IN THE NAME OF GOD

OSTEOPOROSIS TREATMENTS IN PEDIATRIC

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GENERAL MEASURES

Diet:

- *1) Calcium*
- *2) Vit D, A, K, C*
- *3) protein*
- *4) trace elements*

Lifestyle:

- ***1) physical activity****(Children with types III, IV, V, VI, and XI OI benefit from gait aids and a program of swimming and conditioning)*
- ***2) reduced alcohol intake and smoking***
- ***3) exposure of skin to sunlight*** *(hands, limbs and face for a minimum time of 6–8 min a day during the summer and half an hour a day during fall and winter)*

DAILY CALCIUM AND VITAMIN D REQUIREMENTS ACCORDING TO AGE

Age	Calcium (mg)	25 OH Vitamin D (IU)
0–6 months	200	400
6–12 months	260	400
1–3 years	700	600
4–8 years	1000	600
9–18 years	1300	600

PHARMACOLOGIC APPROACHES TO THE TREATMENT OF OSTEOPOROSIS

Antiresorptive Agents:

- ***1) Bisphosphonates***
- ***2) Estrogen***
- ***3) Selective Estrogen Receptor Modulators***
- ***4) Calcitonin***
- ***5) Denosumab***
- ***6) Strontium Ranelate***
- ***7) Cathepsin K Inhibitors***

BISPHOSPHONATE

- **Intravenous** administration is considered to provide a greater benefit to **vertebral** fractures.
- **oral** administration: in **mild forms (OI)** and in the **absence of VFs** or **phobia of IV BP therapy.**
- Low-bone formation/turnover conditions, such as immobility-induced osteoporosis (**DMD or cerebral palsy) or OPPG** ***(Osteoporosis-pseudoglioma syndrome),*** would be expected to respond less to BP therapy than high-turnover conditions, such as **ALL, HCS** ***(Hematopoietic cancers)*** **or OI.**
- **Ca, Ph, 25OHD, bone ALP, PTH, osteocalcin,** N-terminal propeptide of procollagen type 1-P1NP can be checked **every 6months.**
- **DXA** is performed **every 12months** to evaluate changes in BMD during treatment.
- Bisphosphonate therapy administered for **one to three years** appears to be safe.
- In **OI** After the initial phase of treatment and once BMD Z-score is **above – 2 SD,** BPs should be continued on a maintenance regimen (e.g., half dose) to enhance and stabilize the increase of BMD. After a **BMD Z-score value above 0** is reached, administration at a lower dosage or reduced frequency should be considered **until the end of growth.**

BISPHOSPHONATE

Contraindications:

- **Pregnancy.**
- **Vitamin D deficiency**
- **Hypocalcaemia**
- **Documented allergic reaction to bisphosphonates.**
- **History of osteonecrosis of the jaw or recent (healing) / imminent dental extraction**
- **Renal impairment** *(relative contraindication, dose adjustment can be considered)*
- **Acute fracture** *(delay zoledronate for 6 weeks or until callus formation)*

Side effect:

- **fever**
- **Malaise**
- **Diarrhea**
- **nausea**
- **myalgia**
- **Transient Hypocalcemia, hypophosphatemia**
- **CRP rising**

Drug	Contraindications	Administration	Dose
Pamidronate (2nd generation)	Hypocalcemia, severe renal failure, hypersensitivity	IV, diluted in 100–250 mL physiological saline solution for 3–4 h	<1 year: 0.5 mg/kg every 2 months 1–2 years: 0.25–0.5 mg/kg/day for 3 days every 3 months 2–3 years: 0.375–0.75 mg/kg/day for 3 days every 3 months >3 years: 0.5–1 mg/kg/day for 3 days every 4 months Maximum dose: 60 mg/dose and 11.5 mg/kg/year
Neridronate (3rd generation)	Hypocalcemia, severe renal failure, hypersensitivity	IV, diluted in 200–250 mL physiological saline solution for 3 h	1–2 mg/kg every 3–4 months
Zolendronate (3rd generation)	Hypocalcemia, severe renal failure, hypersensitivity	IV, diluted in 50 mL physiological saline solution for 30−45 min	0.0125–0.05 mg/kg every 6–12 months (maximum dose: 4 mg)
Alendronate (2nd generation)	Hypocalcemia, delayed esophageal emptying, severe renal failure, hypersensitivity, inability to stand or sit for at least 30 min	Oral	1–2 mg/kg/week <40 kg: 5 mg/day or 35 mg/week >40 kg: 10 mg/day or 70 mg/week Maximum dose: 70 mg/week
Risendronate (3rd generation)	Hypocalcemia, delayed esophageal emptying, severe renal failure, hypersensitivity, inability to stand or sit for at least 30 min	Oral	15 mg/week (<40 kg); 30 mg/week (>40 kg) Maximum dose: 30 mg/week

	Indications	Contraindications	Route of administration	Dosing*	Most common adverse effects**	Notes
Alendronate	Osteoporosis, OI, Gaucher's disease	Hypocalcemia, delayed esophageal emptying, severe renal failure, hypersensitivity, inability to stand or sit for at least 30 min	Oral	Up to 30 kg: 5 mg once daily 30–40 kg: 5–10 mg once daily Above 40 kg: 10 mg once daily Continuously for 24 months	Hypocalcemia and/or hypophosphatemia, esophagitis (possible ulcers), dysphagia, retrosternal pain, abdominal pain, diarrhea, constipation, rash, musculoskeletal pain	Children > 2 years old
Neridronate	OI, Paget's disease	Hypocalcemia, severe renal failure, hypersensitivity	Intravenously	1–2 mg/kg in one day (max 100 mg) every 3 months	Hypocalcemia, acute phase reaction, rash	Possible intramuscular administration (same dose divided in 4 days)
Pamidronate	Hypercalcemia, OI, Steroid-induced osteoporosis, Idiopathic Juvenile Osteoporosis, Paget's disease	Hypocalcemia, severe renal failure, hypersensitivity	Intravenously	Hypercalcemia: 0.5–1.5 mg/kg over 4 h 2–3 consecutive days, every 6–8 weeks. OI and osteoporosis: 0.5–1 mg/kg once a day per 3 days or 2 mg/kg once, every 4 months, max 9 mg/kg/year	Hypocalcemia, acute phase reaction, rash, hypophosphatemia, hypomagnesemia, hypokalemia, anemia, hypertension, cough	Possible reduction of the first dose to reduce the acute phase reaction symptoms and hypocalcemia
Risedronate	Osteoporosis, Paget's disease	Hypocalcemia, delayed esophageal emptying, severe renal failure, hypersensitivity, inability to stand or sit for at least 30 min	Oral	5 mg/daily for 1 year (30 mg/daily for Paget's disease) or 35 mg/weekly	Hypocalcemia, abdominal pain, esophagitis, gastritis, constipation, diarrhea, headache, musculoskeletal pain, rash	Possible use in children with OI (2.5–5 mg/daily)
Zoledronate	OI, steroid-induced osteoporosis, immobility-induced osteoporosis	Hypocalcemia, severe renal failure, hypersensitivity	Intravenously	children aged 1–3 years: 0.025 mg/kg every 3 months, children aged 3–17 years: 0.05 mg/kg (max 4 mg/dose) every 3–6 months	Hypocalcemia, acute phase reaction, rash, hypophosphatemia	Possible reduction of the first dose to reduce the acute phase reaction symptoms and hypocalcemia. Not used < 2 years old

Table 2. Authors' approach for use of zoledronate in children with osteoporosis.

(A) Disuse osteoporosis secondary to CP, Retts and similar central neurological conditions (not primary muscle disorders):
2 years of full dose every 6 months (year 1 and 2 of treatment)
Then: 1 year of half dose (1/2) every 6 months (year 3 of treatment)
Then: one quarter (1/4) of the dose every 6 months (after 3 years of treatment)
If BMAD (height adjusted BMD) is >+2 SDS, change to 1/4 of the dose every 12 months
(B) Primary bone fragility such as OI—primary muscle disorders such as DMD, or CMD—haematological disorders such as Thalassaemia, Sickle Cell Anaemia:
Full dose every 6 months until BMAD is >0 SDS
If BMAD is >0 SDS, give half (1/2) dose of zoledronate every 6 months
If BMAD is >+2 SDS, give one quarter (1/4) dose of zoledronate every 12 months
(C) Conditions where the underlying condition may be controlled or treated such as ALL—IBD—renal transplant:
If commenced, they should have full dose every 6 months, but the duration of treatment will be individualised based on the continuation of steroid treatment, their BMD, pubertal status and their underlying condition.
Before each infusion vitamin D level ⩾50 nmol/l, normal calcium and renal function is ensured. All patients are admitted for the first infusion which is half dose and continue with full dose at the day unit for subsequent ones. Prophylactic paracetamol is used to mitigate pyrexia and aches and pains. Treatment is stopped once skeletal maturity is achieved.
Full dose based on age:
<2 years 0.025 mg/kg max dose: 2 mg 3 monthly
2–5 years 0.035 mg/kg max dose: 2 mg if <3 years, 4 mg if >3 years 4 monthly
>5 years 0.05 mg/kg max dose: 4 mg 6 monthly

ALL, acute lymphoblastic leukaemia; BMAD, bone mineral apparent density; BMD, bone mineral density; CMD, congenital muscular dystrophy; CP, cerebral palsy; DMD, Duchenne muscular dystrophy; IBD, inflammatory bowel disease; OI, osteogenesis imperfecta; SDS, standard deviations.

The Treatment of Bone Fragility in Children with Confirmed Primary or Secondary Osteoporosis

Start intravenous bisphosphonate therapy at published, initiation doses* for children with:

≥ 1 *low trauma* vertebral fracture[&] or ≥ 1 *low trauma* long bone fracture
(multiple fractures are not required for children with a known clinical context associated with osteoporosis)

[#]For children with an ***unconfirmed*** etiology, but nevertheless a clinically significant fracture history, see text at the end of the algorithm

Plus less potential for spontaneous recovery:

- Older age (≥ 8 years in girls or ≥ 9 years of age in boys), irrespective of ongoing risk factors

OR

- Younger age, but persistence of risk factors, including:
  - Primary osteoporosis
  - Secondary osteoporosis (e.g. ongoing glucocorticoid exposure, sub-normal mobility, poorly-controlled illness)

Intravenous bisphosphonate therapy may still be indicated in younger children with bone fragility, in the absence of persistent risk factors, if the fractures significantly impact the young child's quality of life (e.g. back pain due to vertebral fractures)

Monitor on treatment to ensure stabilization of osteoporosis, defined as:

- Absence of new vertebral fractures on annual spine imaging, ***AND***
- Reshaping of previously fractured vertebral bodies, ***AND***
- Absence of back pain, ***AND***
- Absence of new long bone fractures, ***AND***
- Restoration of normal mobility (as appropriate for the underlying disease), ***AND***
- Normalization of BMD Z-score trajectories for age, sex and height

YES

Reduce bisphosphonate therapy to maintenance doses:**

- Primary osteoporosis:
  - o Until epiphyseal fusion
- Secondary osteoporosis:
  - o For as long as risk factors persist

NO

Continue bisphosphonate therapy at initiation doses*

If bone fragility is ongoing (provided BMD Z-scores are not excessive for age, sex and height). Titrate doses down once stabilization of the osteoporosis is achieved.

GONADAL HORMONES

- **Estrogen** treatment inhibits both **cortical and trabecular** bone loss, and BMD generally increases by **3% to 5% after 3 years.**
- Indication: **Turner** and **HH**, **Thalassemia**, …
- Complications: troublesome is the increased risk of **breast cancer** with the long-term use.
- **Testosterone** administration in boys with **delayed puberty** will increase their BMD, but also muscle strength, and subsequently reduce the risk for fractures.
- Testosterone treatment on **DMD** confirmed that there is interestingly motor functions scores in non_ambulatory boys improved and there was statistically significant increase in median BMD of the lumbar spine.
- **Oxandrolone** is not commonly used to induce puberty and prevent osteoporosis.

SELECTIVE ESTROGEN RECEPTOR MODULATORS

- Inhibit bone resorption by the same mechanisms used by estradiol.
- Only Raloxifene is approved by the FDA for the prevention and treatment of osteoporosis (increases spine BMD slightly, and lowers the risk of vertebral fracture by 40%,although it has no effect on nonvertebral fracture risk)
- Low-density lipoprotein cholesterol levels are also reduced.
- bazedoxifene/conjugated estrogen as “TSEC” is more effective than only raloxifene and approved for osteoporosis.

CALCITONIN

- Rapidly inhibit bone resorption.
- Nasal(200 IU/day) and subcutaneous(100 IU/day) calcitonin are both approved for the treatment of postmenopausal osteoporosis.
- Reduced vertebral fracture incidence by one third.
- Reduced the pain associated with new spine fractures.
- Not enough potency only and first choice recommendation.

HUMAN MONOCLONAL ANTIBODY

- Denosumab : antibody (IgG2) against receptor activator of nuclear factor kappa-B ligand (RANKL) (1 mg/kg q 12 w)
- The inhibitory effects of osteoprotegerin and decrease in bone turnover(inhibits osteoclast formation without binding to bone)
- short degradation period(half-life of approximate 30 days), which lasts for around three to four months, avoiding the long-term accumulation side effects of BPs
- first biologic approved by the FDA for the treatment of osteoporosis in both men and women.

DENOSUMAB INDICATION IN PEDIATRIC

- OI types I, III, IV and VI not responsive to BPs has shown promising benefits with relatively high safeness.
- Choice treatment for Hypercalcemia of hematopoietic stem cell transplantation in patients with osteopetrosis.
- Children (3 and 12 years) with loss-of-function mutations in the TNFRSF11A gene encoding RANK.
- Rheumatoid arthritis and bone metastases in adults.
- Giant cell tumors
- juvenile Paget's disease
- DMD
- fibrous dysplasia and spinal aneurysmal bone cysts

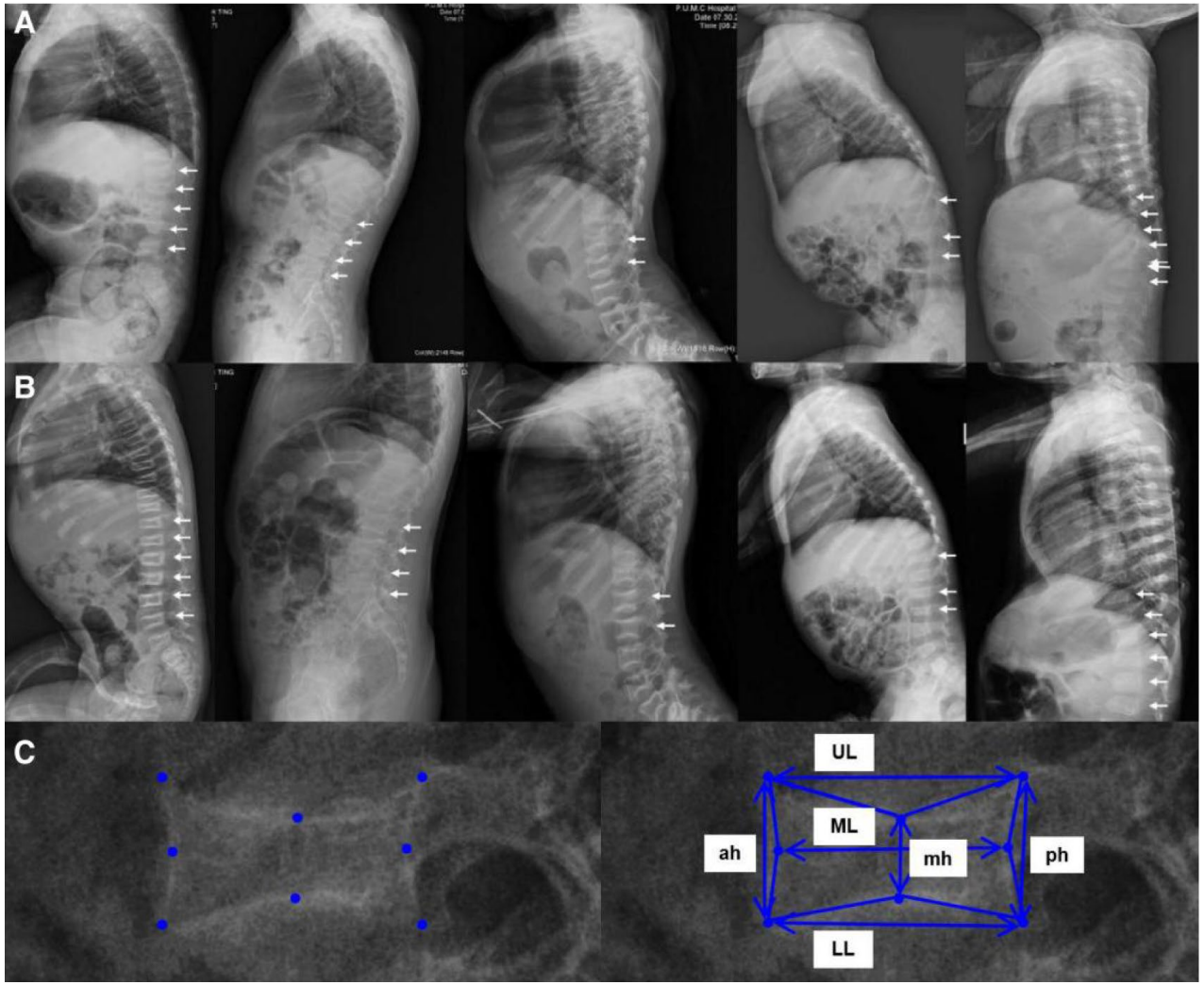
DENOSUMAB EFFICACY

- Increase in BMD
- Normalization of vertebral shape
- Reduced fracture rate
- Bone turnover markers
- Growth (Vertebral height and projection area significantly increased after denosumab and zoledronic acid treatment)
- Mobility : Contradictory results

- Monitor calcium and mineral levels (phosphorus and magnesium) within 14 days of administration in patients with risk factors for hypocalcemia

DENOSUMAB

- Reshape of fractured vertebrae after denosumab treatment. A, Thoracolumbar lateral films at baseline. B, Thoracolumbar lateral films after 12-month denosumab treatment. C, Quantitative measurement of vertebral morphometry on lateral films.



DENOSUMAB COMPLICATIONS:

- Hypocalcemia
- Rebound effect(an increase in vertebral fractures after discontinuation of treatment, and severe hypercalcemia is observed within ۴ weeks of administration 14.3%)
- Dermatitis
- Metaphyseal sclerosis and the retention of calcified cartilage
- Osteonecrosis of the jaw (ONJ) high doses are used to treat a giant cell tumor of the bone (GCTB)

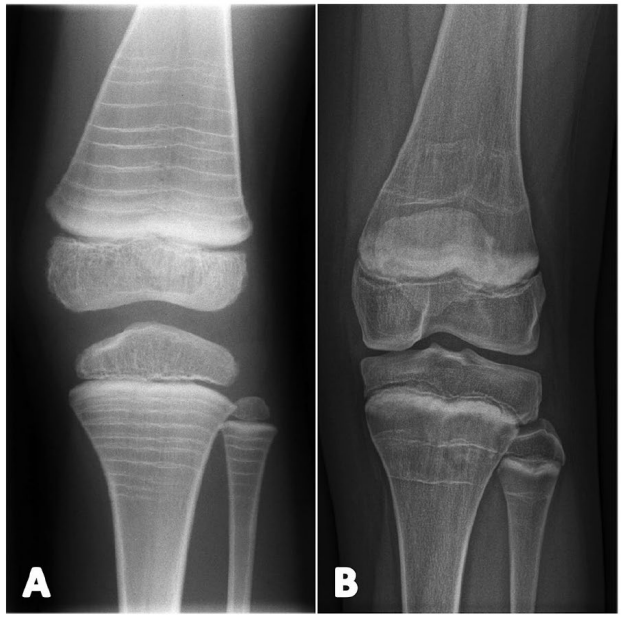
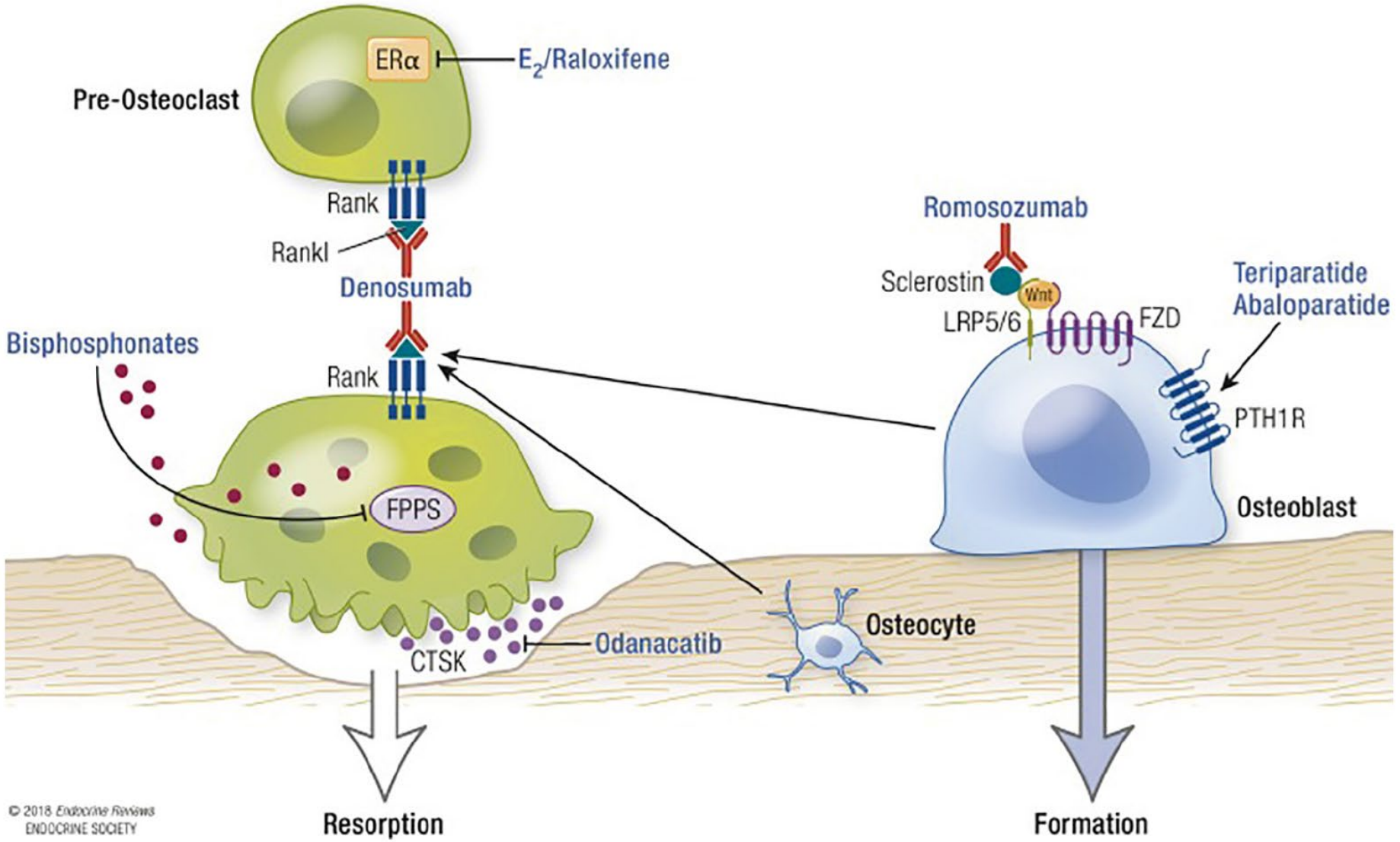


Fig. 1 Effect of BPs and denosumab on bone metaphysis; left knee radiographs. **A** Band-like metaphyseal sclerosis in a boy diagnosed with OI by the age of 3.5 years, 3 years after the start of BPs (pamidronate intravenously at 4-month intervals). **B** Metaphyseal sclerosis in a 13-year-old girl long-term treated with denosumab because of a recurring spinal aneurysmal bone cyst

CATHEPSIN K INHIBITORS

- **Odanacatib:** effective suppressor of bone resorption in postmenopausal women with osteoporosis.
- odanacatib in the setting of bony metastases from breast cancer demonstrated that it suppressed a biochemical marker of bone resorption, N-terminal telopeptide, in much the way that zoledronic acid did.


Pre-Osteoclast
ERα
E_2/Raloxifene
Rank
RankL
Denosumab
Rank
Bisphosphonates
FPPS
CTSK
Odanacatib
Osteocyte
Romosozumab
Sclerostin
Wnt
LRP5/6
FZD
Teriparatide
Abaloparatide
PTH1R
Osteoblast
Resorption
Formation
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ENDOCRINE SOCIETY

STRONTIUM RANELATE

- stimulates **calcium uptake in bone** while it inhibits bone resorption.
- **postmenopausal** women with established disease, daily strontium reduced the risk of **vertebral** fractures by 40% (approved by **European**).
- Complication: severe allergic skin reactions, **venous thromboembolism**, stroke, and heart ischemia.

PHARMACOLOGIC APPROACHES TO THE TREATMENT OF OSTEOPOROSIS

Anabolic Agents:

- ***1) Growth Hormone***
- ***2) PTH-Related Protein***
- ***4) Monoclonal Antibodies to Sclerostin***
- ***5) Future Agents***

GROWTH HORMONE

- Increase bone remodeling presumably by directly synthesis of osteoprotegerin by osteoblasts, regulating phosphate homeostasis (Osteocytes), IGF1 stimulates osteoclasts, increase in osteocalcin and in bone resorption markers, stimulation of cartilage cell proliferation.
- patients with hypopituitarism and GHD have a 2–5 times increased fracture risk.
- mostly with OI types I and IV, may respond to growth hormone treatment by increasing linear growth rate with a mild improvement in bone density.
- Overall, growth hormone treatment appears to be less efficient in the more severe OI type III.

GROWTH HORMONE IN OSTEOPOROSIS OF ADULTS

- Two hundred patients had adult-onset (AO) GHD which Most patients had multiple pituitary hormone deficiencies. Fifteen years of rhGH replacement in GHD adults resulted in a sustained increase in BMD values at the lumbar spine, particularly in men, and stabilization of BMD values at the femoral neck. Clinical fracture incidence was suggested not to be increased during long-term rhGH replacement.
- Adulths with GHD, human immunodeficiency virus associated cachexia and short bowel syndrome, have beifit of GH use to treat age-related bone loss.
- A significant decrease in fracture risk as compared to control in post-menopausal women.

RECOMBINANT HUMAN PTH 1–34

- The N-terminal fragment of PTHrelated peptide analogue (abaloparatide) received approval from the FDA(2017) for subcutaneous application in postmenopausal women with osteoporosis at high risk for fracture.

- Teriparatide therapy in adult OI patients showed a significant increase in BMD in OI type I, although therapy does not seem to be as effective in moderate to severe OI types III and IV.

- Triparatide 20 mcg/day S/C was approved for only 2 years for moderate to severe osteoporosis.(Europe and Asia postmenopausal osteoporosis)

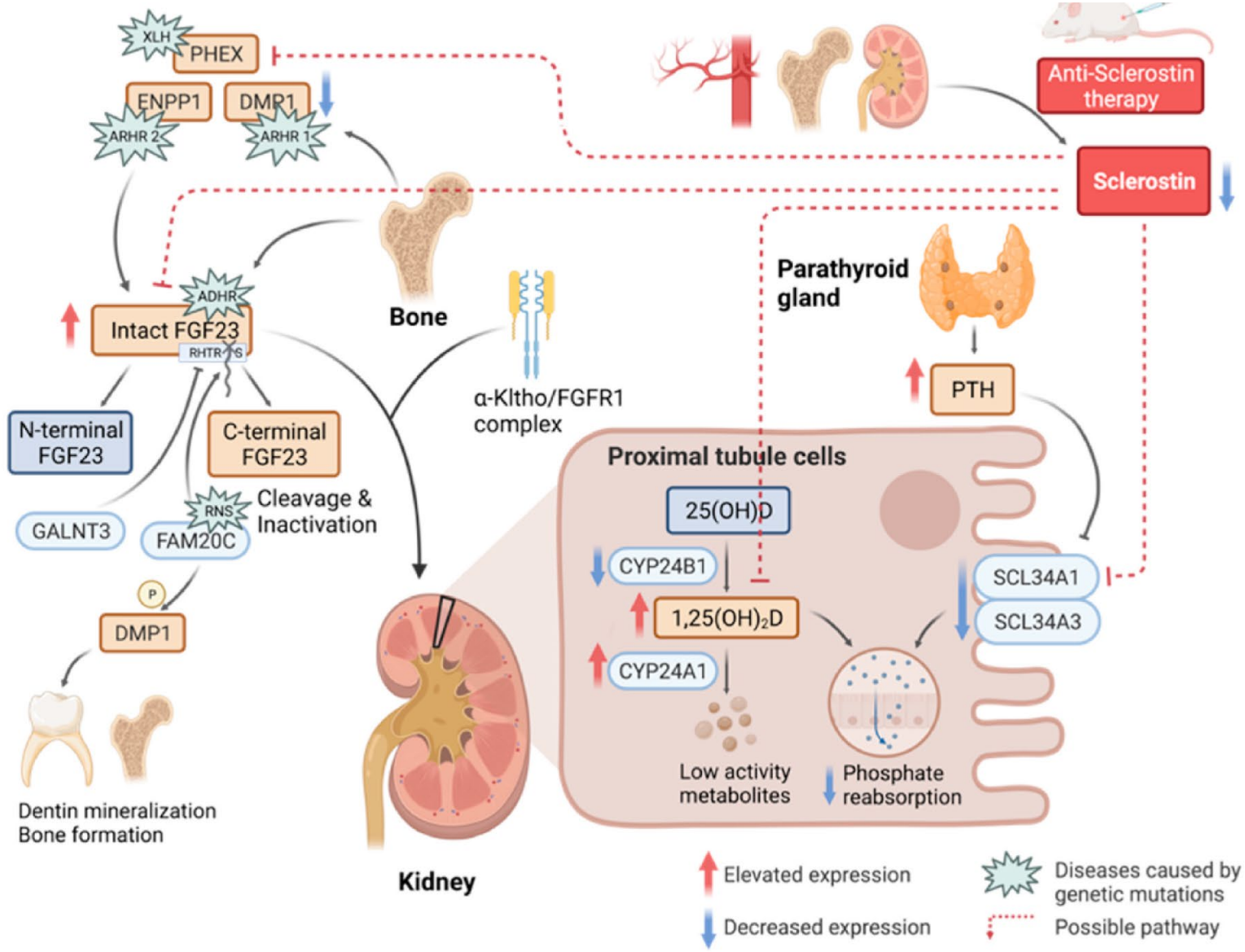
RECOMBINANT HUMAN PTH 1–34

- PTH plus bisphosphonates initiated together do not raise BMD more than PTH alone in either men or women.
- PTH plus denosumab has been shown to increase BMD in the spine to 13% after just 1 year.
- CMPLICATIONS: nausea, flushing, hypotension, and mild but asymptomatic hypercalcemia, Cost and compliance, osteosarcoma.

SCLEROSTIN-INHIBITORY ANTIBODIES(MONOCLONAL ANTIBODIES)

- **Inhibits Wingless-type MMTV integration site family, member 1 (WNT) signaling involved in osteocytes—osteoblasts stimulation.**
- **Serum sclerostin levels were higher in young OI-I patients, while lower in adult OI-I/III/IV.**
- **Romosozumab((210 mg subcutaneously monthly): increased bone density at the lumbar spine, total hip, and femoral neck in posmenopausal.**
- **setrusumab is currently under evaluation in patients with OI.**

- **CMPLICATION: cardiovascular adverse events in the highrisk patients for CVD (vascular calcification, heart valve calcification and atherosclerosis, myocardial infarction)**


XLH
PHEX
ENPP1
DMP1
ARHR 2
ARHR 1
Anti-Sclerostin therapy
Sclerostin
ADHR
Intact FGF23
RHTR-1S
Bone
α-Klotho/FGFR1 complex
Parathyroid gland
PTH
N-terminal FGF23
C-terminal FGF23
GALNT3
RNS
FAM20C
Cleavage & Inactivation
P
DMP1
Dentin mineralization
Bone formation
Proximal tubule cells
25(OH)D
CYP24B1
1,25(OH)2D
CYP24A1
SCL34A1
SCL34A3
Low activity metabolites
Phosphate reabsorption
Kidney
Elevated expression
Decreased expression
Diseases caused by genetic mutations
Possible pathway

ANTI-TGFB ANTIBODY(TRANSFORMING GROWTH FACTOR-BETA)

- **Anti-resorptive and anabolic treatments improve bone mass.**
- **A clinical trial is currently ongoing to evaluate the safety and efficacy of TGF beta inhibition in adult OI patients.**
- **Fresolimumab(GC1008 antibody): previously used to treat cancer patients, currently in the treatment of OI in adult patients and systemic sclerosis patients**
- **Losartan as an angiotensin II-receptor agent with anti-TGF- properties.**

CELL AND GENE THERAPY

- **Stem Cells Transplantation: Increase in growth and mineral content and decrease in fractures rates were reported in OI patients with bone marrow transplanted from HLA-matched siblings.**
- **isolated bone marrow/mesenchymal stem cells (BMSCs) was needed.**
- **Results depend mostly on the type of transplant, whole bone marrow, MSCs, human foetal mesenchymal stem cells (hfMSCs), transplantation technique, and the age of the animals employed in the studies.**
- **Successful application of stem cell therapy in paediatric patients, both prenatally (severe OI) and postnatally, has been also reported in other studies.**

WHOLE BODY VIBRATION THERAPY

- Children with CP and paediatric disabling conditions have demonstrated a beneficial effect of wholebody vibration (WBV)
- Improving walking speed, muscle strength, spasticity, and balance is helpful in managing osteoporosis.
- In children with OI, WBV resulted increase in lean mass without changes in muscle function or bone mass, suggesting reduced biomechanical responsiveness of the muscle-bone unit.
- WBV is most beneficial in children affected by muscular impairment rather than in children affected by primary bone defects.

SURGICAL INTERVENTIONS

- Correct deformities of the limbs (corrective osteotomy and intramedullary rodding), to improve limb function, or to treat progressive scoliosis and kyphosis of the spine to prevent pulmonary insufficiency, pain, and disability.
- Indications to perform surgery (rodding of severely deformed long bones with or without frequent fractures) usually start from the age when the child can stand more or less independently to assist locomotion and reduce the risk of fractures.
- Surgical treatment for OI is based on the Sofield-Millar technique, described in 1959, which consists of multiple osteotomies of the bowed long bones followed by intramedullary rodding using, at that time, Kuntscher or Rush rods.
- Utilizing Faisser-Duval rods in a surgical setting to correct lower extremity deformities and fractures.

THANK YOU