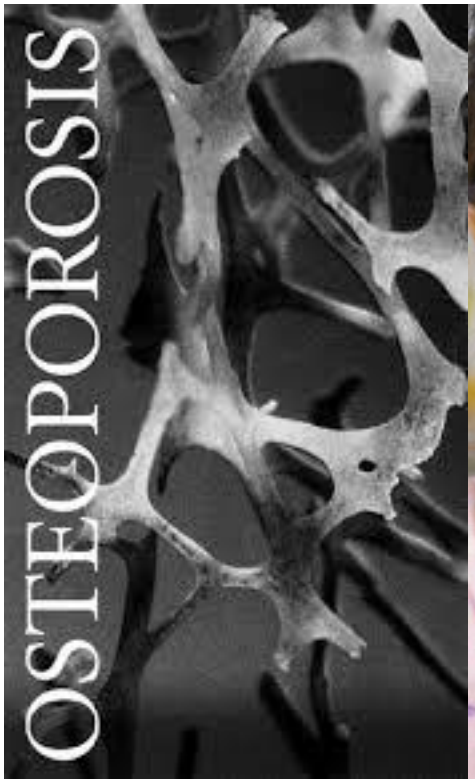
THE EFFICACY & SAFETY OF INTRAVENOUS ZOLEDRONIC ACID TREATMENT OF PEDIATRIC OSTEOPOROSIS



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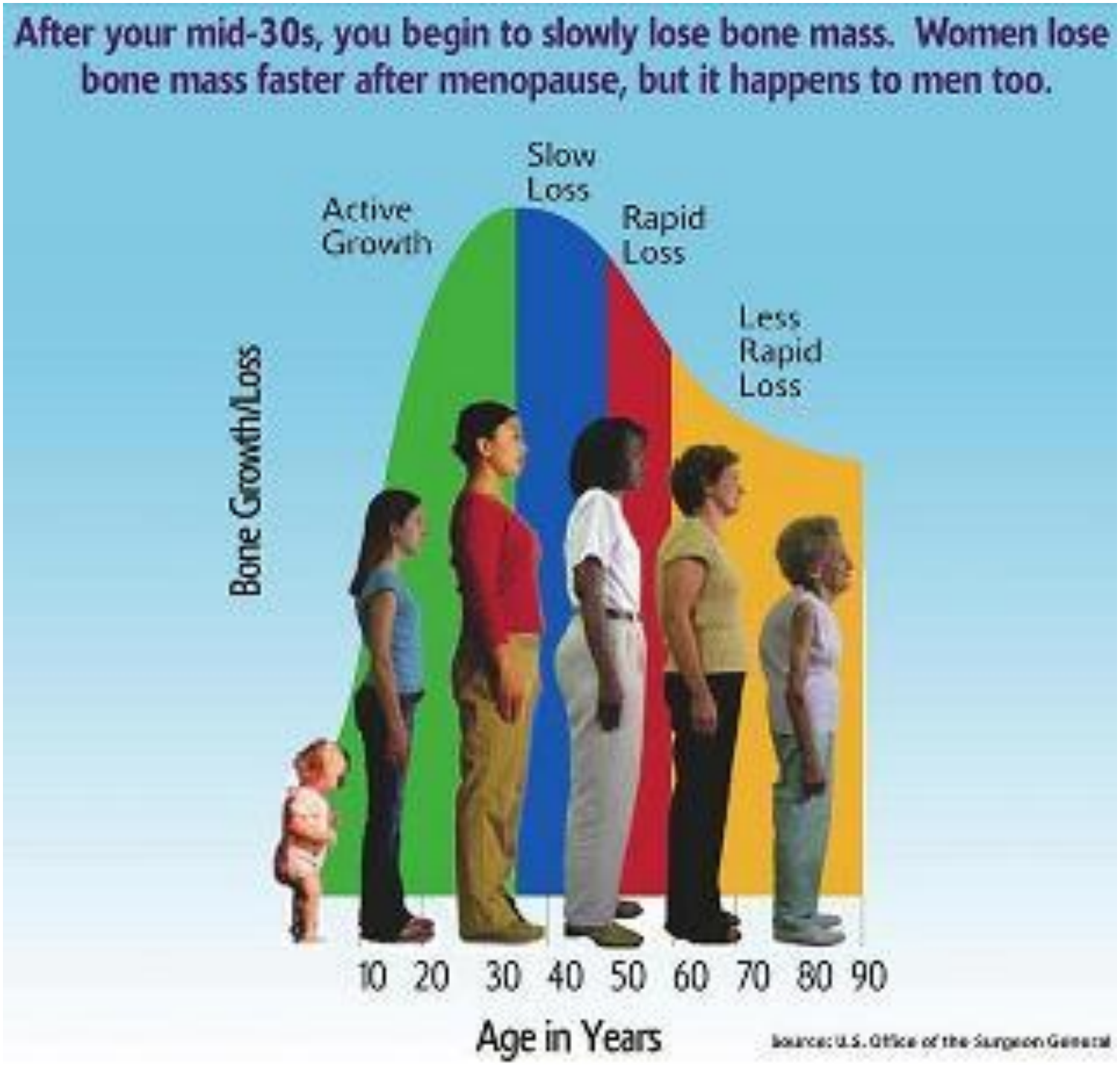

After your mid-30s, you begin to slowly lose bone mass. Women lose bone mass faster after menopause, but it happens to men too.
Active Growth
Slow Loss
Rapid Loss
Less Rapid Loss
Bone Growth/Loss
10 20 30 40 50 60 70 80 90
Age in Years
Source: U.S. Office of the Surgeon General

OUTLINES

- **Introduction**
- **Methods**
- **Statistical analysis.**
- **Assessments:**
  - Clinical
  - Laboratory
  - Radiological
  - Fracture assessment
  - Adverse events
- **Results**
- **Clinical Safety**
- **Discussion**
- **Conclusion**
- **References**

INTRODUCTION

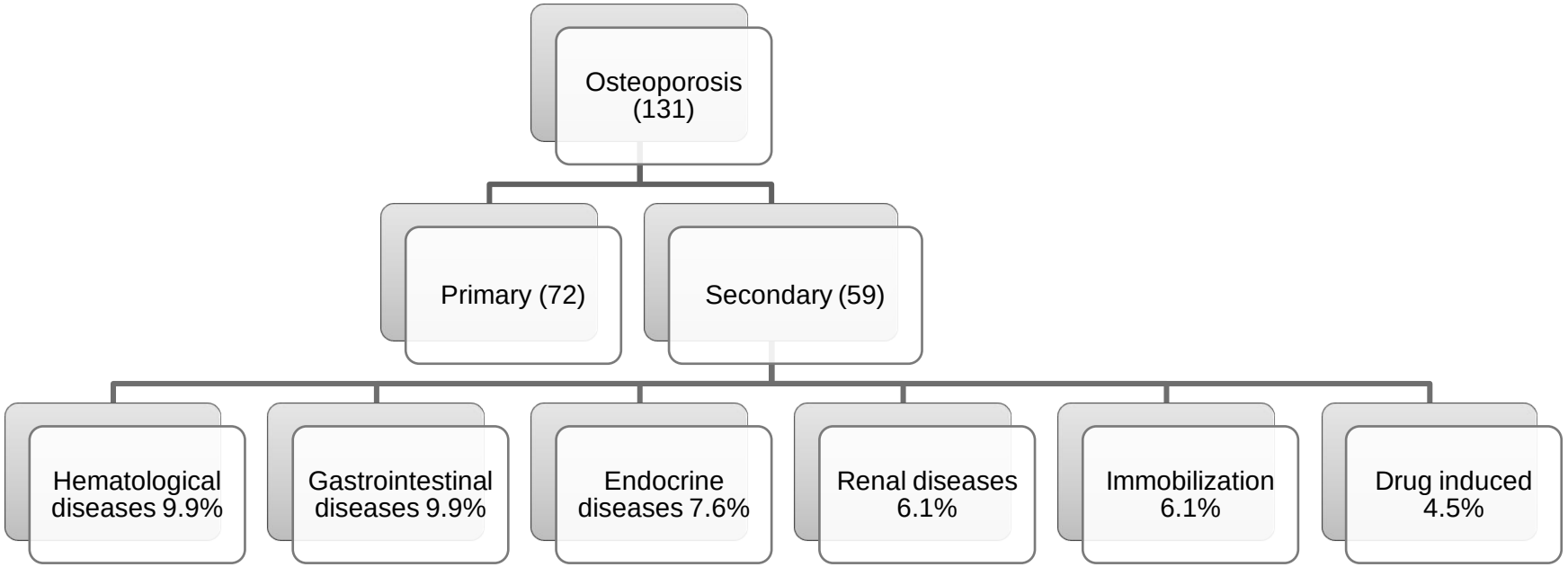
- **Childhood osteoporosis are classified:**
  - primary (usually genetic in origin)
  - Secondary; those that are due to underlying medical conditions, or their treatment
- **Bisphosphonates are pyrophosphate analogs that increase bone mineral density (BMD) by inhibiting bone resorption, which favors bone formation during remodeling**
- **Zoledronic acid (ZA): latest generation, heterocyclic nitrogen-containing bisphosphonate that has demonstrated markedly higher potency, and a greater therapeutic ratio in clinical trials than earlier generation bisphosphonates, including Pamidronate**


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)

STATISTICAL ANALYSIS

- The data analysis was performed using IBM SPSS Statistics version 20.0 software (IBM Corp., Armonk, NY, USA).
- Continuous variables are expressed as mean ± standard deviations, while categorical variables are shown as percentages.
- A 2-tailed paired-sample t-test was used to assess the clinical and biochemical efficacy of the drug with a 95% confidence interval.
- Values of p <0.05 were considered statistically significant for individual variables.
- Two main search engines were used to find prior related research, Google Scholar and PubMed database of Maastricht University

CLINICAL ASSESSMENT

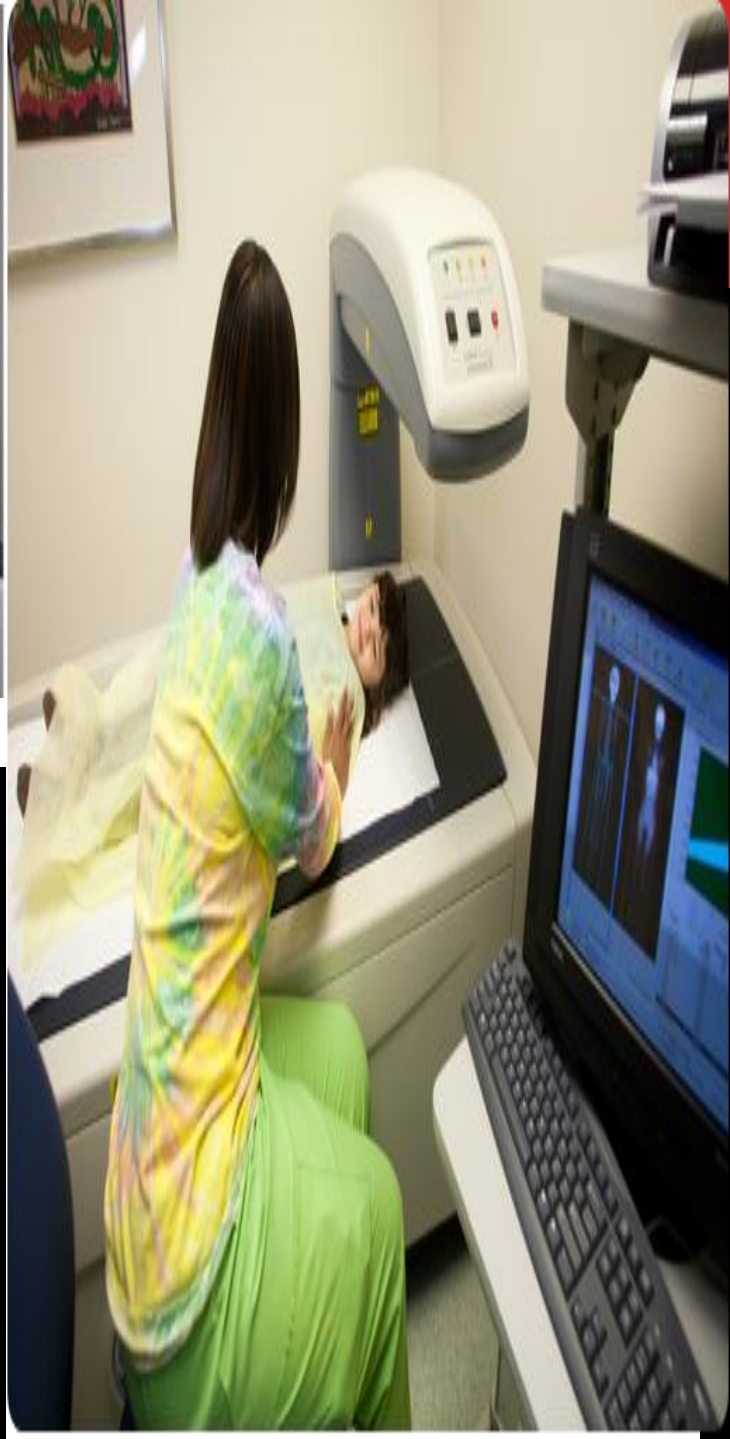
- **A questionnaire form was filled in by patients and/or their with the symptoms they have had experienced before and after starting intravenous ZA treatment**
- **Most common symptom was pain (generalized, lower back, hip, neck, and/or upper or lower extremities), and the estimated frequency of pain (daily, weekly defined as pain more than one day per week, or infrequently defined as less than one day per week).**
- **Body height and weight were measured for all patients in the study.**
  - For children aged 2-18 years, body height and weight were converted to age- and gender- standardized scores with SD according to Children's Hospital Boston Growth Calculator 2.018 since short stature is a feature associated with osteogenesis imperfecta (OI)

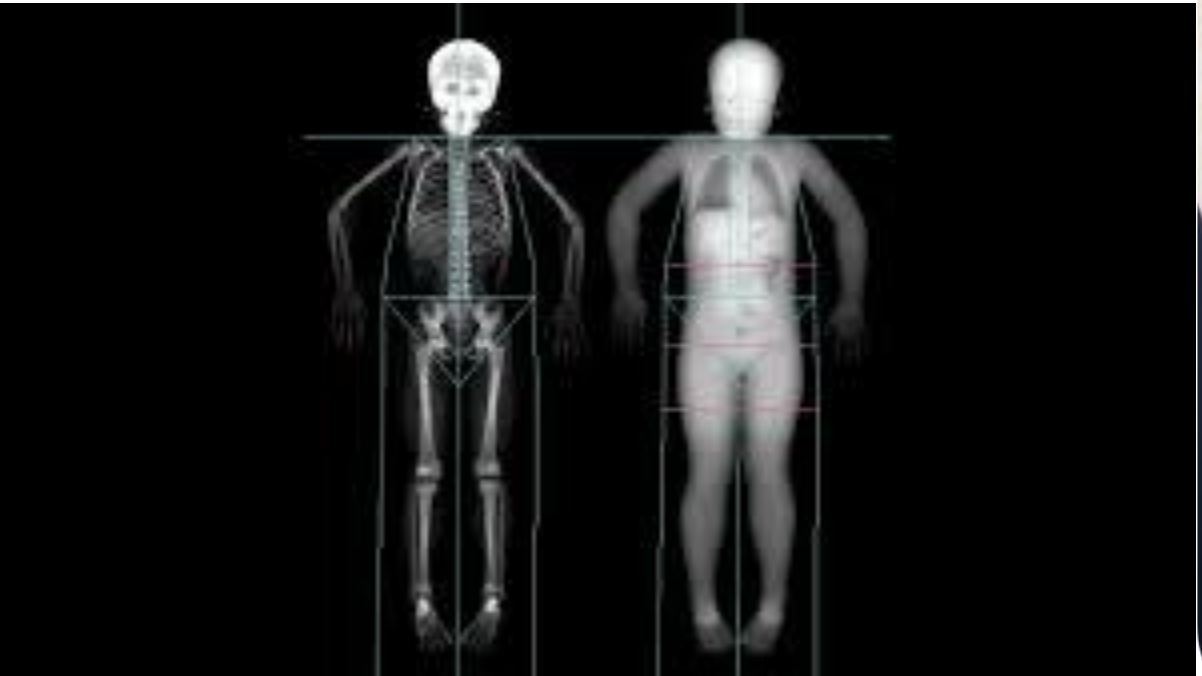
LABORATORY ASSESSMENTS

- 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

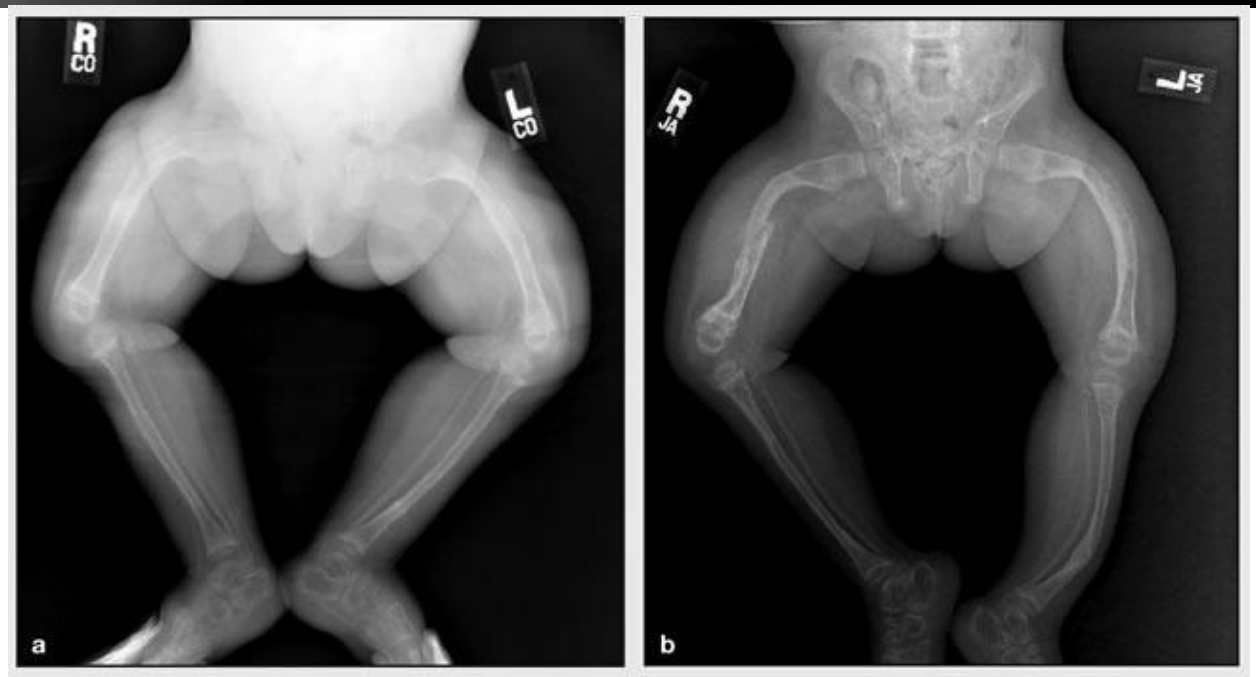
- Data from our institute's system were obtained only for 57/131 (31.6%) patients who had their BMD measured before treatment, and 18/57 (13.7%) underwent the measurements after starting their treatment course for comparison
- In all patients, total body and lumbar spine BMD measurement Z scores were 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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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

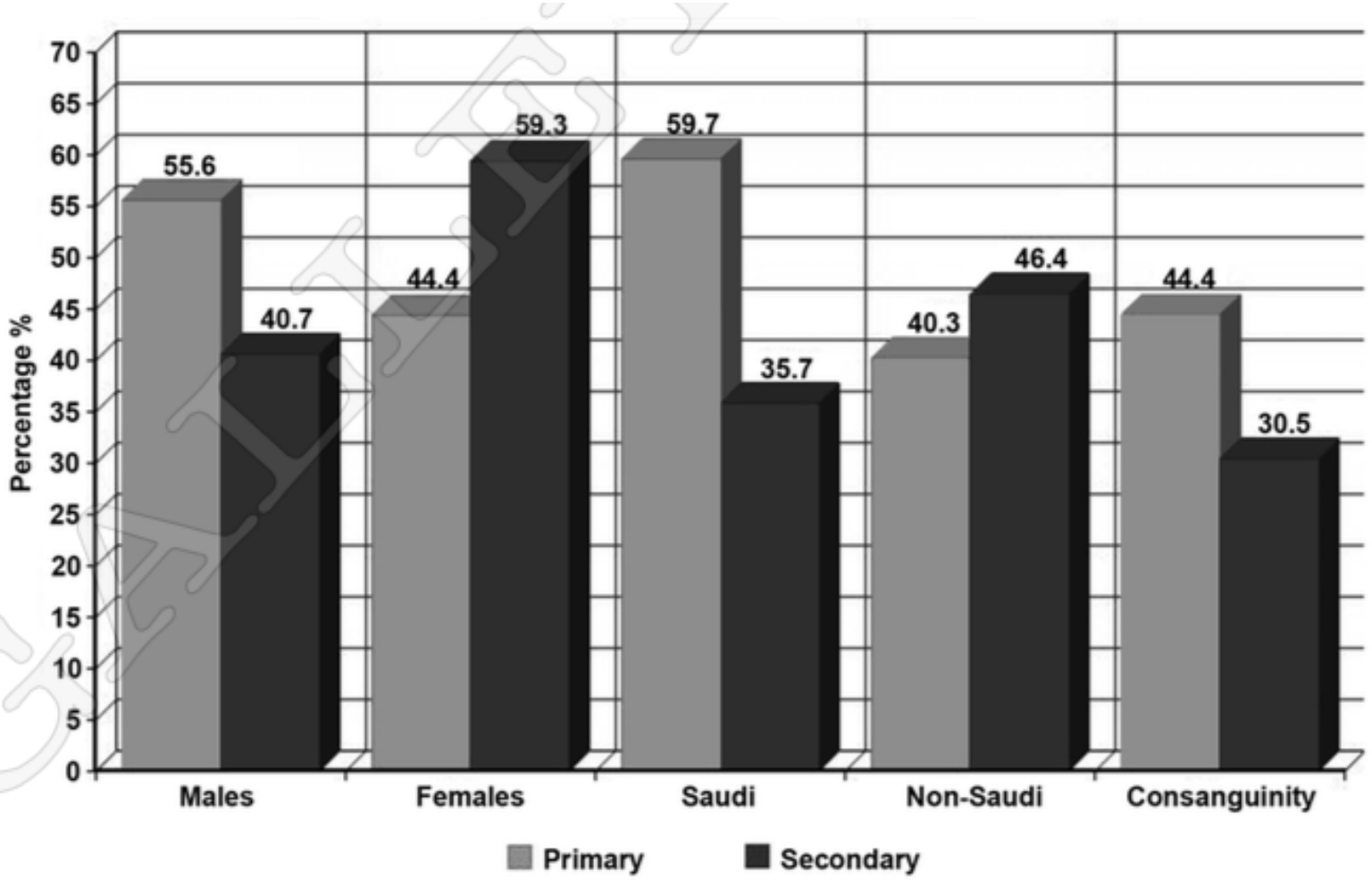

Figure 2 - Patient demographics of primary and secondary osteoparosis at King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia.

RESULTS

Group one (primary osteoporosis)

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%

RESULTS

Biochemical Results

- Mean osteocalcin pre-treatment value was 91.03 ± 53.48, and post- treatment value was 60.78 ± 28.25 ng/mL,
- Mean CTX pre-treatment value was 0.74 ± 0.72, and post- treatment was 0.42 ± 0.31 ng/mL.
- There was a significant decrease in both osteocalcin (p=0.001) and CTX levels after treatment (p=0.003)

RESULTS

Group two (secondary osteoporosis)

- Fractures and bone deformity:
  - Bone deformity was present in 10/59 (16.9%) of the study subjects.
  - Regarding fractures, 10/59 (16.9%) patients presented with fractures with a mean pre-treatment number of 0.34 ± 0.73, which showed statistically significant improvement after treatment to 0.01 ± 0.04 ($t(37) = 2.96$, $p=0.005$).
- Quality of life (QOL)
  - Concerning QOL, 17/59 (28.8%) patients subjectively reported a below normal QOL.
  - After treatment, 11/17 (64.9%) patients reported improved QOL, while 5/17 (29.4%) patients reported no change in their QOL

RESULTS

Biochemical Results

- The mean osteocalcin pre-treatment value was 72.52 ± 46.96, and post- treatment was 39.53 ± 23.33 ng/ml
- The mean pre-treatment CTX level was 1.08 ± 0.72, while post-treatment was 0.44 ± 0.24 ng/ml
- There was a significant post- treatment decrease in both osteocalcin (p=0.003) & CTX levels (p=0.008)

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

CONCLUSION

- pediatric osteoporosis is an alarming growing health problem affecting children and adolescents; as such, a high index of awareness should be raised among pediatricians worldwide.
- Our 13-year experience shows that ZA use should be considered strongly for treatment of children and adolescents with primary or secondary osteoporosis.
- Children & adolescents with symptomatic osteoporosis should be considered candidates for ZA therapy
- All patients starting on ZA infusion must be given a continuous prophylaxis infusion of calcium, antipyretics, and analgesia to reduce the risk of these deficits

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THANK YOU