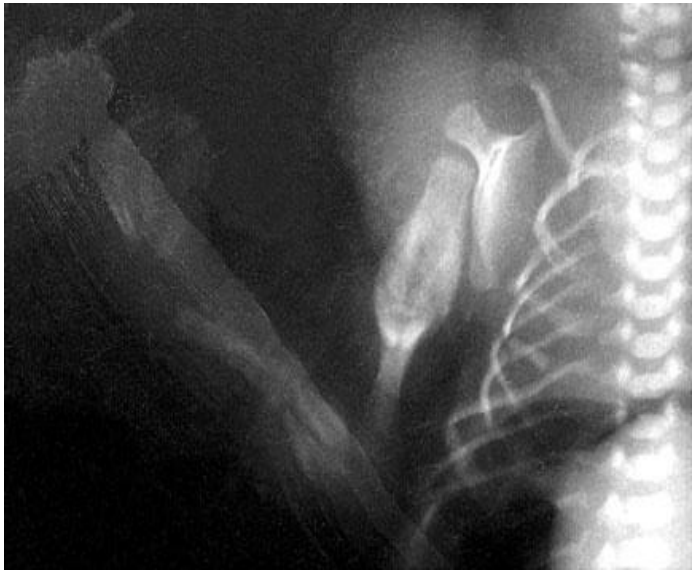
- Repeated respiratory infections
- Basilar impression caused by a large head, which causes brainstem compression
- Cerebral hemorrhage caused by birth trauma
- High risk for complications of anesthesia

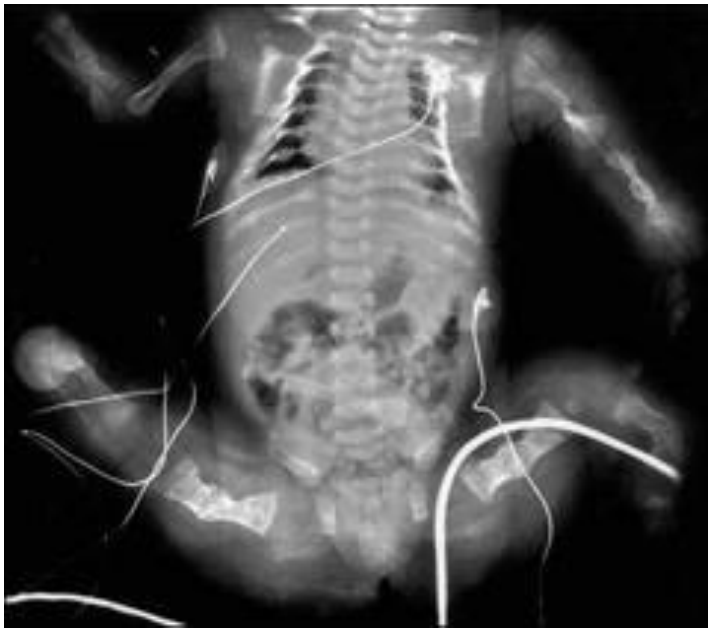


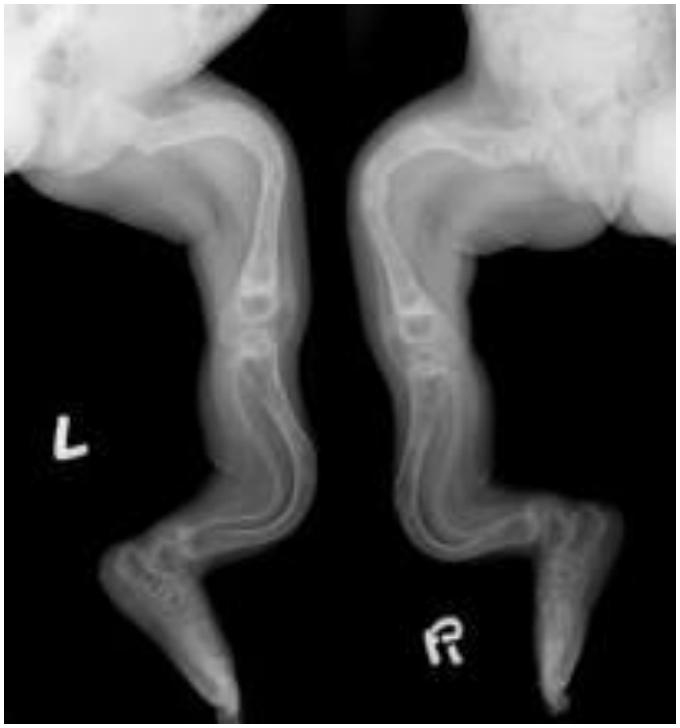


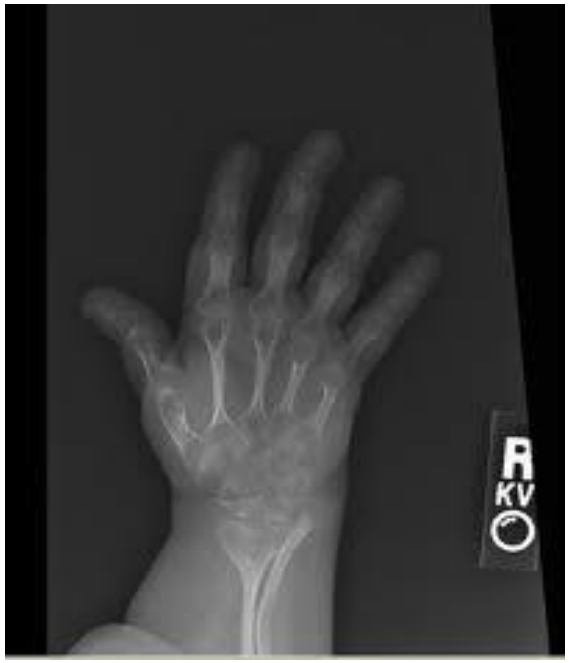
DIFFERENTIAL DIAGNOSES

- Achondroplasia
- Menkes Kinky Hair Disease
- Hereditary Rickets
- Thanatophoric Dysplasia
- Jeune dystrophy
- Camptomelic dysplasia
- Chondrodysplasia punctata
- Chondroectodermal dysplasia (Ellis–van Creveld syndrome)
- Non- accidental injury
- Hypophosphatasia






L
R


R
KV

DIAGNOSTIC WORK-UP

- Rule-out systemic disease
- Consider insidious celiac disease
- 25-hydroxyvitamin D
- PTH
- Calcium, phosphorus, magnesium
- Other:
  - Ceruloplasmin, copper, IGF-I, DHEAS
- Bone age
- Urinary calcium/creatinine (spot/24 h)
- If amenorrhea: thyroid function, FSH, prolactin

MEASUREMENT OF SKELETAL STATUS

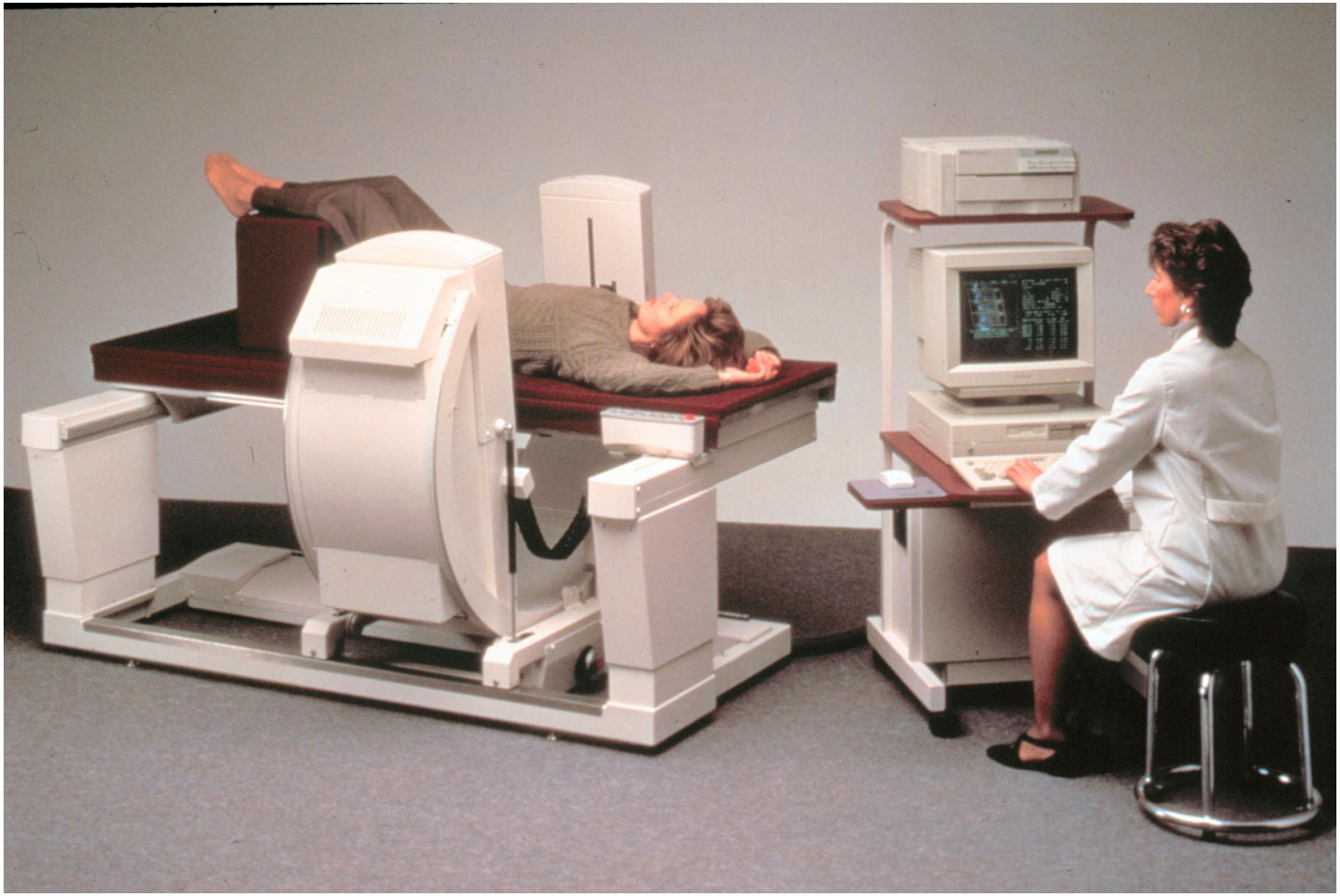
Bone density

- Dual energy x-ray absorptiometry (**DXA**) – 2D
- Quantitative ultrasound (**QUS**)
- Quantitative CT – 3D (including **pQCT**)
- High-resolution pQCT (XtremeCT)
- Peripheral vs. axial (central) measurements

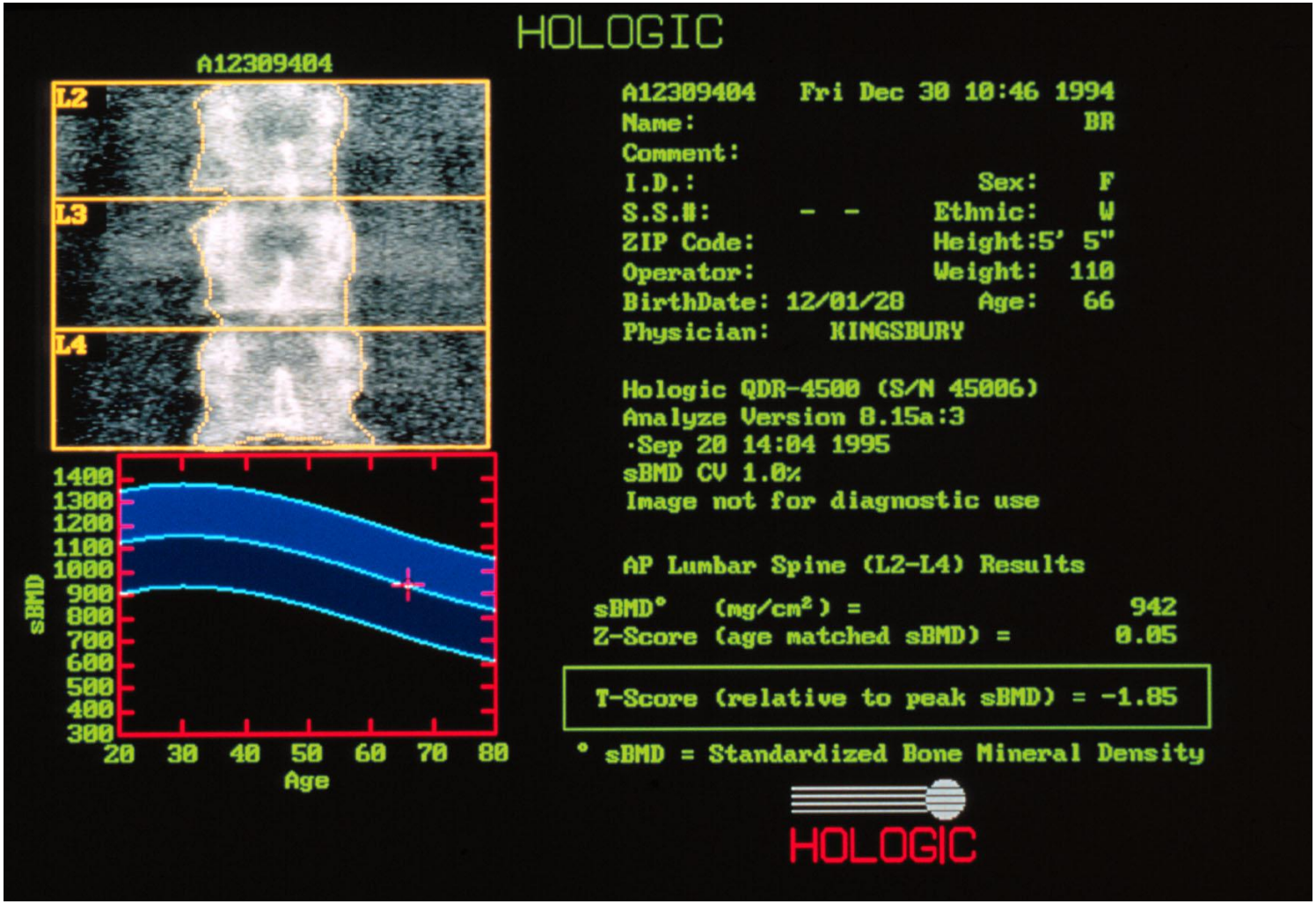
Bone quality

- High-resolution **MRI**
- Micro-CT (from biopsy specimens)
- Hip structural analysis (bone geometry)
- Fracture rates

DXA SCANNER – OPEN CONFIGURATION



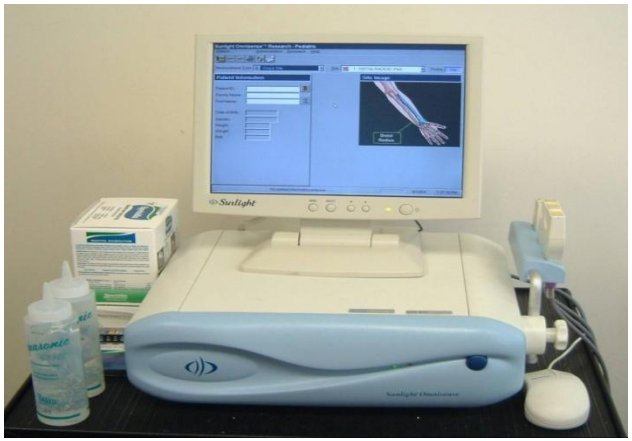
DXA RESULTS: RATE-OF-CHANGE CURVE



RADIAL AND TIBIAL MEASUREMENTS

Peripheral QCT

Quantitative Ultrasound



OSTEOPOROSIS TREATMENT WITH ZOLEDRONIC ACID IN PEDIATRIC POPULATION AT A UNIVERSITY HOSPITAL IN WESTERN SAUDI ARABIA: *A 13-YEAR EXPERIENCE*

ABDULMOEIN E. AL-AGHA, FRCPCH, RAHAF S. HAYATALHAZMI, MBBS.

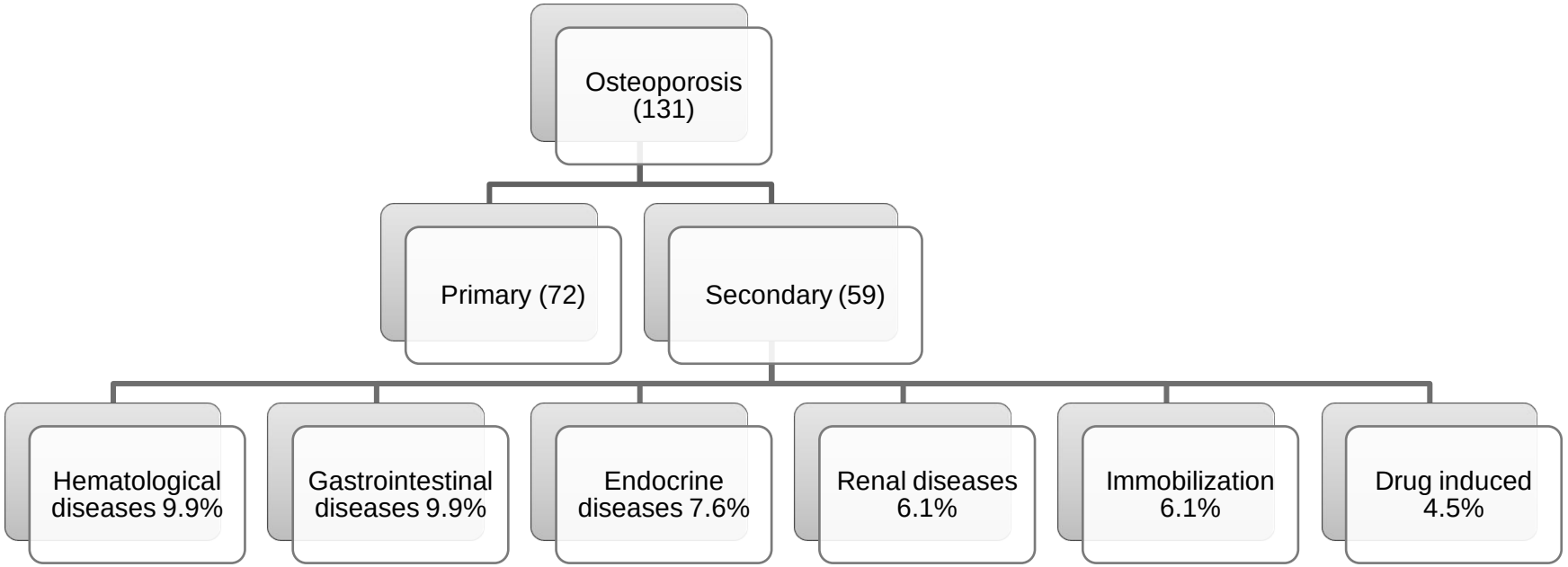
SAUDI MED J 2015; VOL. 36 (11): 1312-1318


NDC 47335-952-41
Zoledronic Acid for Injection
4 mg/vial
For Intravenous Infusion
Sterile Concentrate
Lyophilized
Dose must be diluted.
Do not mix reconstituted solution with calcium-containing infusion solutions.
Rx only
SUN PHARMA
Zoledronic Acid for Injection
4 mg/vial
5 mL

- Up to date, many studies have investigated bisphosphonate treatment primarily with the use of Pamidronate in many bone related diseases
- As to the ZA treatment of pediatric osteoporosis, there are no much published data on long-term use, safety and efficacy
- There were no Saudi local, Arabian, or even internationally published data on a large study number of children receiving ZA (when our study conducted)
- **In our study, we aimed to review a 13-year experience with primary and secondary causes of osteoporosis, as well as the efficacy, and safety of intravenous ZA as the treatment of choice in our pediatric population at the King Abdulaziz University Hospital (KAUH),Jeddah, Kingdom of Saudi Arabia (KSA)**

METHODS

- **A retrospective observational study *Patients population:***
- **131 patients aged 6 weeks to 18 years with primary and secondary osteoporosis followed up at the Pediatric Endocrine Outpatient Clinic at KAUH, Jeddah, KSA between January 2002 and January 2015.**



Data

- Data were obtained from direct interview of patients and/or their parents
- All laboratory results were obtained from the KAUH electronic Phoenix system
- Informed verbal consent was acquired from all patients and/ or their parents prior to the start of therapy

METHODS

Inclusion criteria:

- **Patients with confirmed diagnosis of osteoporosis based on:**
  - clinical or biochemical high bone turnover markers of C-terminal telopeptide [CTX], and osteocalcin levels
  - and/ or a z-score ≤-2.0 SD on a bone densitometry DXA scan were included in the study.
- **Patients with a normal bone profile**
  - calcium, phosphate, and alkaline phosphatase (as well as normal total vitamin D , parathyroid hormone levels before the start of treatment

Exclusion criteria:

- **mineral metabolism disturbances, major data insufficiency, and a creatinine clearance rate < 30-35 mL/ min**

METHODS

Treatment administration:

- Intravenous ZA was used as the treatment of choice in both groups throughout study
- Was administered intravenously at a dose of 0.05 mg/kg maximum dose to be given is 2 mg/infusion, in neonates and infants, the dose was 0.025 mg/kg
- The first 5 infusions were given once every 3 months, then once every 6 months, depending on the clinical and biochemical marker response
- All patients were admitted to the general ward for 2 days to receive their first infusion to enable close monitoring of the acute complications that might occur
- Subsequent ZA infusions were given during day care unit admissions OVER 30-60 minutes duration

METHODS

Precautions for the treatment:

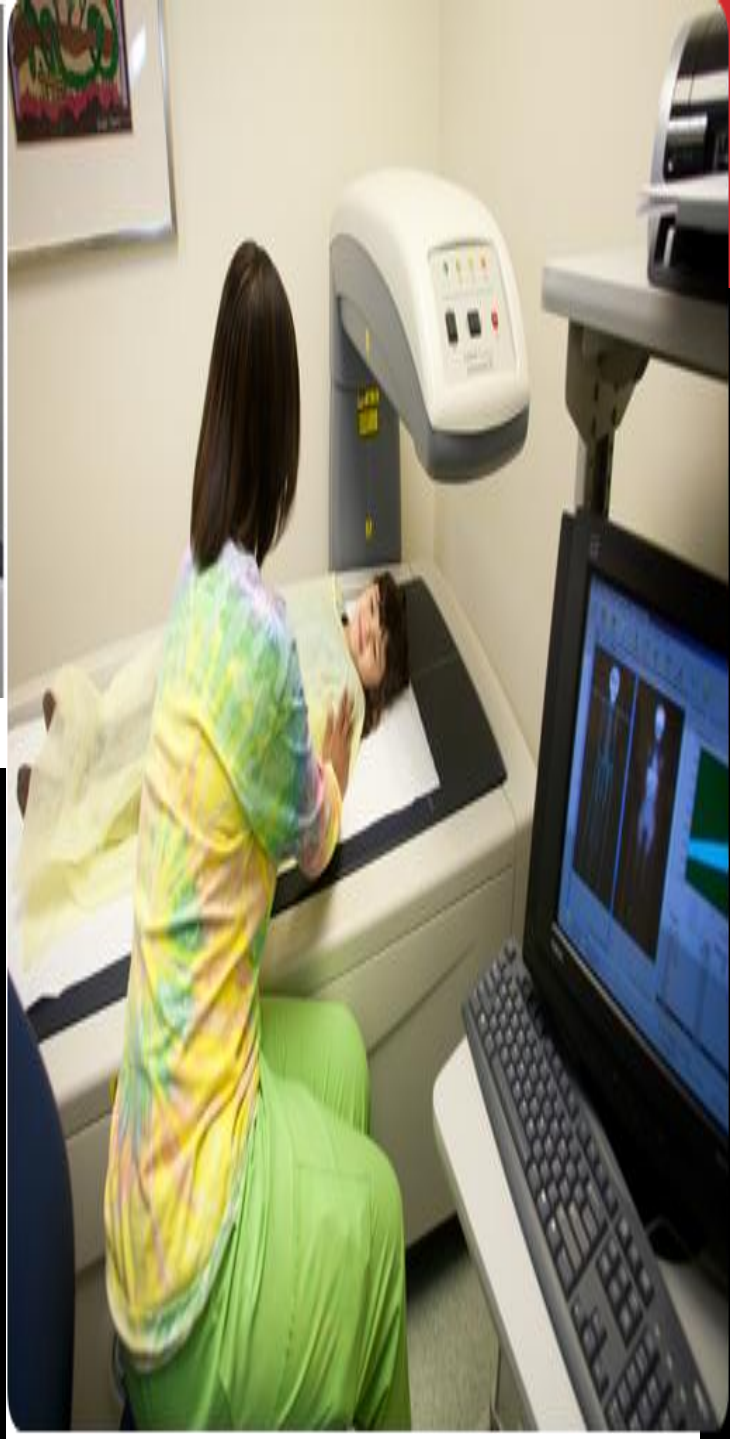
- Acute complications of the first dose were:
  - fever, myalgia, hypocalcemia, flu-like symptoms, and bone pain
- To prevent hypocalcemia, all patients were given a continuous intravenous calcium infusion of 200-400 mg/kg/day
- ibuprofen 10 mg/kg was administered 3-4 times per day to minimize the fever and myalgia that were frequently observed in patients after the first infusion
- All patients were advised to maintain sufficient oral calcium intake consisting of a daily dose of 1200 mg together with a daily dose of prophylactic vitamin D (400-800 IU)

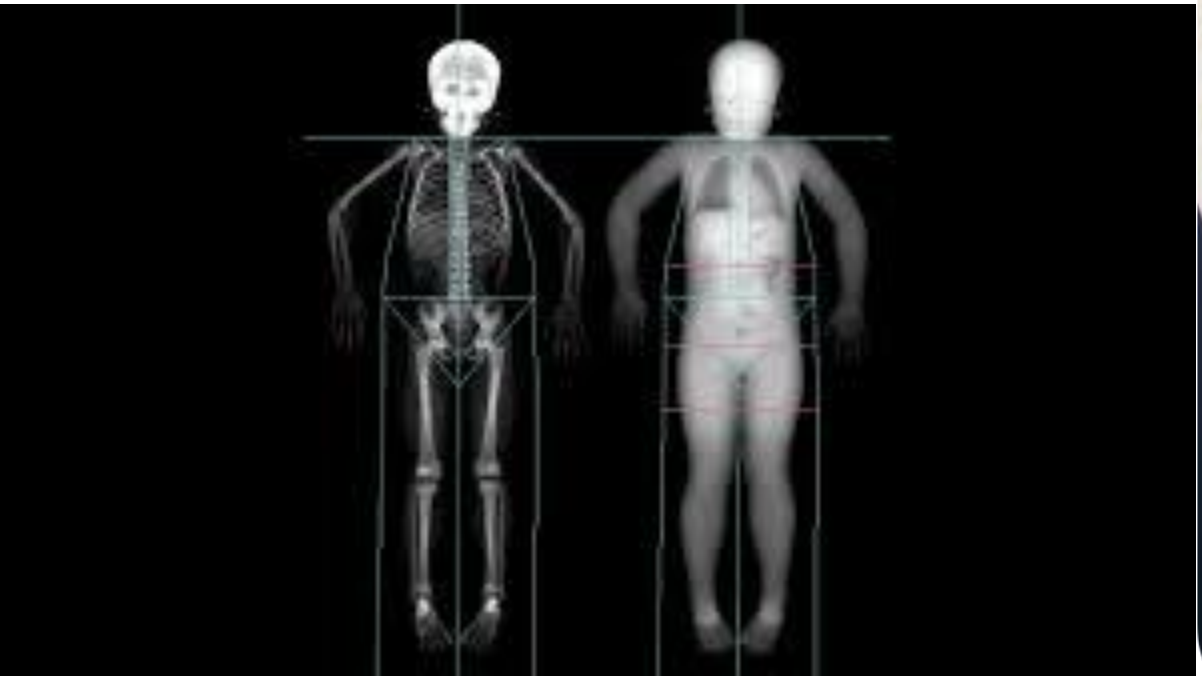
LABORATORY ASSESSMENTS

- Serum calcium, vitamin D, phosphate, PTH, & alkaline phosphatase levels were measured before the start of treatment
- Levels of both bone markers serum osteocalcin and CTX were measured at baseline, before treatment, and then every 3-6 months throughout the treatment period
- Creatinine level was calculated at baseline, and at each treatment visit before the ZA infusion

RADIOLOGICAL ASSESSMENT

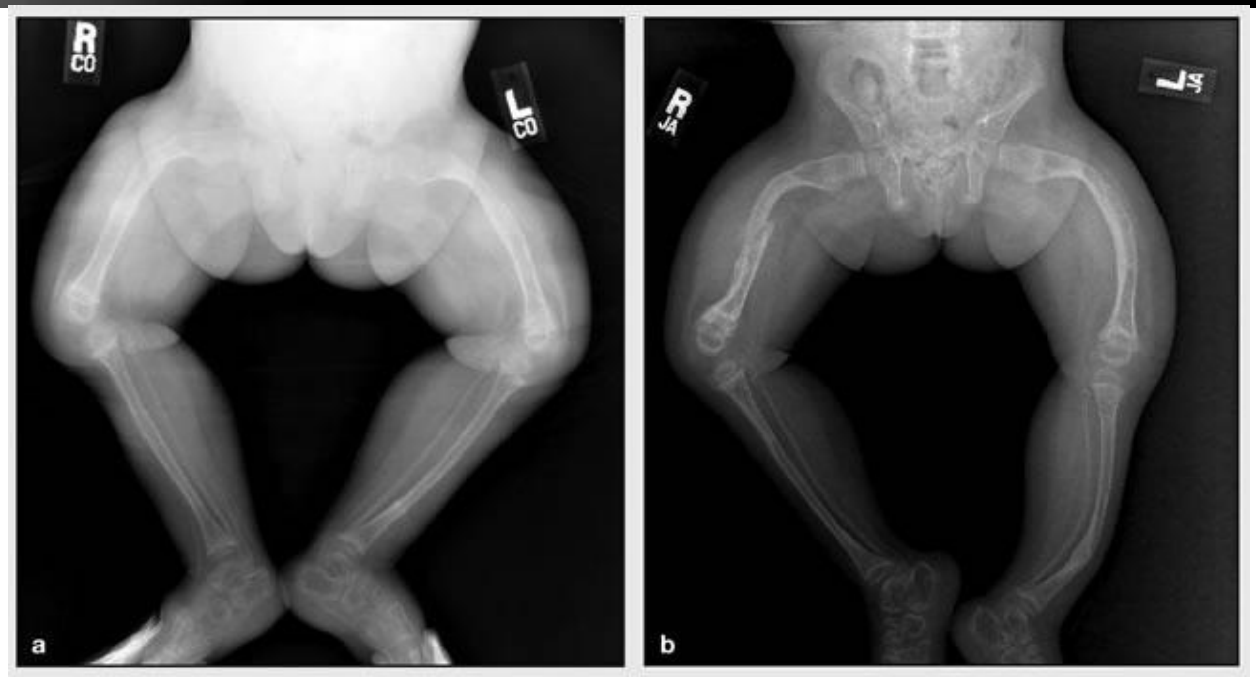
- Data from our institute's system were obtained only for 57/131 (31.6%) patients who had their BMD measured before treatment, and 18/57 (13.7%) underwent the measurements after starting their treatment course for comparison
- In all patients, total body and lumbar spine BMD measurement Z scores were adjusted for age, gender, puberty, and body size as appropriate. Low BMD was defined as a BMD z-score ≤ -2.0 SD
- Z score of -1.0 to -2.0 SD was defined as osteopenia
- Eventually, due to lack of sufficient follow-up DXA measurement data, BMD measurements were excluded from the subsequent statistical analysis





FRACTURE ASSESSMENT

- The fracture rate / year was calculated by dividing the number of fractured bones prior to the start of treatment by the number of years from the first fracture to the first dose
- For those in which treatment started before one year of age, fracture rate was calculated by dividing the number of fractures by the duration in months, and then multiplying it by 12
- Quality of life (QOL) was also considered and defined as normal, or below normal compared with that in children their age and according to post-treatment improvement


R
CO
L
CO
a
R
JA
L
JA
b

ADVERSE EVENTS

- Acute & chronic adverse events were observed and monitored throughout the study
- Acute side effects were reported after the first ZA infusion:
  - fever, hypocalcemia, decreased intake, bone pain, myalgia, and flu-like symptoms
- Nephrocalcinosis was assessed by renal ultrasound at baseline before the start of treatment, and then annually
- The renal profile at baseline and after each infusion cycle was checked for any complications

RESULTS

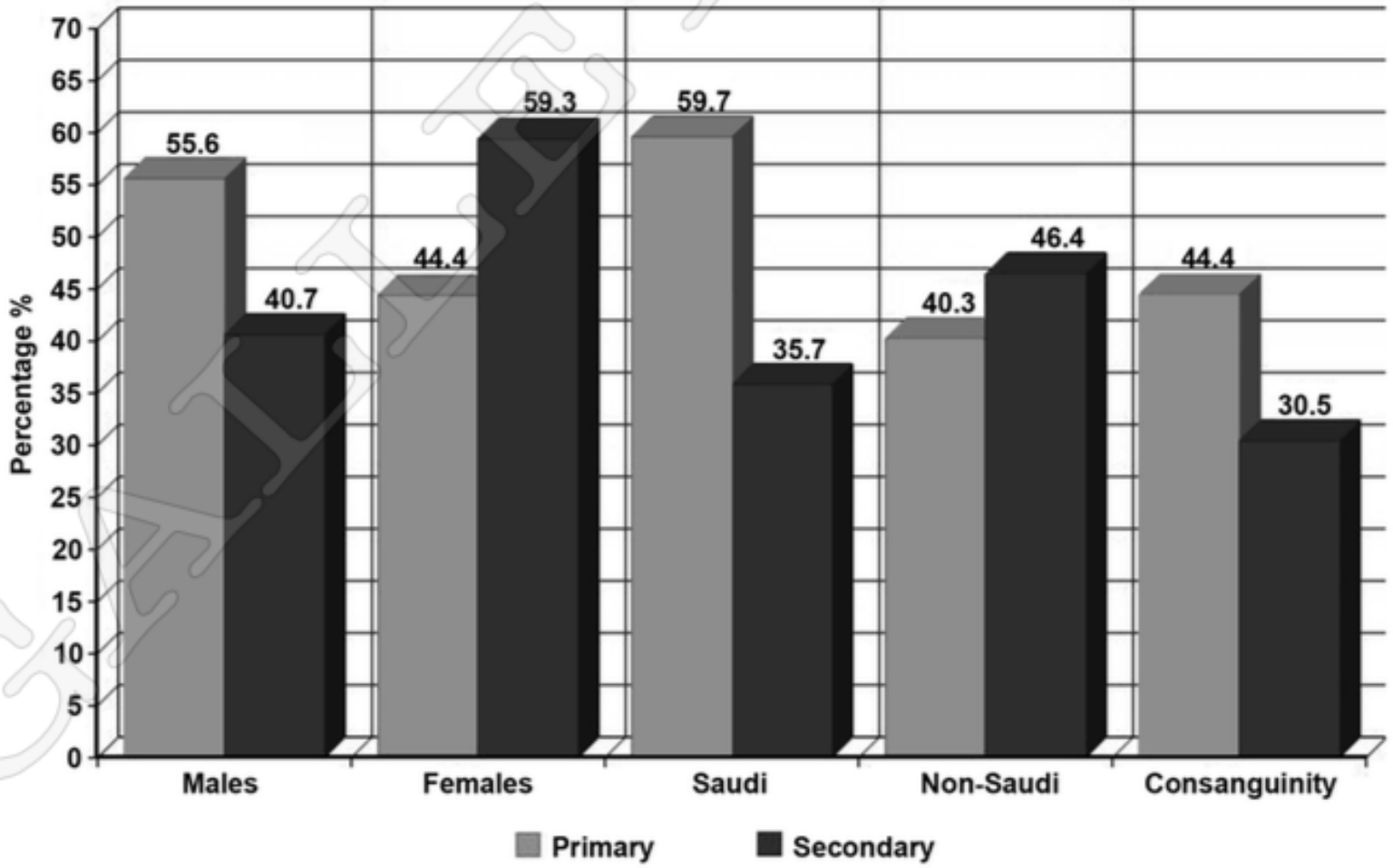


Figure 2 - Patient demographics of primary and secondary osteoparosis at King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia.

RESULTS

Fractures and bone deformity:

- A bone deformity was present in 43/72 (59.7%) patients before the start of treatment
- Fractures were the initial presentation in 53/72 (73.6%) patients, which represents more than 2-thirds of the group's subjects
- The mean number of fractures before treatment was 4.86 ± 8.10, which significantly decreased after treatment to 1.47 ± 5.10 (p=0.000)

Quality of life (QOL)

- 40/72 (55.6%) patients were assessed as having below normal QOL prior to treatment
- After treatment with ZA infusion, 38/40 (95%) patients reported improved QOL and 2/40 (5%) patients reported no change
- A 2-tailed paired-sample t-test revealed a significant subjective improvement in QOL ($t(52) = 6.385$, $p=0.001$) with a confidence interval (CI) of 95%

CLINICAL SAFETY

- **Acute-phase reaction, including fever, hypocalcemia, flu-like symptoms, decreased intake, and bone pain usually occurs in most children with the initiation of intravenous or oral agents.**
- **patients with primary osteoporosis:**
  - Using a paired t-test, we found a statistically significant improvement in pain frequency after ZA treatment ($t(17) = 4.994$, p=0.000, 95% CI).
- **patients with secondary osteoporosis:**
  - Using the same paired t-test, evidence proved a statistically significant improvement in pain frequency post-treatment in the secondary group ($t(18) = 4.53$, p=0.000, 95% CI)

CLINICAL SAFETY

- **Another acute adverse event of ZA infusion was the decrease in calcium level**
- **patients with primary osteoporosis:**
- **Mean pre-treatment calcium level in group one was 2.296 ± 0.18 and post- treatment calcium level was 2.149 ± 0.129**
- **patients with secondary osteoporosis:**
- **mean pre-treatment calcium level was 2.22 ± 0.17 and mean post-treatment calcium level was 2.01 ± 0.25**
- **This decrease in calcium level was observed during the first ZA infusion, while no chronic events were reported throughout our 13-year experience with ZA**

SUMMARY

- To summarizes our 13-year experience using ZA therapy in a pediatric population with osteoporosis at KAUH, Jeddah, KSA
  - This study is considered the first reported long-term observational clinical trial of a Middle-Eastern pediatric population.
- The main goals of pharmacological therapy in osteoporosis, including decreasing the fracture rate, decreasing bone pain, increasing mobility, increasing independence, and decreasing bone turnover marker levels were achieved, the results of this study prove that cyclic intravenous ZA is an efficient treatment for children and adolescents with osteoporosis.
- In our patient cohort, clinical symptoms improved dramatically after the start of ZA treatment. Fractures and bone pain were the 2 dominant presenting symptoms in our population. We had an encouraging result regarding pain relief and a reduction in fractures after ZA treatment

THANK YOU