
به نام خدا

How to manage Osteoporosis before the age of ۵۰

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۹۹/۱۰/۱۵

Agenda

- What is the definition of osteoporosis before the age of ٥٠?
- Do WHO criteria apply to osteoporosis before age ٥٠?
- Do the WHO criteria used to define postmenopausal women work in this group as well?
- Is there a link between Low BMD and fracture risk in this group?
- How significant is the serial BMD in evaluating this group?
- What are the types of osteoporosis under the age of ٥٠?
- What are the diagnostic and therapeutic measures in this age group?

Definition

Osteoporosis is a skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture.

J.Endocrinol.Invest.٤٢oct(١٠)(٢٠١٩)١١٤٩-١١٦٤

According to the WHO, in postmenopausal women, osteoporosis is diagnosed when hip or spine bone mineral density (BMD) is two and a half standard deviations or more below that of the young adult mean (T-score ≤–٢.٥).

There is no consensus, however, on the diagnostic criteria for osteoporosis in premenopausal women.

Evaluation and treatment of premenopausal osteoporosis. Des (٥)(٢٠١٩)

Osteoporosis in premenopausal women

In premenopausal women, the WHO criteria for diagnosis of osteoporosis and osteopenia do not apply to, and generally should not be used to categorize, BMD measurements.

The International Society for Clinical Densitometry (ISCD) recommends using Z score measurment in premenopousal women.

Z-Score ≤ -٢

J.Clin.endocrinol.Metab.٩٧(١١)(٢٠١٢)٤١٧٤-٤١٨٤

Low bone mass

Bone loss

\+ fragility fracture or fracture history

A fracture (excluding fracture of the face, skull, or digits) that occurs with trauma equivalent to a fall from a standing height or less may be a sign of decreased bone strength, regardless of BMD.

Osteoporos. Int. ۲۷ (۴) (۲۰۱۶) ۱۲۸۱-۱۳۸۶

Low Bone Mass

- PBM, is defined as the maximum amount of bone that is accrued during skeletal maturation and the subsequent consolidation in early adulthood.
- PBM is generally considered to be achieved during the second or third decade of life, but the exact timing is site and gender-dependent , genetic factors, pregnancy duration, birth weight, pubertal timing, nutrition, height and lean mass.
- These findings suggest that certain life-long traits, such as fall frequency, neuromuscular protective response to falls, or various aspects of bone quality can affect life-long fracture risk.

Osteoporos. Int. ۲۷ (۴) (۲۰۱۶) ۱۲۸۱-۱۳۸۶

Bone Loss

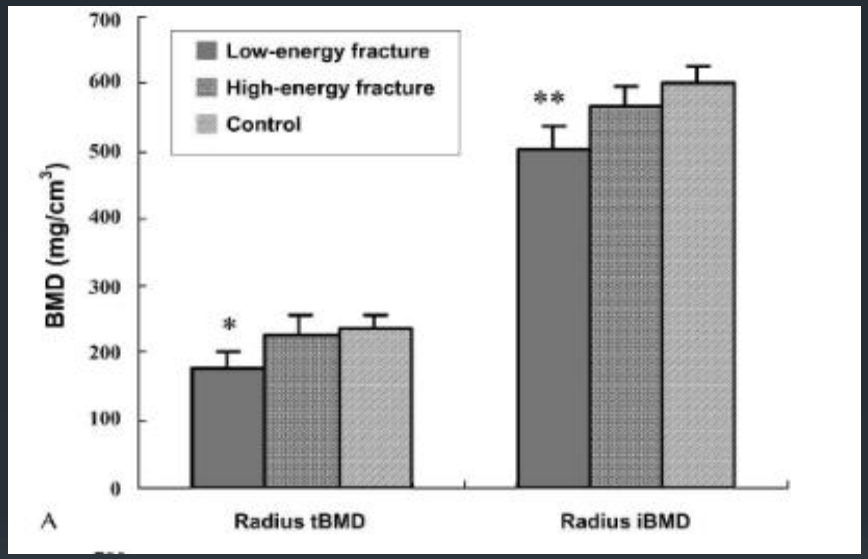
- Age
- Weight changes
- BMI
- Calcium and Vitamin D intake
- Physical activity
- Alcohol consumption , smoking
- Family history of osteoporosis
- Number of peregnancies

Osteoporos. Int. ۲۷ (۴) (۲۰۱۶) ۱۲۸۱-۱۳۸۶

- As a matter of fact, the relationship between low BMD, low bone mass and fracture risk is not so well established in premenopausal.

- BMD measurement should not be used as the sole guide for diagnosis and treatment of osteoporosis.

Low BMD is a risk factor for low-energy Colles' fractures in women before and after menopause



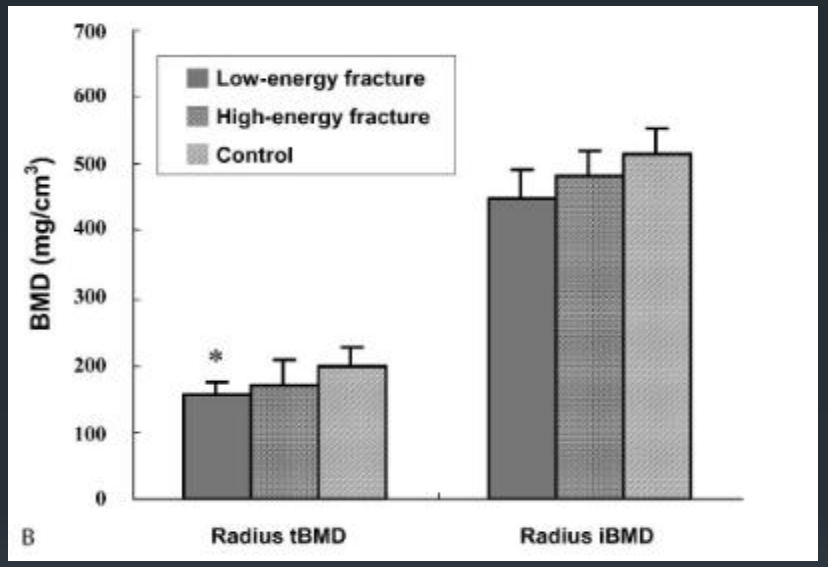
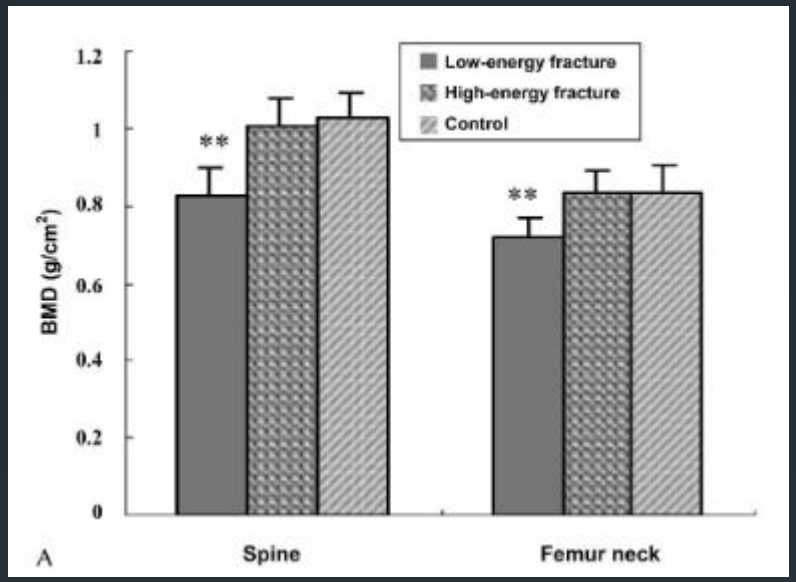


Fig 3A–B. (A) Lower pQCT vBMD (mg/cm^3) of distal radial tBMD and iBMD was seen in the group of patients with low-energy fractures in the premenopausal group, but only lower tBMD was seen in patients in the (B) postmenopausal group, when comparison was made with control subjects. tBMD = trabecular BMD; iBMD = integral BMD; *$p < 0.05$, **$p < 0.01$

Clin orthop Relate Res. ۲۰۰۵ Jun ;(۴۳۵) :۲۱۹-۲۵



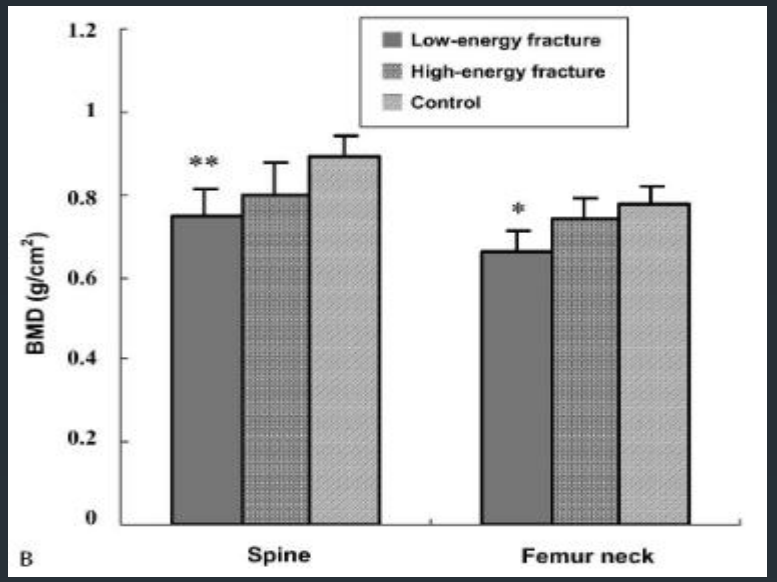


Fig 4A–B. Patients with low-energy fractures had a lower DXA areal BMD (g/cm^2) at the lumbar spine and the femoral neck than patients with high-energy fractures and control subjects in (A) the premenopausal and (B) postmenopausal groups. *$p < 0.05$, **$p < 0.01$

SECONDARY CAUSES OF OSTEOPOROSIS IN PREMENOPAUSAL WOMEN

Most premenopausal women with low-trauma fractures or low BMD have an underlying disorder or medication exposure that has interfered with bone mass accrual during adolescence and/or has caused excessive bone loss is common.

Semin Arthritis Rheum. ۲۰۰۲ ;۳۲:۶۴–۷۰

Table 55.1. Secondary causes of osteoporosis in premenopausal women.

Premenopausal amenorrhea (eg, hypothalamic amenorrhea, pituitary diseases, medications)
Anorexia nervosa
Cushing syndrome
Hyperthyroidism
Primary hyperparathyroidism
Hypercalciuria
Vitamin D, calcium, and/or other nutrient deficiency
Gastrointestinal malabsorption (celiac disease, inflammatory bowel disease, cystic fibrosis, postoperative states)
Rheumatoid arthritis, systemic lupus erythematosus, other inflammatory conditions
Renal disease
Liver disease
Diabetes mellitus
Alcoholism

Connective tissue diseases:
- Osteogeneis imperfecta
- Marfan syndrome and Ehlers–Danlos syndrome
- Hypoposphatasia

Other rare conditions (eg, hemochromatosis, Gaucher disease, mastocytosis, thalassemia)

Medications:
- Glucocorticoids
- Immunosuppressants (eg, cyclosporine)
- Antiepileptic drugs (particularly cytochrome P450 inducers such as phenytoin, carbamazepine)
- Cancer chemotherapy
- GnRH agonists (when used to suppress ovulation)
- Heparin

Idiopathic osteoporosis

Diagnostic Methods

Bone densitometry is not routinely recommended for premenopausal women, FRAX are not valid for young and should not be used.

ISCD guidlines that suggests BMD screening for premenopausal women:

J.Clin.Endocrinol.Metab.٩٧(١١)(٢٠١٢)٤١٧٤–٤١٨٤.

Guidelines for bone mineral density testing in premenopausal women

Guidelines for bone mineral density testing in premenopausal women

International Society for Clinical Densitometry
History of fragility fracture
Diseases, conditions, or medications associated with low bone mass or bone loss
Considering pharmacologic therapy for osteoporosis
Monitoring drug therapy for osteoporosis
Women in the menopausal transition if there is a specific risk factor for fracture (eg, low body weight, prior low-trauma fracture, or high-risk medication)

Serial BMD Measurements

- **Serial BMD testing in combination with clinical assessment of fracture risk, bone turnover markers, and other factors including height loss and trabecular bone score, can be used to determine whether treatment should be initiated in untreated patients, according to locally applicable guidelines.**
- Serial BMD testing can monitor response to therapy by finding an increase or stability of bone density.
- **Serial BMD testing should be used to monitor individuals following cessation of osteoporosis pharmacologic therapy.**
- **Serial BMD testing can detect loss of bone density, indicating the need for assessment of treatment adherence, evaluation of secondary causes of osteoporosis, and re-evaluation of treatment options.**

- **Follow-up BMD testing should be done when the results are likely to influence patient management.**
- Intervals between BMD testing should be determined according to each patient's clinical status: typically one year after initiation or change of therapy is appropriate, with longer intervals once therapeutic effect is established.
- In conditions associated with rapid bone loss such as glucocorticoid therapy, testing more frequently is appropriate.

Table 55.2. Laboratory evaluation.

Initial laboratory evaluation

- Complete blood count
- Electrolytes, renal function
- Serum calcium, phosphate
- Serum albumin, transaminases, total alkaline phosphatase
- Serum TSH
- Serum 25-hydroxyvitamin D
- 24-hour urine for calcium and creatinine

Additional laboratory evaluation

- Estradiol, LH, FSH, prolactin
- PTH
- 1,25-dihydroxyvitamin D
- 24-hour urine for free cortisol
- Iron/total iron binding capacity, ferritin
- Celiac screen
- Serum/urine protein electrophoresis
- Erythrocyte sedimentation rate or C-reactive protein
- Tryptase
- Bone turnover markers
- Transiliac crest bone biopsy
- Genetic testing

Management of premenopausal osteoporosis

Management of premenopausal osteoporosis

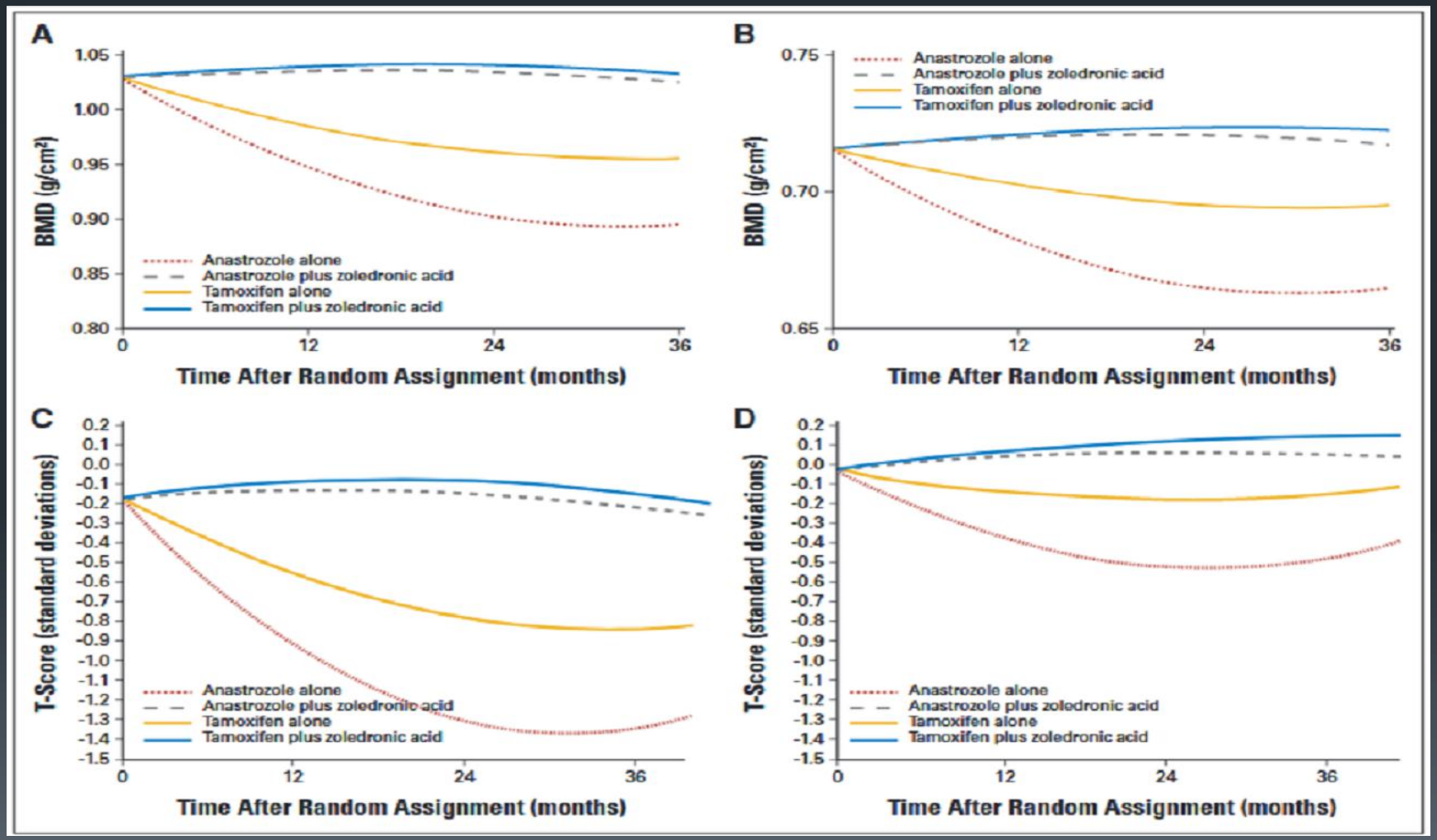
Calcium 1000 mg daily
Vitamin D 600 international units daily
Weightbearing exercise
Changes in habits (avoidance of smoking, excess alcohol, poor nutrition)
Treatment of secondary causes
Pharmacologic treatment in selected cases

Bisphosphonates

- Bisphosphonates have been shown to :
- improve BMD
- prevent bone loss

J Rheumatol. ۲۰۰۸;۳۵:۲۳۴۴–۷

Zoledronic Acid Effectively Prevents Cancer Treatment–Induced Bone Loss in Premenopausal Women Receiving Adjuvant Endocrine Therapy for Hormone-Responsive Breast Cancer: A Report From the Austrian Breast and Colorectal Cancer Study Group



Joreal of Clinical oncology,December ۱۲, ۲۰۰۶ from ۸۵,۱۲۵,۷,۲۴۲.

Human PTH(۱–۳۴)

- For premenopausal women,as long as epiphyses are fully fused highest risk for fracture
- IOP
- It is not recommended for more than two years based upon the potential risk of osteogenic sarcoma.

J Clin Endocrinol Metab. ۲۰۱۴;۹۹:۱۳۲۲–۹.

Teriparatide Increases Bone Formation and Bone Mineral Density in Adult Women With Anorexia Nervosa

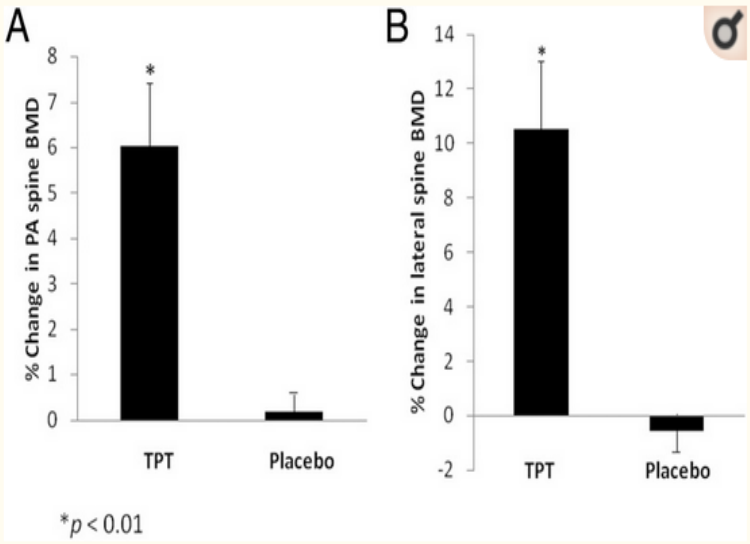
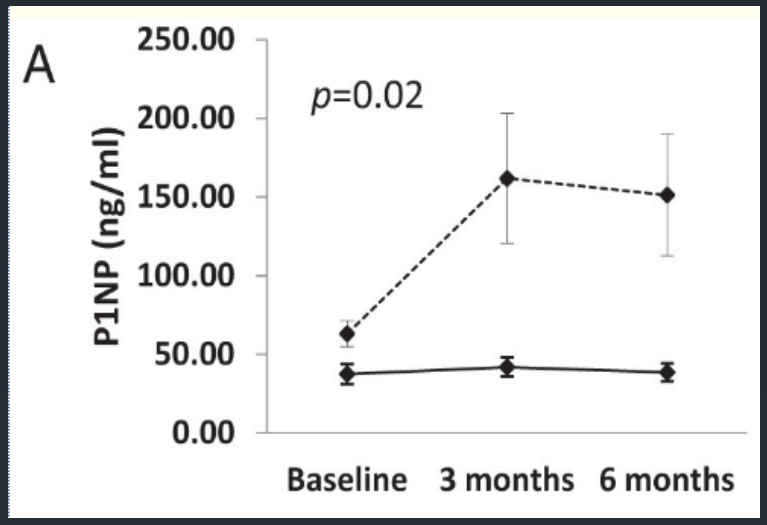
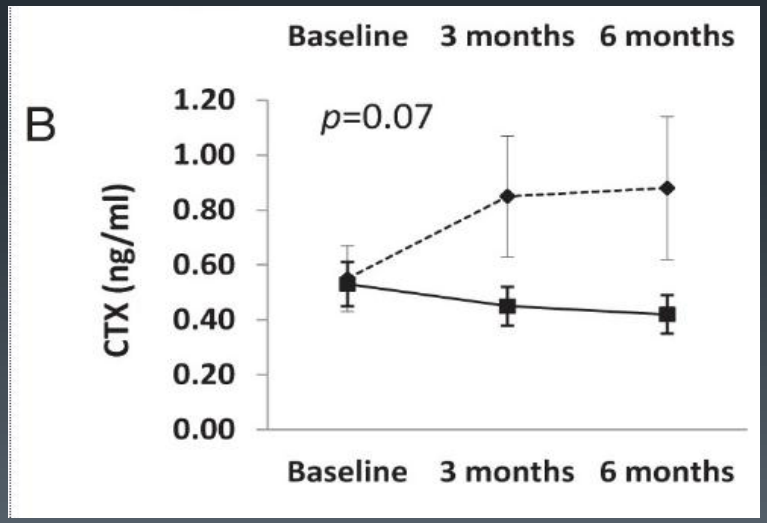


Figure 1.

There was a significantly greater increase in BMD after 6 months of TPT as compared with placebo in the PA spine ($P < .01$) (A) and lateral spine ($P < .01$) (B).





J Clin Endocrinol Metab. ۲۰۱۴ Apr; ۹۹(۴): ۱۳۲۲–۱۳۲۹.

Teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: an analysis by gender and menopausal status

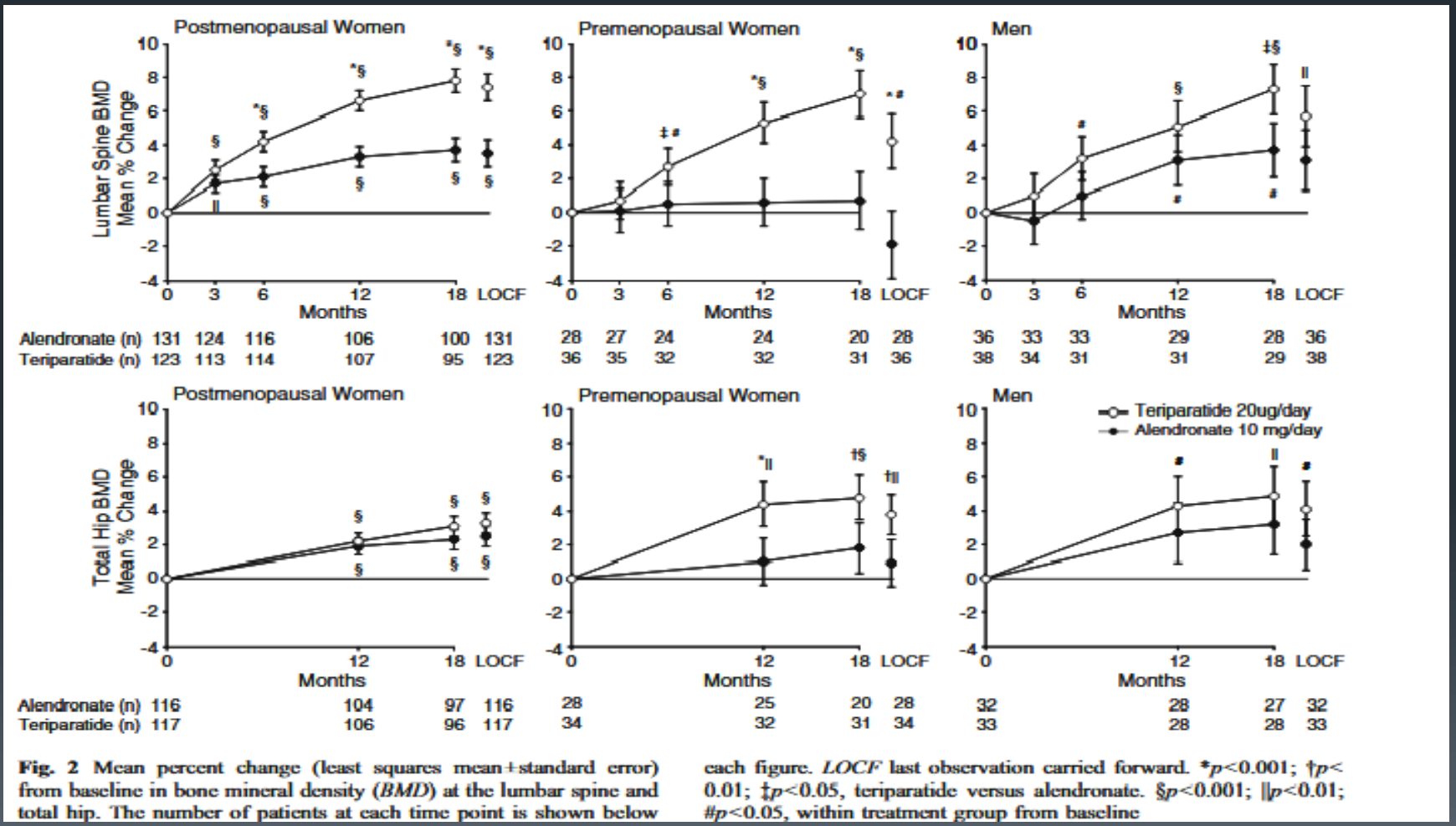


Fig. 2 Mean percent change (least squares mean+standard error) from baseline in bone mineral density (*BMD*) at the lumbar spine and total hip. The number of patients at each time point is shown below each figure. *LOCF* last observation carried forward. *$p<0.001$; †$p<0.01$; ‡$p<0.05$, teriparatide versus alendronate. §$p<0.001$; ‖$p<0.01$; #$p<0.05$, within treatment group from baseline

Osteoporosis Int ۲۰۰۹ Dec;۲۰(۱۲):۲۰۹۵-۱۰۴

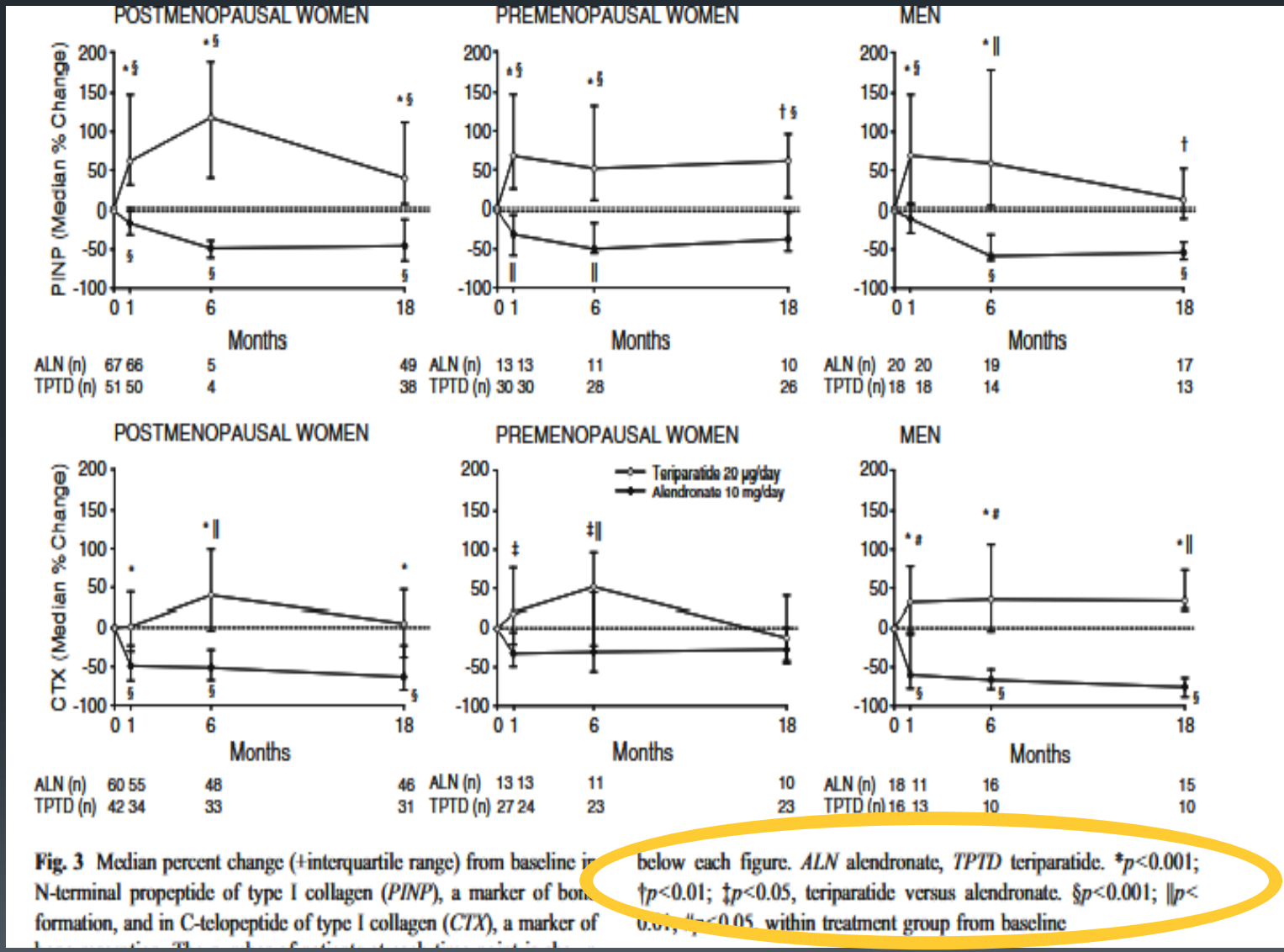


Fig. 3 Median percent change (+interquartile range) from baseline in N-terminal propeptide of type I collagen (*PINP*), a marker of bone formation, and in C-telopeptide of type I collagen (*CTX*), a marker of

below each figure. *ALN* alendronate, *TPTD* teriparatide. *$p<0.001$; †$p<0.01$; ‡$p<0.05$, teriparatide versus alendronate. §$p<0.001$; ‖$p<$ 0.01; #$p<0.05$ within treatment group from baseline

Denosumab

Denosumab is currently approved for the treatment :

- Osteoporosis in postmenopausal women & men
- Denosumab have not been defined in this group.

- Journal of Bone and Mineral Research.۲۰۲۰،۱-۱۳

ESTROGEN

In women with hypoestrogenism from various causes, treatment should be directed at the underlying cause.

Calcif.Tissue Int.١٠١(August(٢))(٢٠١٧)١١١–١٣١

Physiologic Estrogen Replacement Increases Bone Density in Adolescent Girls with Anorexia Nervosa

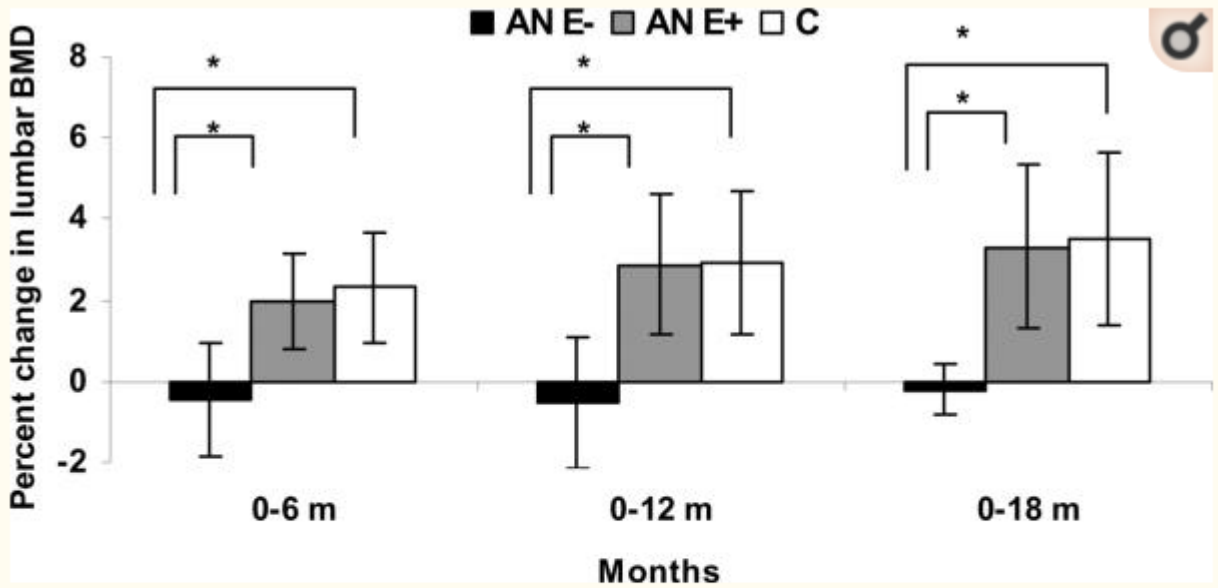


Figure 2

Percent change in lumbar spine bone mineral density (LBMD) in adolescent girls with anorexia nervosa (AN) randomized to placebo (AN E−) (black bars), girls with AN randomized to estrogen (AN E+) (gray bars) and normal-weight controls (C) (white bars). AN E+ had significant increases in LBMD at 6, 12 and 18 months compared with AN E−. When compared with C, AN E− had significant decreases in LBMD at 6, 12 and 18 months, whereas AN E+ did not differ from C for changes in BMD over time. Analysis was performed for differences between means for pairs * $p<0.05$

J Bone Miner Res. ۲۰۱۱ Oct; ۲۶(۱۰): ۲۴۳۰–۲۴۳۸

Idiopathic osteoporosis of young adults (IO)

Definition

- Mean age at diagnosis is ٣٥ years
- All secondary cause of osteopenia and osteoporosis : negative
- Involving sites rich in cancellous bone, such as the vertebrae.

  Hip(١٠%), or long bone fracture
- FH positive for FX

Osteoporos Int. ٢٠١٢;٢٣:١٧١–٨٢

- Low BMD , Low PBM in both gender
- Low trauma fractures
- Low trabecular volume
- Low cortical thickness
- Low trabecular wall thickness

Bone ٣٦ (٢٠٠٥) ٩٢٦-٩٣٠

Deficient osteoblastic function

- osteoblast proliferation and/or function were altered.
- expression of genes linked to osteoblast proliferation and function has been found decreased in males with idiopathic osteoporosis.

J.Bone Miner. Res. ٢٦ (٢٠١١) ١٥٨٤-١٥٩٢

Trabecular bone microstructure and local gene expression in iliac crest biopsies of men with idiopathic osteoporosis

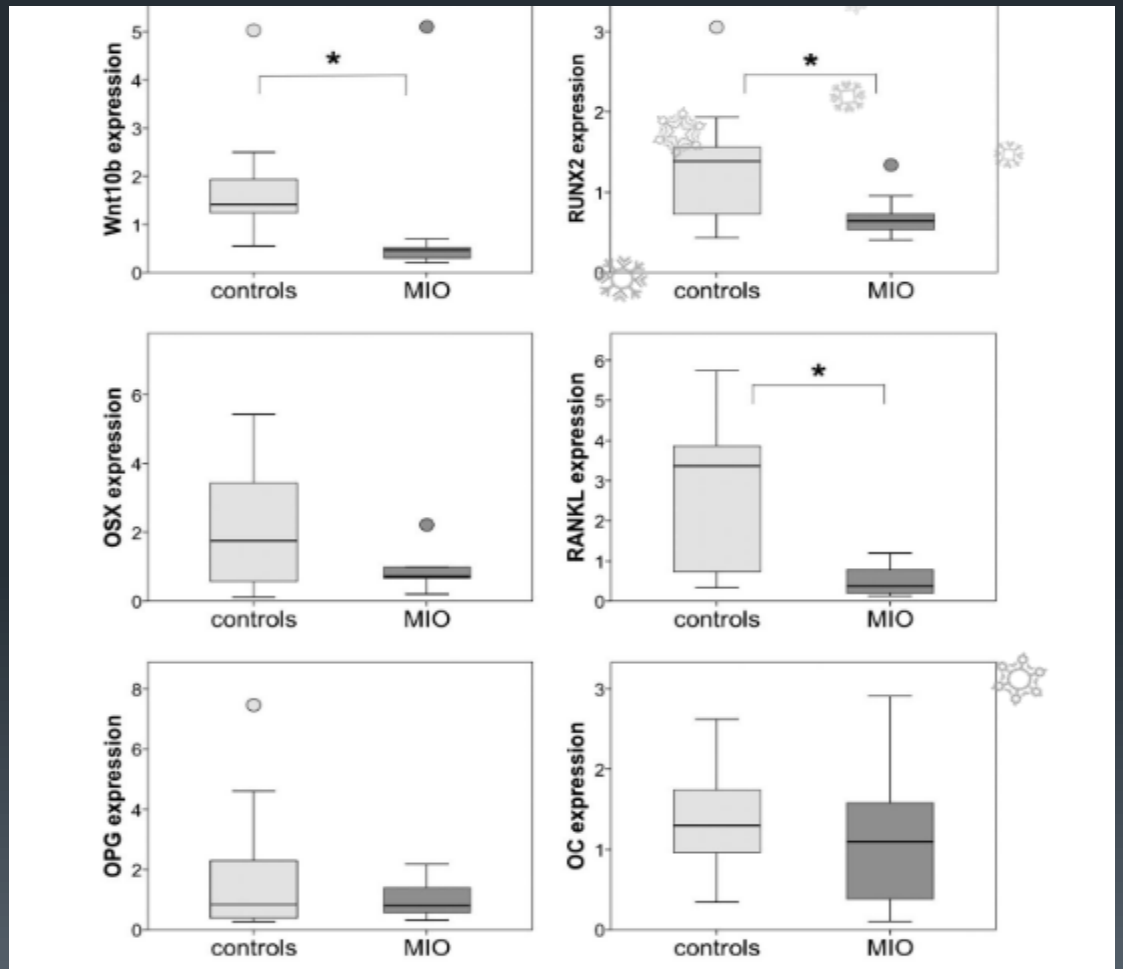


Fig. 2. Gene expression ($\Delta\Delta C_t$) of *WNT10B*, *RUNX2*, *Osterix* (*OSX*), *RANKL*, *OPG*, and *Osteocalcin* (OC). The asterisk (*) indicates $p < .05$. Data are shown as box-and-whisker plots.

J Bone Miner Res ۲۰۱۱ Jul;۲۶(۷)

Low IGF١

Low formation could result from a low free-IGF١, found to be associated to osteoblastic surface, particularly in men, are lative IGF١ in sensitivity in women.

J.Clin. Endocrinol. Metab. ٩٦ (٢٠١١) ٣٠٩٥-٣١٠٥

IGF-١ reduces osteoblast apoptosis and promotes osteoblastogenesis by stabilizing β-catenin, enhancing Wnt-dependent activity.

The role of GH/IGF-١/IGFBP signaling in bone loss is very important: they promote osteoblastic cell proliferation and differentiation and bone formation.

International Journal of EndocrinologyVolume ٢٠١٤, Article ID ٢٣٥٠٦٠, ٢٥ page

In women with low bone turnover, microstructural deficits were more profound, serum IGF-١ concentrations were higher and osteoblasts appeared to synthesize less bone matrix per remodeling site, suggesting osteoblast resistance to IGF-١.

International Journal of EndocrinologyVolume ٢٠١٤, Article ID ٢٣٥٠٦٠, ٢٥ page

A sub clinical low free serum estradiol

free serum estradiol was also found as sociated with wall thickness in males.

Lapauw, also observed a low estradiolin young male patients, which could explain in part low PBM acquisition.

J. Clin. Endocrinol. Metab. ۹۴ (۱۱) (۲۰۰۹) ۴۳۰۰-۴۳۰۸

Anthropometric and Skeletal Phenotype in Men with Idiopathic Osteoporosis and Their Sons Is Consistent with Deficient Estrogen Action during Maturation

	Probands (n = 107)	Controls (n = 107)	P	Sons (n = 23)	Controls (n = 23)	P
SHBG (nmol/liter)[a]	29.7 (22.9–37.5)	24.8 (19.8–34.4)	0.009	33.1 (24.7–41.8)	26.8 (20.3–38.5)	0.19
T (ng/dl)	546 ± 165	546 ± 158	0.98	565 ± 138	585 ± 160	0.66
Free T (ng/dl)	11.7 ± 3.8	13.1 ± 4.2	0.013	12.0 ± 4.1	13.1 ± 3.0	0.31
Estradiol (pg/ml)[a]	17.3 (15.1–21.3)	20.0 (16.8–23.7)	0.001	19.1 (16.8–21.8)	19.4 (15.7–21.2)	0.64
FE_2 (pg/ml)	0.33 (0.27–0.41)	0.40 (0.34–0.49)	<0.001	0.37 (0.27–0.42)	0.38 (0.30–0.44)	0.72
P1NP (μg/liter)[a]	40.2 (28.5–52.0)	45.1 (35.3–55.1)	0.022	59.1 (47.3–79.6)	60.2 (46.8–78.1)	0.85
bAP (μg/liter)	12.4 ± 4.0	12.3 ± 3.7	0.85	14.1 ± 3.9	13.6 ± 3.3	0.48
CTX (ng/ml)	0.36 ± 0.19	0.39 ± 0.17	0.20	0.55 ± 0.24	0.51 ± 0.17	0.66

Serum level of IGF١ (p=٠,٨۶) vs (p=٠,١)

J Clin Endocrinol Metab, November ٢٠٠٩, ٩۴(١١):۴٣٠٠–۴٣٠٨

Hypercalciuria

Some patients have hypercalciuria (IHC), but for most there is no alteration of calcium metabolism.

Ther Adv Muscuoskel Dis(٢٠١٠)٢(١)٢٩-٣٥

Femoral Neck Fracture in Idiopathic Hypercalciuria with Excessive Cola Consumption: A Case Report

Items	Score	Regulated	Normal range
White blood cell count	20.65×10^9/L	High	$4–10\times10^9$/L
Neutrophil percentage	78.9%	High	50.0–70.0%
C-reactive protein	28.5 mg/L	High	≤10 mg/L
Serum K^+	3.02 mmol/L	Low	3.5–5.5 mmol/L
Blood glucose	8.31 mmol/L	High	3.89–6.11 mmol/L
Urine occult blood	1+	High	–
Alkaline phosphatase	686 U/L	High	45–125 U/L
Plasma phosphorus	0.72 mmol/L	Low	0.90-1.34 mmol/L
Urinary Ca^{2+}	9.93 mmol/24 h	High	2.7–7.5 mmol/24h
Serum Ca^{2+}	2.46 mmol/L	Normal	2.25–2.75 mmol/L
Serum creatinine	87 μmol/L	Normal	54–106 μmol/L
Procollagen type I N-terminal propeptide	353.2 ng/mL	High	0.016–0.055 ng/mL
β-C-terminal telopeptide of type I collagen	1.70 ng/mL	High	0.1–0.65 ng/mL
N-MID osteocalcin	48.40 ng/mL	High	10–23 ng/mL
25-hydroxy-vitamin D	55.22 nmol/mL	High	8.0–30.5 ng/mL
Total protein	56.0 g/L	Low	65–85 g/L
Albumin	39.3 g/L	Low	40–55 g/L
γ-Globulin	16.7 g/L	Low	20–40 g/L
Albumin/γ-globulin	2.4	Low	1.5–2.5

Case Rep Orthop Res ۲۰۱۹;۲:۱۴–۲۰

Diagnostic Methods

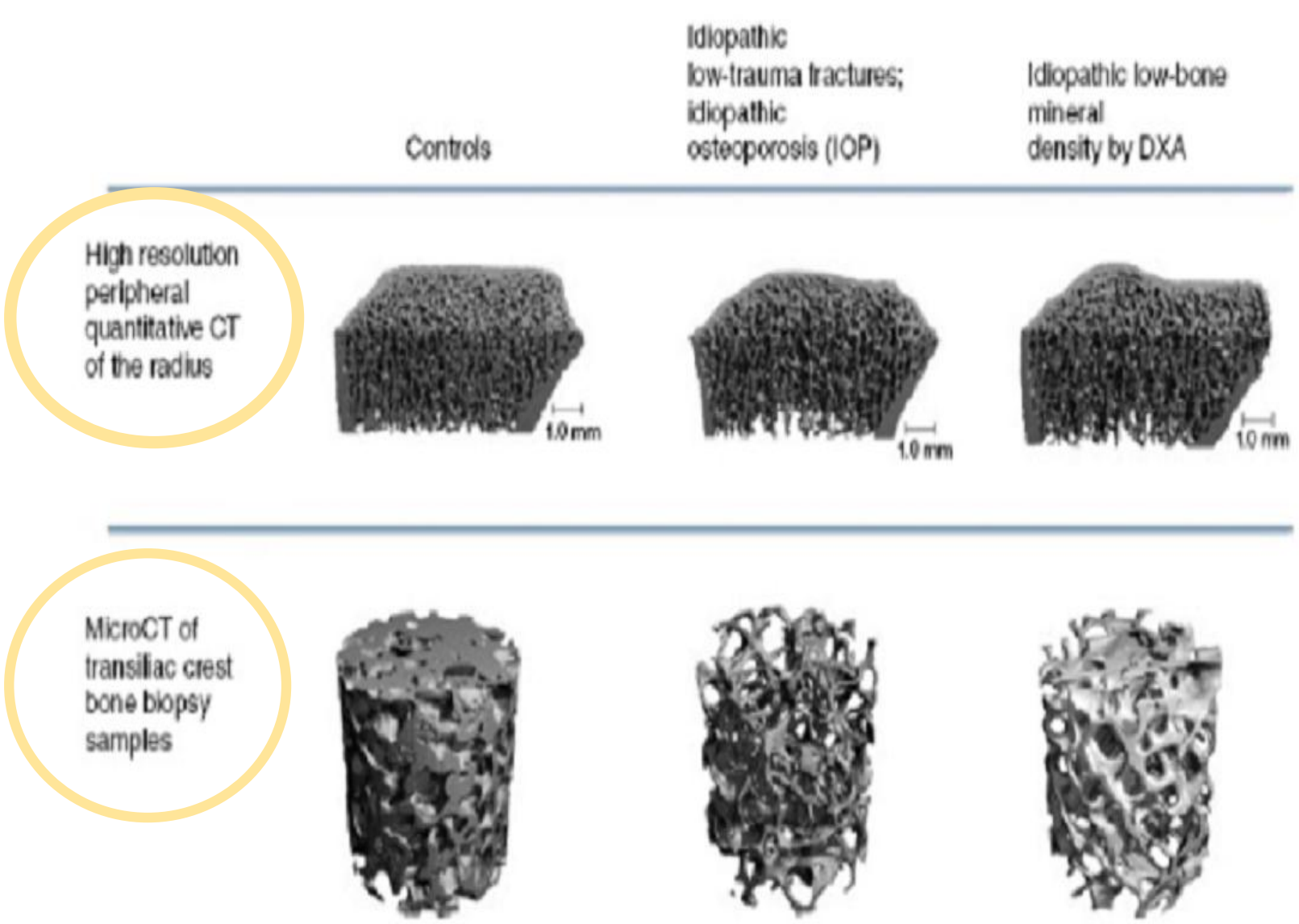


Fig. 55.1. Premenopausal women with idiopathic low bone mineral density by DXA have deficient bone microstructure in comparison to healthy premenopausal controls and similar bone microstructure in comparison to premenopausal women with idiopathic low trauma fractures, as shown by high resolution peripheral QCT of the radius and microCT of transiliac crest bone biopsy. Adapted from Cohen et al. [10] and Cohen et al. [12].

Most histomorphometric studies did not show increased activation frequency; some indicated that the eroded surface tended to be higher than incontrols, which would indicate an increased delay between resorption and formation.

Rheumatol. Int. ٣٢ (٢٠١٢) ٢١٠١-٢١٠٤

Treatment

Pharmacological treatment should be proposed only in those with a history of fracture or with a high absolute risk of fracture, or severe structural alterations at bone biopsy or HRpQCT.

Bone۷۹(۲۰۱۵)۲۵۹–۲۶۶.

Bisphosphonates

There is not much RCT on the effect oft of bisphosphonate on idiopathic osteoporosis, and only results on the effect of this drug on OI disease.

Bone Mineral Density and Fracture Rate in Response to Intravenous and Oral Bisphosphonates in Adult Osteogenesis Imperfecta

Table 3 Comparison of annualized linear rates of BMD change (gm/cm^2/year) between treatments for type I and types III/IV OI patients

OI type I	Treatment/comparison[a]	L1–L4 ($n = 57$) Rate[b] (95% CI)	P	Total hip ($n = 51$) Rate (95% CI)	P	Femoral neck ($n = 53$) Rate (95% CI)	P
	Not treated	−0.002 (−0.009, 0.006)	0.6	−0.005 (−0.012, 0.003)	0.2	−0.0095 (−0.018, −0.001)	0.023
	Pamidronate	0.006 (0.008, 0.012)	0.03	0.005 (−0.003, 0.013)	0.2	0.001 (−0.008, 0.008)	0.98
	Alendronate/residronate	0.004 (0.0006, 0.008)	0.047	0.006 (0.002, 0.011)	0.003	−0.009 (−0.007, 0.005)	0.8
	Pamidronate vs. not treated	0.008 (−0.0009, 0.018)	0.08	0.009 (−0.0019, 0.02)	0.08	0.01 (−0.002, 0.02)	0.1
	Alendronate/residronate vs. not treated	0.006 (−0.002, 0.014)	0.163	0.011 (0.003, 0.019)	0.01	0.009 (−0.002, 0.019)	0.1
	Alendronate/residronate vs. pamidronate	−0.002 (−0.009, 0.004)	0.49	0.001 (−0.007, 0.01)	0.74	−0.001 (−0.011, 0.009)	0.85
III/IV		L1–L4 ($n = 27$) Rate (95% CI)	P	Total hip ($n = 17$) Rate (95% CI)	P	Femoral neck ($n = 18$) Rate (95% CI)	P
	Not treated	0.0045 (−0.01, 0.02)	0.6	0.009 (−0.04, 0.06)	0.7	0.009 (−0.05, 0.07)	0.8
	Pamidronate	0.016 (0.008, 0.023)	<0.001	0.011 (0.0002, 0.02)	0.046	−0.005 (−0.017, 0.01)	0.4
	Alendroante/residroante	0.003 (−0.006, 0.012)	0.5	0.003 (−0.014, 0.02)	0.8	0.003 (−0.013, 0.019)	0.7
	Pamidronate vs. not treated	0.011 (−0.005, 0.027)	0.18	0.002 (−0.47, 0.05)	0.94	−0.014 (−0.073, 0.045)	0.65
	Alendronate/residronate vs. not treated	−0.001 (−0.018, 0.016)	0.88	−0.007 (−0.058, 0.044)	0.8	−0.006 (−0.066, 0.055)	0.85
	Alendronate/residronate vs. pamidronate	−0.013 (−0.024, −0.001)	0.03	−0.009 (−0.029, 0.012)	0.41	0.008 (−0.012, 0.028)	0.43

[a] Analysis of linear combinations of treatment estimates

[b] Adjusted for age at baseline DXA scan, gender

Calcif Tissue Int (۲۰۱۰) ۸۷:۱۲۰–۱۲۹

Denosumab

There is not much RCT on the effect oft of bisphosphonate on idiopathic osteoporosis, and only results on the effect of this drug on OI disease.

Efficacy of Denosumab for Osteoporosis in Three Female Patients with Osteogenesis Imperfecta

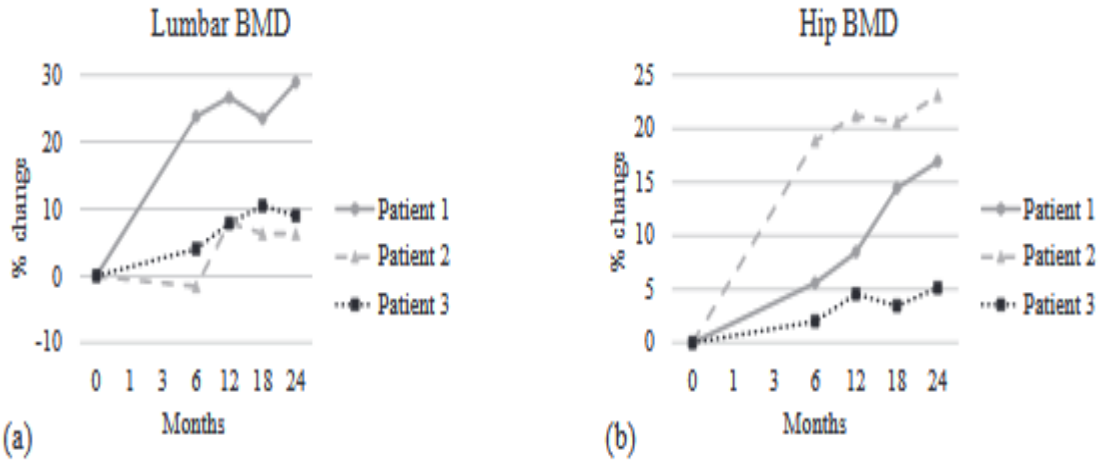
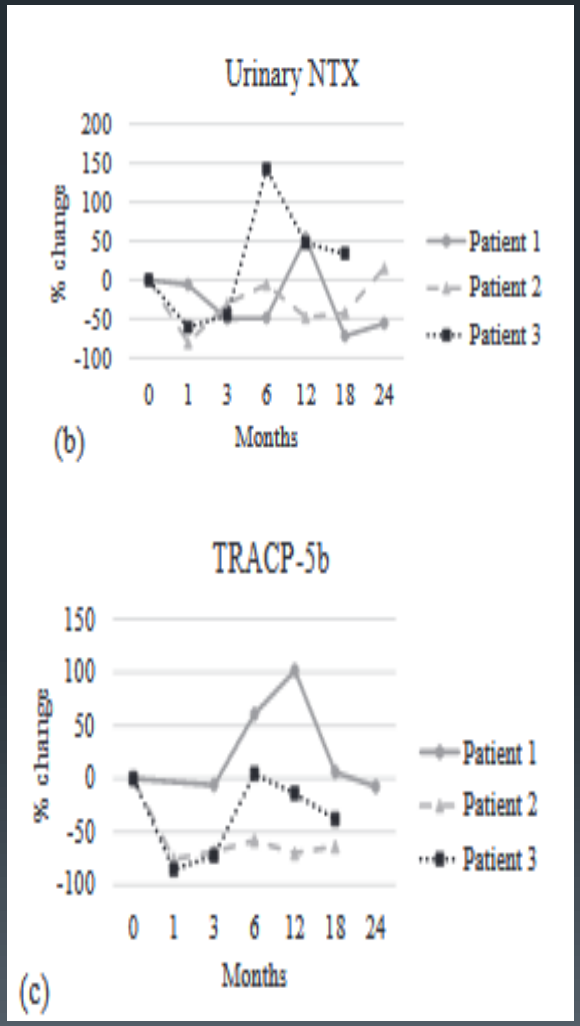


Fig. 1. Changes in BMD before and during denosumab administration.
Both lumbar BMD and hip BMD were increased at 2 years of drug administration.



•Tohoku J Exp ۲۰۱۷ Jun;۲۴۲(۲):۱۱۵-۱۲۰

Teriparatide

- increased spine and hip BMD
- improved trabecular architecture and strength

Teriparatide for Idiopathic Osteoporosis in Premenopausal Women: A Pilot Study

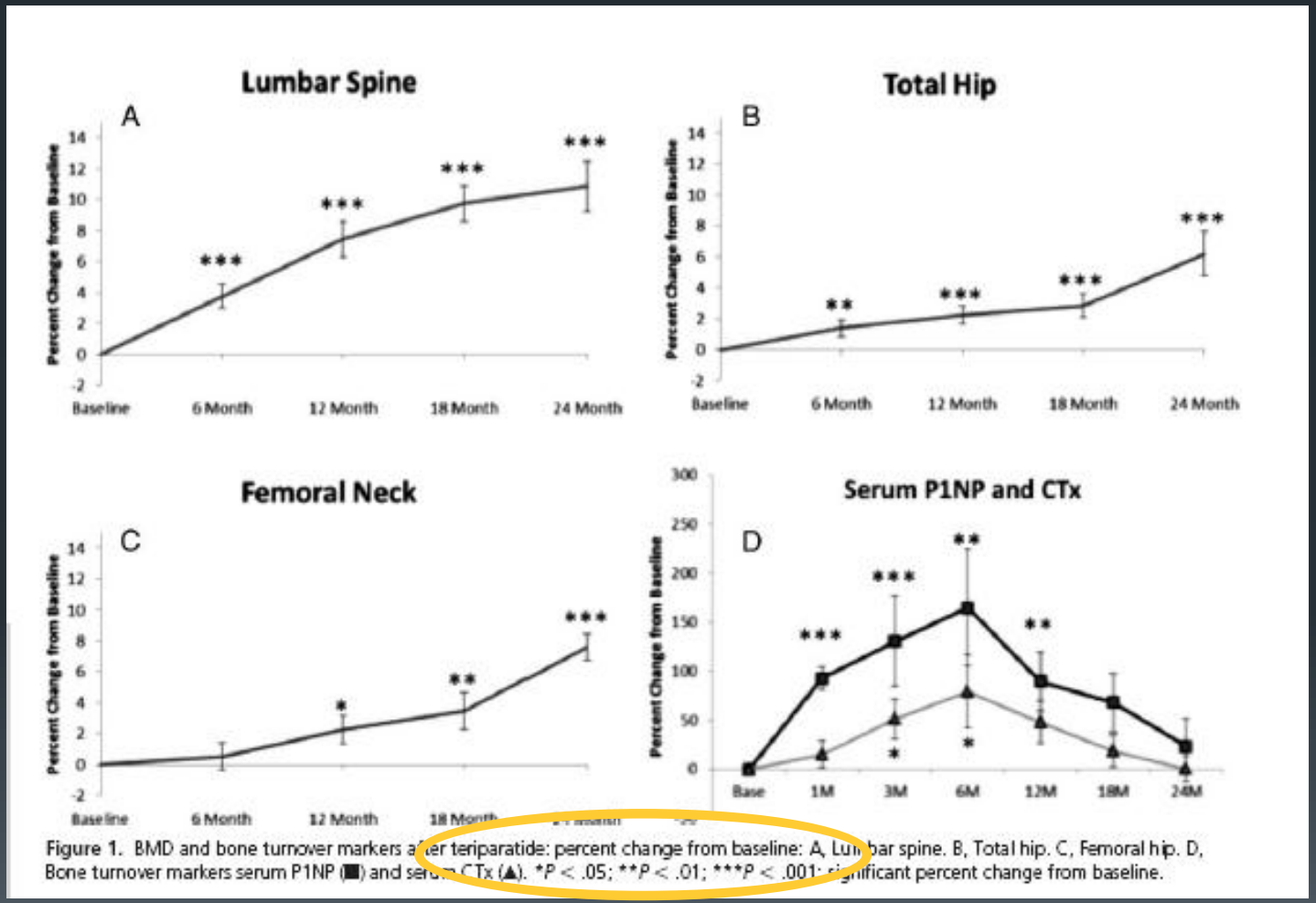


Figure 1. BMD and bone turnover markers after teriparatide: percent change from baseline: A, Lumbar spine. B, Total hip. C, Femoral hip. D, Bone turnover markers serum P1NP (■) and serum CTx (▲). *$P < .05$; **$P < .01$; ***$P < .001$: significant percent change from baseline.

J Clin Endocrin Metab.March ۲۹،۲۰۱۳.

	Baseline	18 Mo	Difference	Value
Cortical microstructure by two-dimensional histomorphometry				
Cortical width, μm	558 ± 209	680 ± 242	+22	.009
Cortical porosity, % cortical area	5.0 ± 1.5	7.3 ± 3.7	+46	.01
Trabecular microstructure and stiffness by three-dimensional μCT and μFE				
Trabecular bone volume fraction, %	20.8 ± 6.9	27.8 ± 7.3	+34	<.001
Trabecular number, n/mm	1.5 ± 0.2	1.8 ± 0.3	+18	<.001
Trabecular thickness, μm	177 ± 40	184 ± 27	+4	.5
Trabecular separation, μm	711 ± 72	650 ± 61	−9	<.001
Trabecular separation SD, mm	199 ± 27	207 ± 34	+4	.2
Connectivity density, 1/mm^3	10.1 ± 12.7	20.7 ± 21.9	+105	.7
Stiffness, Young modulus (E)	401 ± 234	685 ± 358	+71	<.001
Bone remodeling				
Osteoid width, no. lamellae	3.5 ± 1.3	2.8 ± 1.0	−20	.1
Cancellous wall width, μm	34 ± 5	40 ± 5	+16	<.001
Endocortical wall width, μm	39 ± 5	44 ± 5	+12	.002
Intracortical wall width, μm	53 ± 7	54 ± 4	+2	.6
Mineralizing perimeter, %	3.8 ± 2.8	3.1 ± 2.7	−19	.2
Bone formation rate, mm^2/mm/y	0.009 ± 0.007	0.008 ± 0.007	−16	.3
Mineral apposition rate, μm/d	0.623 ± 0.078	0.603 ± 0.125	−3	.4
Adjusted apposition rate, μm/d	0.519 ± 0.400	0.599 ± 0.503	+15	.6
Bone cells and marrow fat				
Osteoblast number, no./mm bone surface	1.15 ± 0.5	1.24 ± 0.9	+31	.70
Osteoclast number, no./mm bone surface	0.043 ± 0.03	0.023 ± 0.03	−46	.04
Adipocyte area, mm^2	0.325 ± 0.09	0.267 ± 0.08	−15	.01
Adipocyte perimeter, mm	31.5 ± 7.8	26.5 ± 5.9	−13	.008
Adipocyte number, no./mm^2 of marrow + bone	207 ± 46	198 ± 40	−1	.44
Adipocyte volume/marrow volume, %	34.6 ± 9.0	29.1 ± 8.8	−13	.02
Adipocyte density, no./mm^2 marrow tissue	220.1 ± 46.0	216.0 ± 44.7	−1	.69

Juvenile osteoporosis

Table 53.1. Forms of osteoporosis in children, according to current literature.

I Primary
Osteogenesis imperfecta
Idiopathic juvenile osteoporosis
II. Secondary
Endocrine disorders
Cushing syndrome
Thyrotoxicosis
Anorexia nervosa
Inflammatory disorders
Juvenile arthritis
Dermatomyositis
Systemic lupus erythematosis
Inflammatory bowel disease
Cystic fibrosis
Chronic hepatitis
Malabsorption syndromes
Biliary atresia
Inborn errors of metabolism
Homocystinuria
Glycogen storage disease type 1
Immobilization
Cerebral palsy
Duchenne dystrophy
Hematology/oncology
Acute lymphoblastic leukemia
Thalassemia
Severe congenital neutropenia

- IJO is a self-limiting disease
- ٨ – ١٣ years old for both gender
- develops in a prepubertal, previously healthy child
- leads to metaphyseal and vertebral compression fractures

International Society of Clinical Densitometry (ISCD) guidelines

Osteoporosis in children has been defined by additional clinical criteria:

- One or more vertebral compression fracture(s) in the absence of local disease or high energy trauma
- Both aBMD z-score below the –٢ SDs with ٢ or more long bone fractures by age ١٠
- ٣ or more long bone fractures by age ١٩ years of age

J.Clin.Densitom.١٧(٢)(٢٠١٤)٢٨١-٤٥.

Symptoms

- Pain in the lower back, hips, feet, knee, and ankle
- Difficulty walking
- Fractures of the lower extremities
- Diffuse muscle weakness
- Vertebral compression fractures are frequent
- Long bone fractures, mostly at metaphyseal sites
- Thoracolumbar kyphosis or kyphoscoliosis, pigeon chest deformity, loss of height, deformities of the long bones, and a limp.

PATHOPHYSIOLOGY

- The etiology of IJO is unknown
- Impaired osteoblast performance
- Decreases the ability of cancellous bone to adapt to the increasing mechanical needs during growth

Diagnosis Methods

DXA is the most widely available and used technique for the evaluation of BMD in children and adolescents.

Whole body BMD and lumbar spine BMD corrected for height are considered as valuable parameters for respectively cortical and trabecular bone strength in children at risk for osteoporosis.

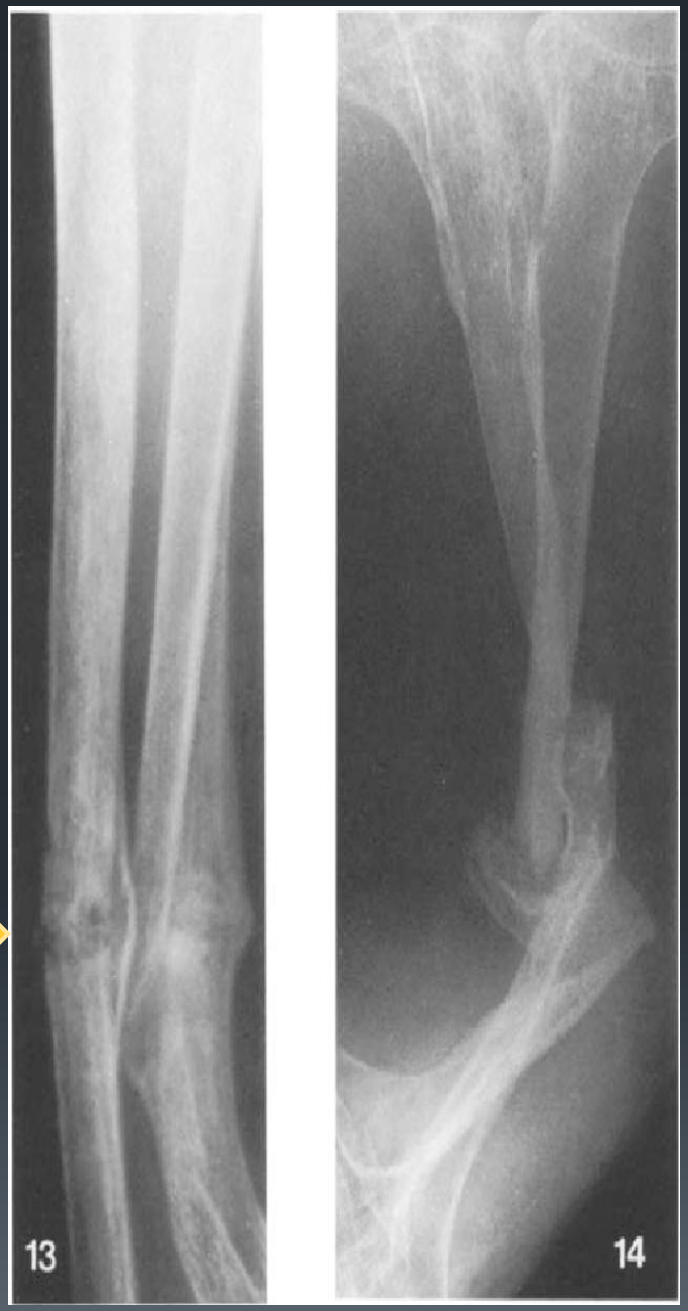
Measurementsat the distal femur can provide a useful alternative, when measurements at wholebody or lumbarspine are notpossible (due to severe scoliosis, metal implant).

Prevalence of vertebral fractures in children with suspected osteoporosis , J. Pediatr. ١٧٩ (٢٠١٦) ٢١٩ – ٢٢٥.

Radiological view

The typical radiographical finding in IJO is neoosseous osteoporosis, a radiolucent band at sites of newly formed metaphyseal bone. This localized metaphyseal weakness can give rise to fractures, often at the distal tibias and adjacent to the knee and hip joints. Nevertheless, “neoosseous osteoporosis” is not a prerequisite for diagnosing IJO.

Lateral thoracolumbar spine radiographs using the Genantsemi-quantitative scoring method to calculate spinal deformity index (SDI) are considered the “gold standard” to identify VFs.


13
14

BIOCHEMICAL FINDINGS

Biochemical studies of bone and mineral metabolism have not detected any consistent abnormality in children with IJO.

J Bone Miner Res. ۲۰۰۳;۱۸:۱۶۷–۷۱.

Treatment

- The finding of alow bone mass not sufficient to install a bisphosphonate therapy, the fracture history and additional risk factors (glucocorticoid therapy, immobilization, familial history of osteoporosis should guide the decision for bisphosphonate treatment.
- Despite low BMD, no consistent increased fracture rate has been described in children.

Efficacy and treatment costs of zoledronate versus pamidronate in paediatric osteoporosis, Arch. Dis. Child. ١٠٣(١)(٢٠١٨) ٩٢-٩٤.

- Addressing vitamin D deficiency
- Encouraging regular physical activity, ensuring normal growth (by increasing caloric and protein intake)
- Pubertal progression (by estrogen or testosterone supplementation)
- Stopping smoking
- Limiting the intake of carbonated drinks

J. Paediatr. Child Health ٥٤ (٣) (٢٠١٨) ٢٢٣–٢٣٣.

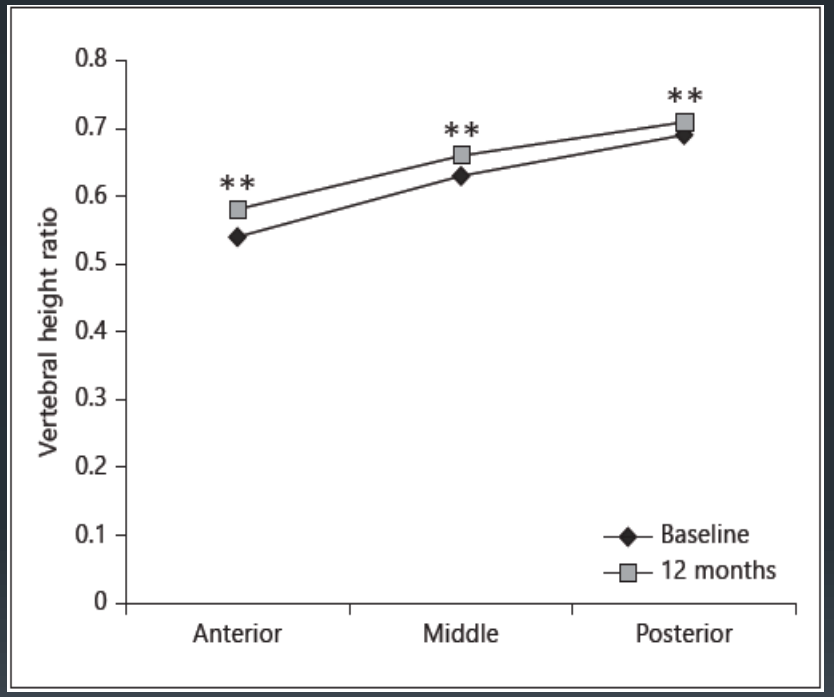
Bisphosphanate

Given the current enthusiasm for pediatric bisphosphonate therapy, especially intravenously in many JO patients probably are receiving treatment with such drugs. The most commonly used compounds are pamidronate and zoledronic acid.

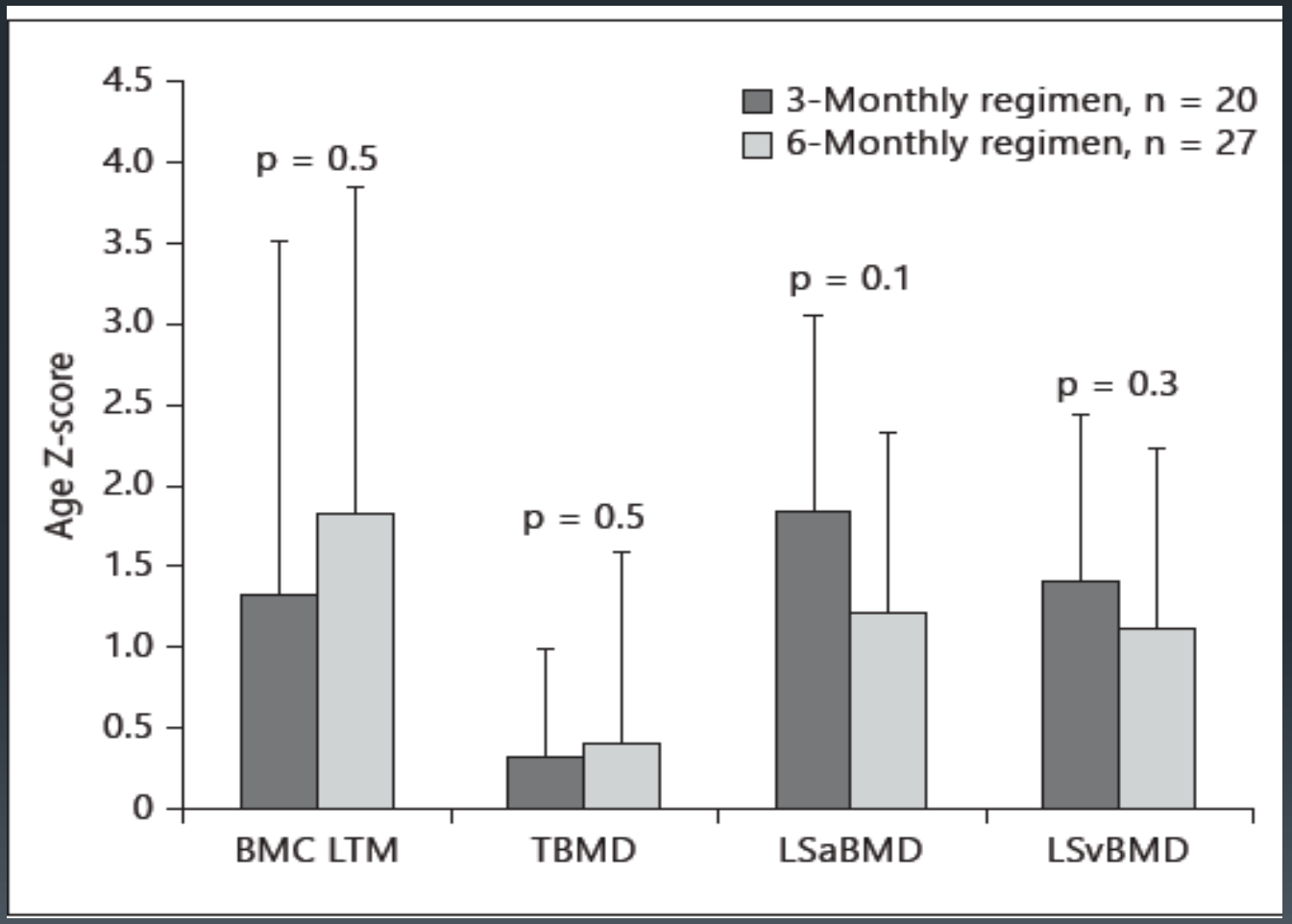
Efficacy and treatment costs of zoledronate versus pamidronate in paediatric osteoporosis, Arch. Dis. Child. ١٠٣(١)(٢٠١٨) ٩٢-٩٤.

Intravenous Zoledronic Acid Given Every 6 Months in Childhood Osteoporosis

	Reference range	Baseline	12 months	p value
Calcium, mmol/l	2.10–2.65	2.38 (2.35–2.44)	2.36 (2.28–2.41)	0.2
Phosphate, mmol/l	1.00–1.80	1.55 (1.49–1.73)	1.41 (1.33–1.64)	0.03
ALP, U/l	80–355	188 (143–271)	148 (122–193)	0.01
PTH, pmol/l	1.0–7.0	3.5 (2.3–4.1)	3.7 (2.9–5.4)	0.2
Osteocalcin, nmol/l	0.3–3.4	7.9 (4.3–11.3)	2.4 (1.1–3.9)	<0.001
25(OH)D, nmol/l	>50	75 (67–94)	78 (58–86)	0.3



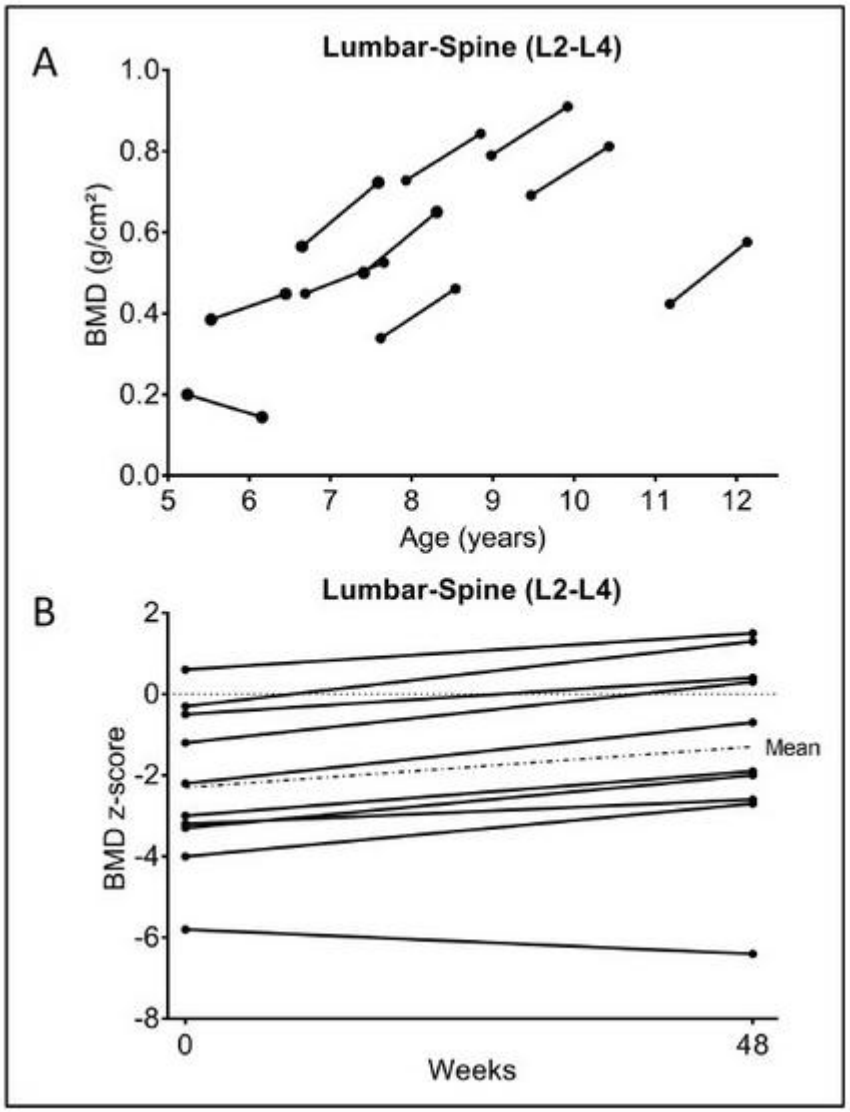
Horm Res Paediatr ۲۰۱۳;۸۰:۱۷۹–۱۸۴

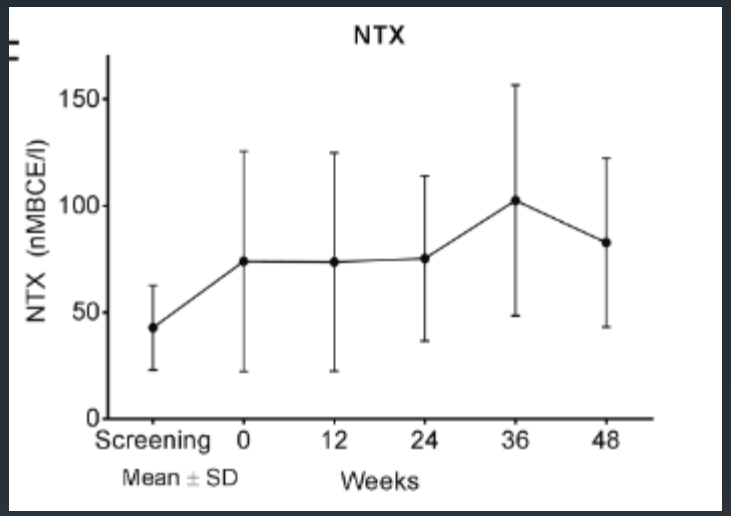

3-Monthly regimen, n = 20
6-Monthly regimen, n = 27
Age Z-score
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
p = 0.5
p = 0.5
p = 0.1
p = 0.3
BMC LTM
TBMD
LSaBMD
LSvBMD

Denosumab

There is not much RCT for the effect Denusomab on the idiopathic osteoporosis, and only results on the effect of this drug on OI disease.

Safety and efficacy of denosumab in children with osteogenesis imperfect--a first prospective trial





J Musculoskelet Neuronal Interact. ۲۰۱۶ Mar; ۱۶(۱): ۲۴–۳۲.

PROGNOSIS

The disease process appears to be active only in growing children, and spontaneous recovery is the rule after ٣ to ٥ years of evolution.

However, in some of the most severe cases reported to date, deformities and severe functional impairment persisted, which left them wheelchair bound with cardiorespiratory abnormalities.


با تشکر
FARS