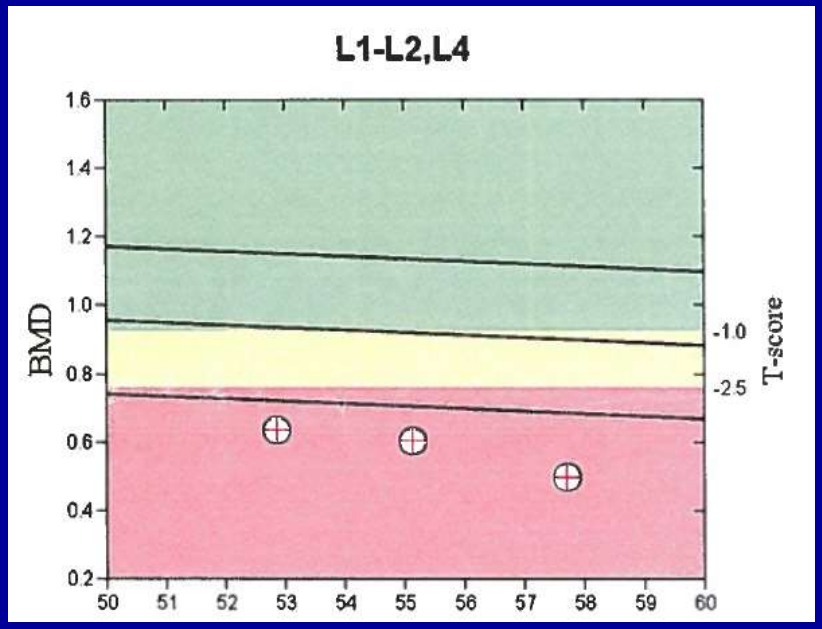
Conduite devant une DMO très basse

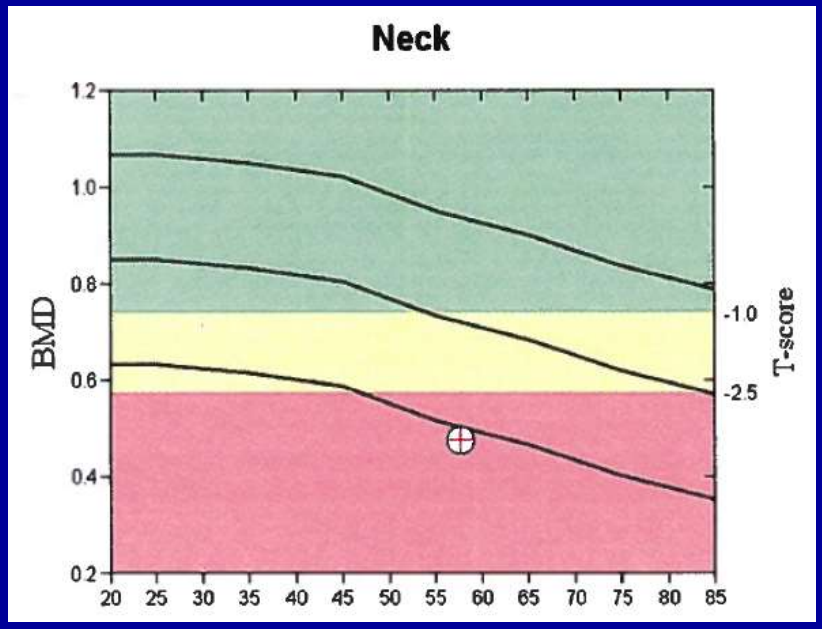
Serge Ferrari

Service des maladies osseuses

Hôpitaux universitaires et Faculté de médecine de Genève

Mme H., fracture vertébrale à 40 ans en jouant au badminton, perte de taille 10 cm depuis lors…





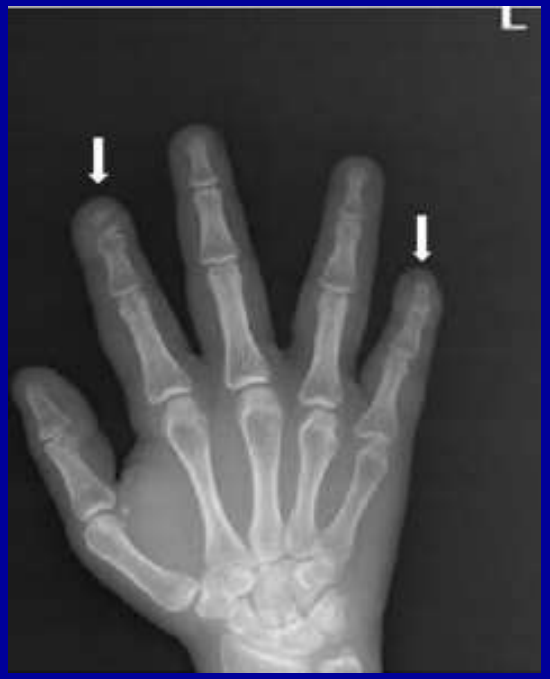
IBN TPT

DXA Results Summary: L1-L2,L4

Messungsdatum	Alter	BMD (g/cm²)	T - Score	BMD-Änderung Vgl. mit Basis	Vgl. Vorherig
26.09.2017	57	0.498	-4.9	-21.4%#	-17.6%#
02.03.2015	55	0.604	-3.9	-4.6%*	-4.6%*
15.11.2012	52	0.633	-3.6		

Mme H, suite

- Parodontolyse juvenile, retro-maxillaire opéré
- Cervicalgies chron. s/ osteochondrose C5/C6
- Acro-ostéolyse phalanges distales
- Hyperlaxité
- 154 cm (était 164), 58kg
- Ménopause 52 ans non-substituée, pas d'autres FR OP
- Bilan sg sp: 0 Sy. Inflamm, 25OHD 105, PTH et Ca N, creat N, CTx 0.19, PAL 54



Canalis and Zanotti *Orphanet Journal of Rare Diseases* 2014, **9**:200
http://www.ojrd.com/content/9/1/200

ORPHANET JOURNAL OF RARE DISEASES

REVIEW **Open Access**

Hajdu-Cheney syndrome: a review

Ernesto Canalis* and Stefano Zanotti

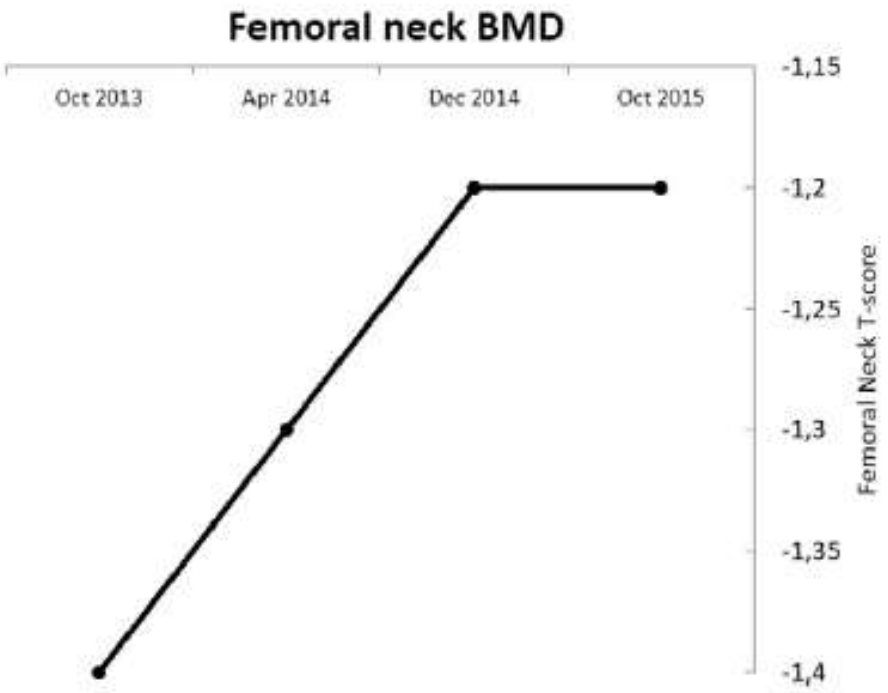
Abstract

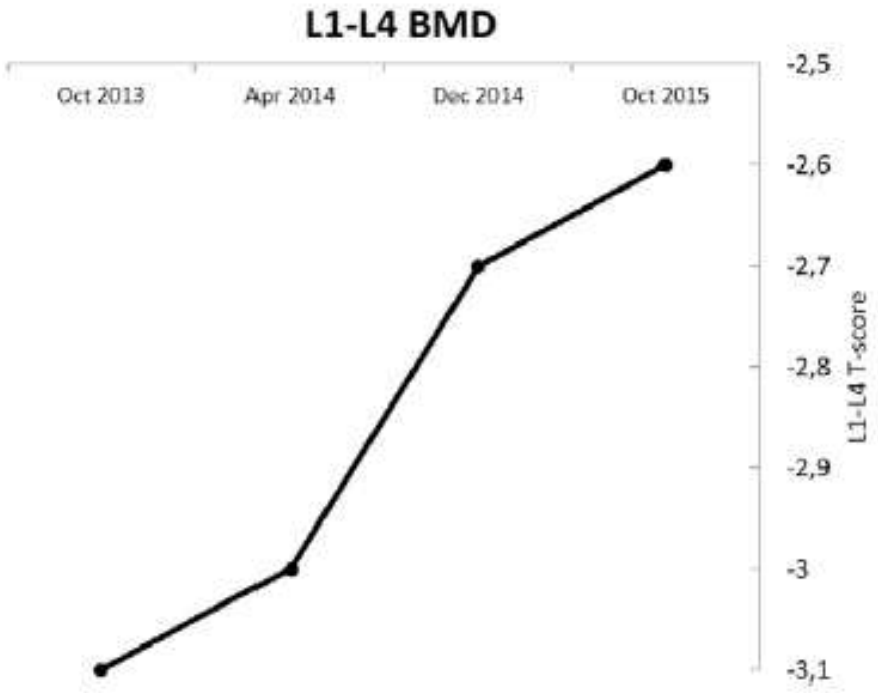
Hajdu Cheney Syndrome (HCS), Orpha 955, is a rare disease characterized by acroosteolysis, severe osteoporosis, short stature, specific craniofacial features, wormian bones, neurological symptoms, cardiovascular defects and polycystic kidneys. HCS is rare and is inherited as autosomal dominant although many sporadic cases have been reported. HCS is associated with mutations in exon 34 of *NOTCH2* upstream the PEST domain that lead to the creation of a truncated and stable NOTCH2 protein with enhanced NOTCH2 signaling activity. Although the number of cases with *NOTCH2* mutations reported are limited, it would seem that the diagnosis of HCS can be established by sequence analysis of exon 34 of *NOTCH2*. Notch receptors are single-pass transmembrane proteins that determine cell fate, and play a critical role in skeletal development and homeostasis. Dysregulation of Notch signaling is associated with skeletal developmental disorders. There is limited information about the mechanisms of the bone loss and acroosteolysis in HCS making decisions regarding therapeutic intervention difficult. Bone antiresorptive and anabolic agents have been tried to treat the osteoporosis, but their benefit has not been established. In conclusion, Notch regulates skeletal development and bone remodeling, and gain-of-function mutations of *NOTCH2* are associated with HCS.

Keywords: Notch, Skeleton, Bone remodeling, Hajdu-Cheney syndrome, Fractures, Polycystic kidneys, B cell lymphoma

Hajdu-Cheney: Response to denosumab (1 case report)

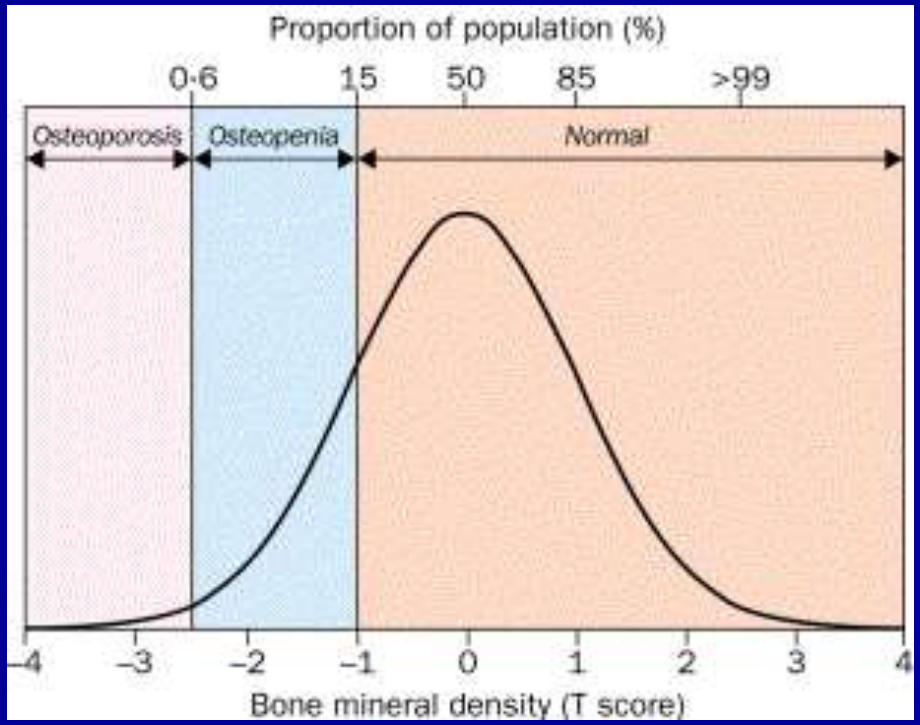
G. Adami et al. / Bone 92 (2016) 150–156





BMD distribution

- Prevalence of osteoporosis in the general population:
  - Osteoporosis: ≤ 0.5 %
  - Osteopenia: 10-15%



(Kanis, OI 1997; Liu, JBMM 2008; Diaz Curiel, Med Clin 2001)

- Osteoporosis in subjects with chronic diseases:
  - 15-50%

Osteoporosis in the young: Definition (IOF)

- T-score ≤ -2.5 (spine or hip) in men and women > 20yrs (when growth is completed)

  And/or

  - Low trauma and/or multiple fractures (vertebrae !)

- In absence of low trauma and/or multiple fractures

  If

  - A chronic disease (secondary osteoporosis)

- Excluding vitamin D deficiency (osteomalacia)

S Ferrari, ML Bianchi, JA Eisman, AJ Foldes, S Adami, J Stepan, MC de Vernejoul, JM Kaufm, for the Osteoporosis Pathophysiology Working group *Osteoporosis Int 2012*

Masse osseuse très basse chez la femme jeune

JCEM 2008

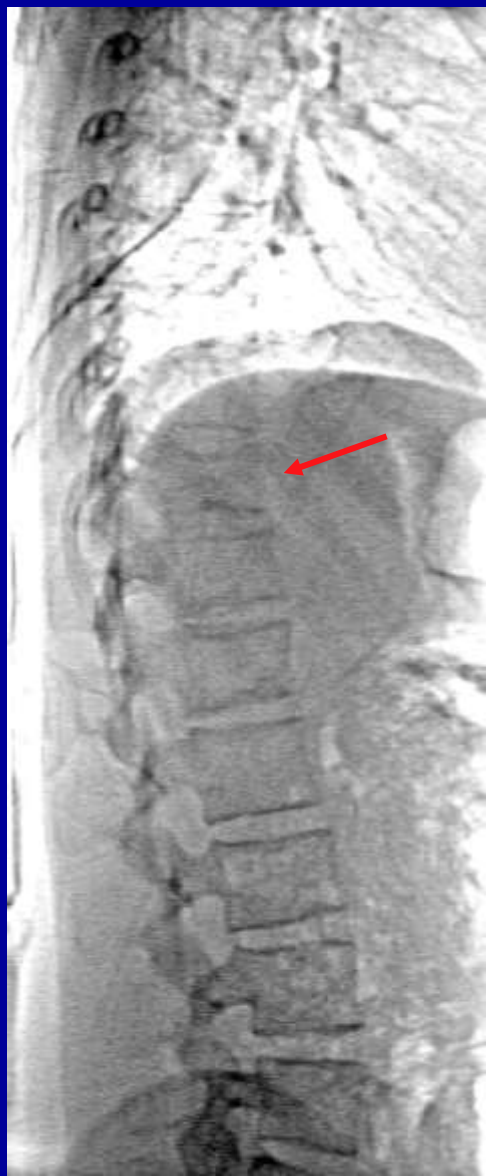
TABLE 1. Body weight composition, BMD, nutritional and food intake parameters, and several hormones (mean levels ± SEM) in AN, CT, and controls

	AN (n = 44)	CT (n = 25)	Controls (n = 28)
Anthropometry and body composition			
Age (yr)	23.4 ± 1.2	23.1 ± 1.2	23.9 ± 1.4
Height (m)	1.62 ± 0.1	1.63 ± 0.02	1.63 ± 0.01
BMI (kg/m^2)	15.5 ± 0.1^a	15.8 ± 0.1^a	20.7 ± 0.4
FM %	9.8 ± 1.1^a	18.6 ± 0.7^{a,b}	26.3 ± 1.2
BMD			
Femoral neck BMD (g/cm^2)	0.795 ± 0.03^a	0.809 ± 0.02^a	0.951 ± 0.02
Lumbar spine BMD (g/cm^2)	0.849 ± 0.03^a	0.873 ± 0.02^a	0.986 ± 0.03
Hormonal parameters			
Leptin (μg/liter)	2.4 ± 0.5^a	6.0 ± 0.8^{a,b}	11.2 ± 1.9
GH (mIU/liter)	8.5 ± 0.7^a	4.8 ± 0.6^b	4.7 ± 0.6
IGF-I (μg/liter)	163 ± 16^a	295 ± 34^b	283 ± 20
Cortisol (ng/liter)	364 ± 31^a	216 ± 12^b	266 ± 17
17β-estradiol (ng/liter)	14.3 ± 1.4^a	73.1 ± 8.6^b	51.6 ± 11.4

Clinical Approach:

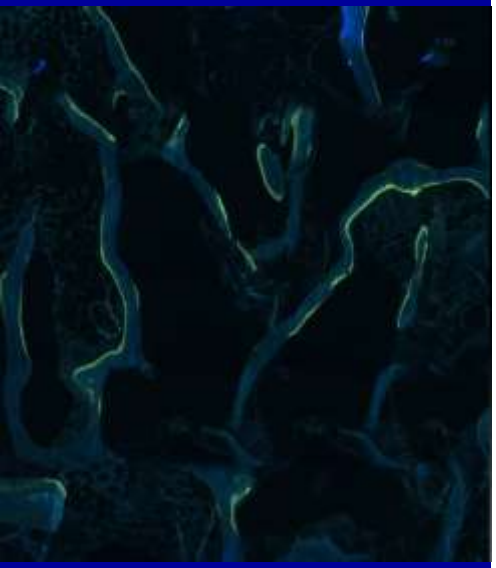
Med Hx, Phys exam
DXA (VFA)
Labs (1st line)

Mineral metabolism	Serum calcium (corrected for albumin)
	Serum phosphate
	Creatinine
	25(OH)D
	iPTH
	ALP (bone specific)
	BTMs (for instance, s-CTX, s-PINP)*
Inflammation, hematopoietic disorder	Blood cell count
	ESR or CRP
Hepatic disease	GOT, GPT, γ-GT
Diabetes (primary or secondary)	Fasting glucose, Hba1C
Thyroid dysfunction	TSH
Hypogonadism (men)	Total testosterone
Malabsorption, Celiac disease	24-h urinary calcium
	Anti-endomysial , anti -transglutaminase



Clinical Approach: Labs (selected conditions)

Background	Test
TSH alterations	Free T4
Altered glucose, Cushing's	24-hour free urinary cortisol
Altered testosterone (men)	LH /SHBG (free testosterone)
Amenorrhea, hypogonadism (women)	FSH/estradiol
Altered renal function (CRF)	$1,25(OH)_2D_3$
Hemochromatosis	Ferritin
Hypophosphatasia	ALP, BALP
Mastocytosis	Tryptase, IgE
Gaucher's disease	Glucocerebrosidase



LOW aBMD (T-sc. < -2.5 spine or hip)
&/or VERTEBRAL FRACTURE &/or MULTIPLE FRACTURES

Medical history and physical examination
(exclude medication associated with bone loss)

Laboratory Tests - General Screening (Table 2)

Positive Test

Negative Test

Measure Bone Turnover Markers

Abnormal BTM

Normal BTM

Laboratory Tests – Selected Conditions
(Table 3)

Positive Test

Negative Test

Refer to disease specialist

Consider extended referrals Imaging and/or Biopsies
(gut, skin, bone marrow, bone)

Assume Low Peak Bone Mass

Constitutional leanness or late puberty

Idiopathic or genetic osteoporosis:
See Figure 2

Stop investigation and reassure

Positive Test

Negative Test

Targeted therapy

Repeat DXA scan (after 2 years)

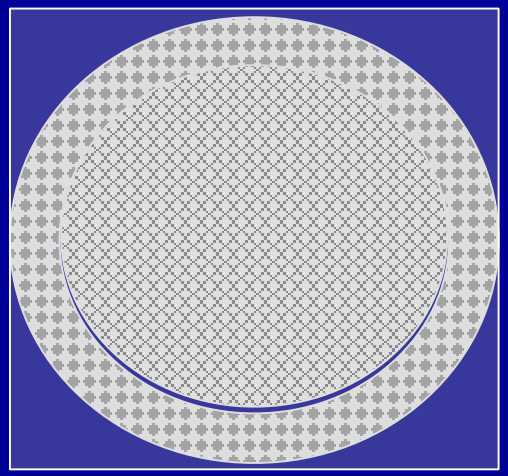
Ferrari et al.
Osteoporosis Int 2012

Mme B., 70 ans

- Minéralo de “routine” à 65 ans: T-sc -4.6 rachis, -2.7 hanche
- Pas de fractures
- Ménopause non-substituée à 52 ans
- Pas de FR OP , histoire familiale ou Sy. Inflamm
- 150 cm / 47kg
- 25OHD 65, CTx 0.76, P1NP 55

What is bone mass (aBMD) ?

- Degree of mineralization (max 1200mg/cm3)
- Trabecular bone volume
- Cortical thickness and porosity
- Bone size



aBMD = how much Bone mineral there is in the square

Hence Bone quantity and quality are inter-related !

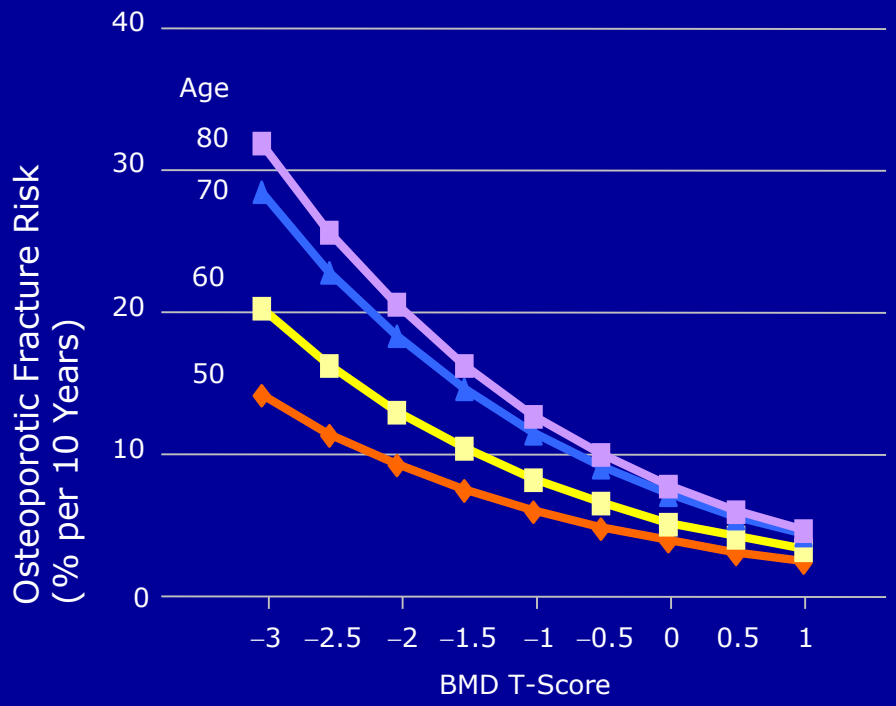
Correlations between spine BMD and microstructure (ex vivo)

Table 2 Pearson correlation coefficients between DXA, microarchitecture parameters, mechanical behavior, and TBS

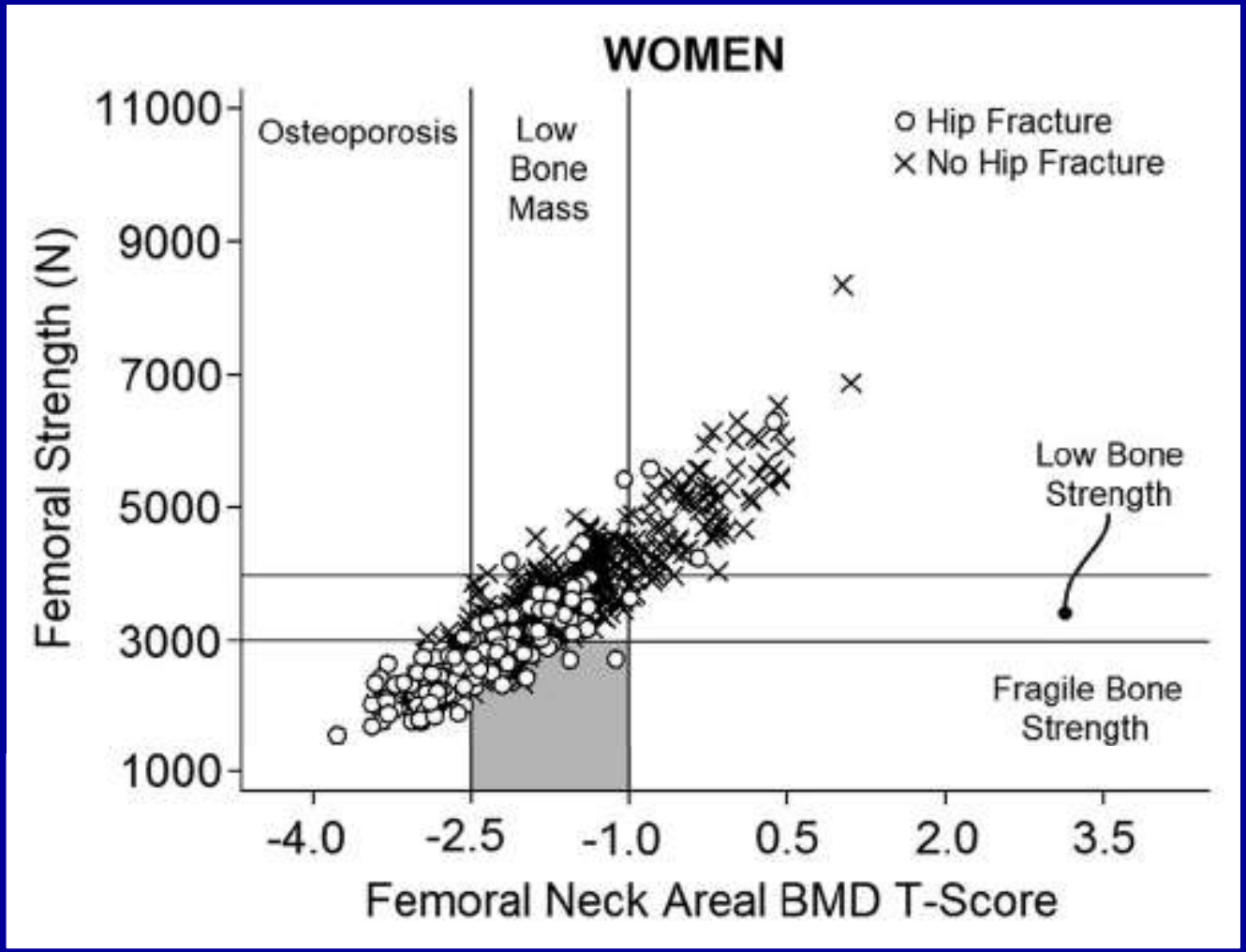
	AP. BMC	AP. BMD	AP. area	Lat. BMC	Lat. area	Lat. BMD	Tb.BV/TV	DA	SMI	Tb.Th	Failure load	Stiffness
AP. BMD	0.72**											
AP. area	0.66**	−0.03										
Lat. BMC	0.86***	0.50*	0.73***									
Lat. BMD	0.91***	0.70**	0.56*	0.86***								
Lat. area	0.42	0.00	0.64**	0.73***								
Tb.BV/TV	0.49	0.68**	−0.05	0.22	−0.17	0.44						
DA	−0.32	−0.49	0.11	−0.23	−0.06	−0.24	−0.69**					
SMI	−0.32	−0.68**	0.29	0.03	0.48	−0.33	−0.85***	0.40				
Tb.Th	0.16	0.40	−0.22	0.16	0.02	0.19	0.49*	−0.87***	−0.28			
Failure load	0.41	0.34	0.26	0.27	−0.13	0.49*	0.33	0.25	−0.56*	−0.37		
Stiffness	0.49*	0.24	0.44	0.32	−0.07	0.52*	0.32	0.22	−0.36	−0.46	0.72**	
TBS	0.25	0.36	−0.04	−0.01	−0.32	0.24	0.58*	−0.09	−0.62**	−0.03	0.46	0.64**

Roux, OI 2013

DMO basse et risque fracturaire



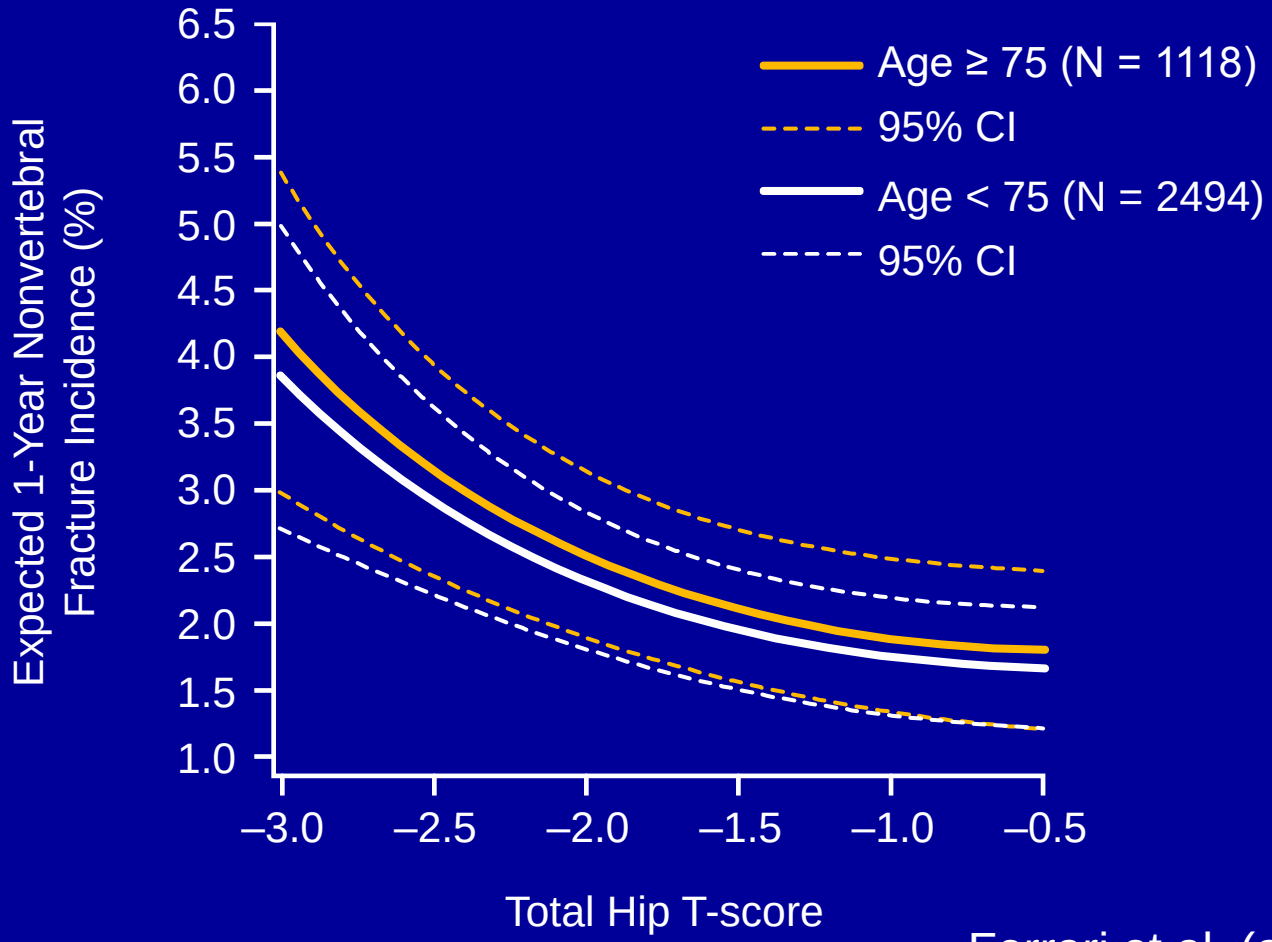
aBMD vs CT-derived hip strength (FEA) and incident hip fractures



Case-control study, 5 yrs follow-up, from the AGES-Reykjavik cohort

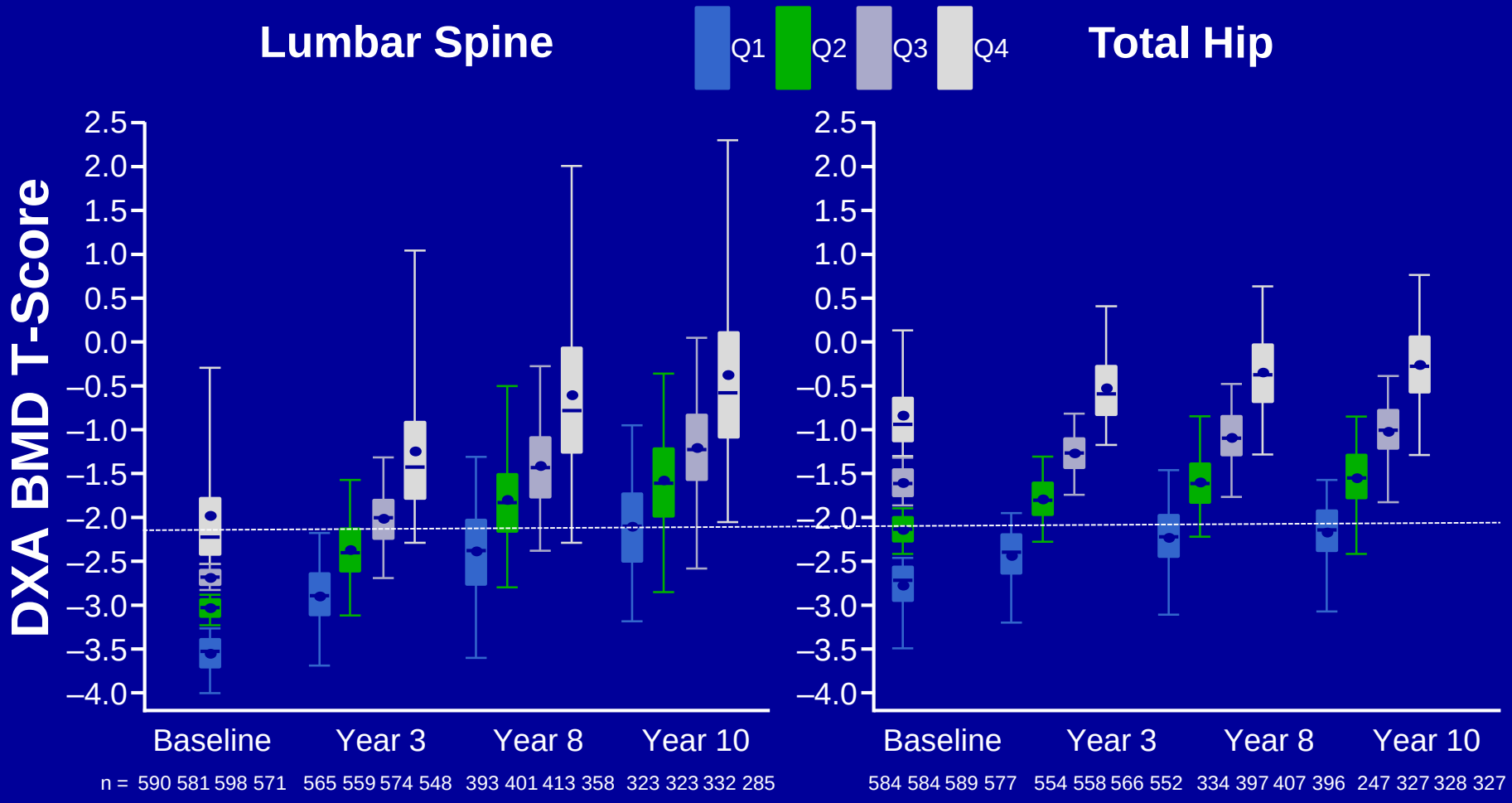
Kopperdahl, JBMR 2014

Relationship Between Total Hip T-score and Nonvertebral Fracture by Age in denosumab-treated subjects: Freedom extension



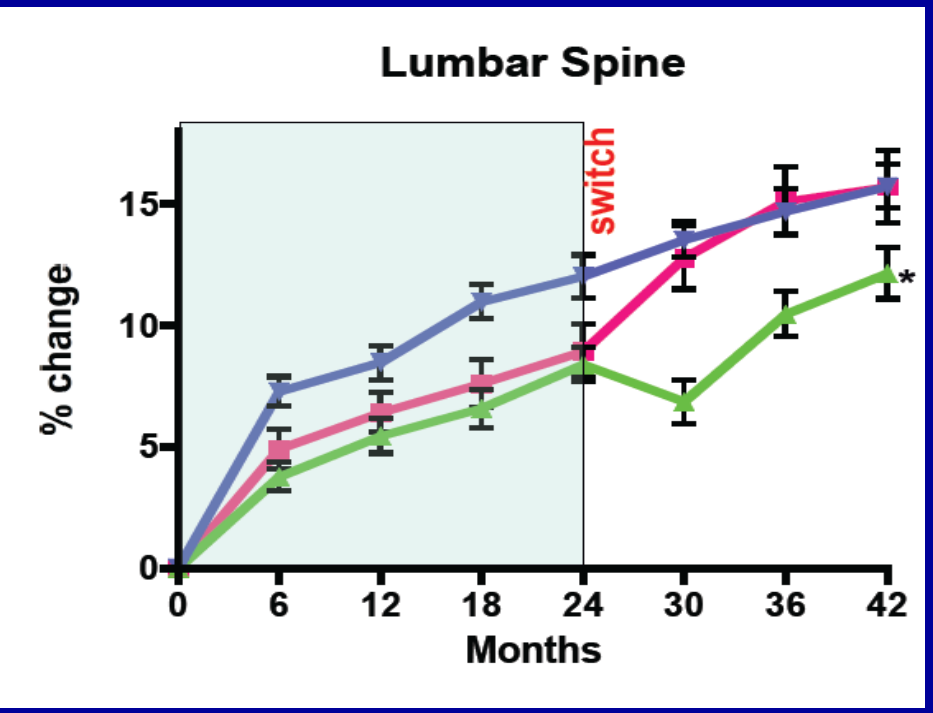
Ferrari et al. (*submitted)*

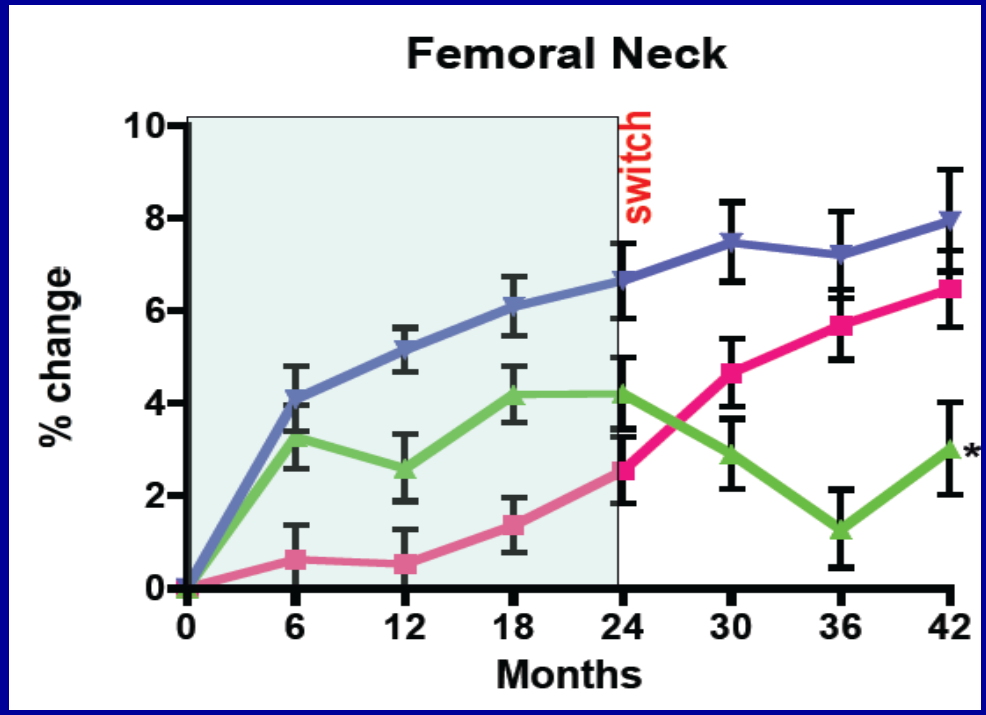
Improvement in BMD T-scores Remained Largely Consistent With the Respective Baseline BMD T-score Quartile



- The T-scores showed a similar magnitude of improvement in BMD across subjects regardless of their initial BMD

Transition from Denosumab to TPTD or from TPTD to Denosumab in Postmenopausal Women with Osteoporosis: The DATA-Switch Study

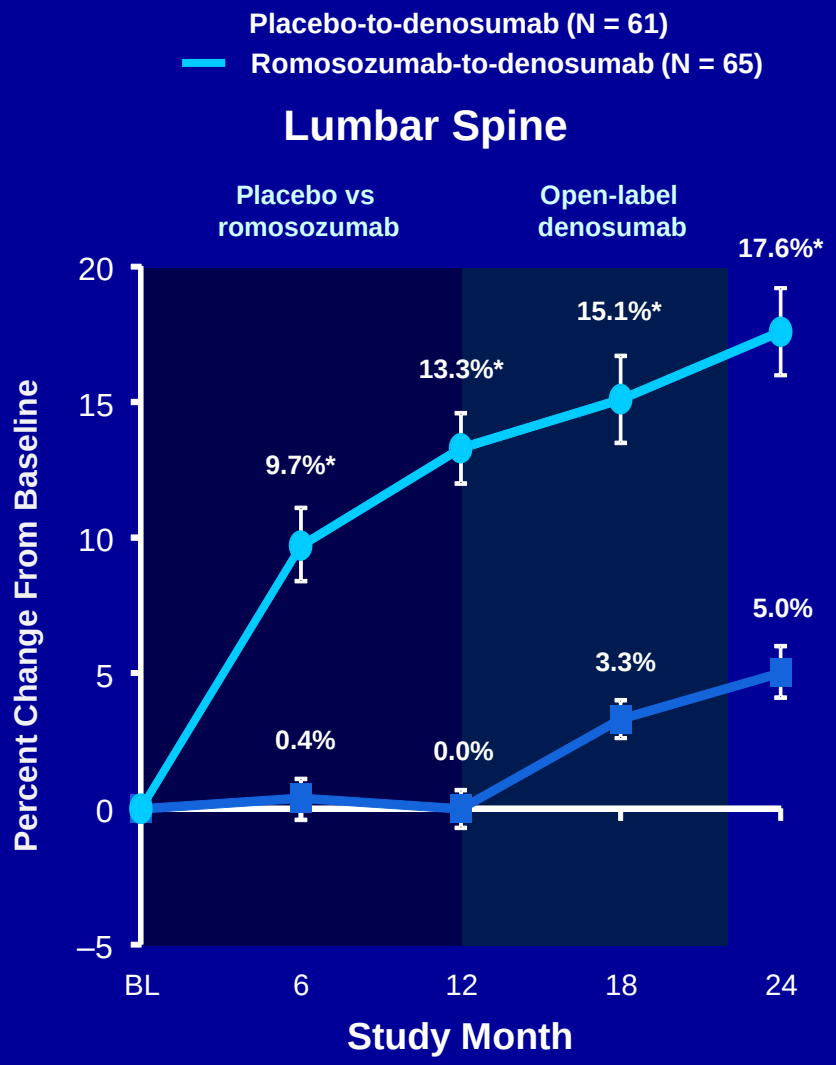


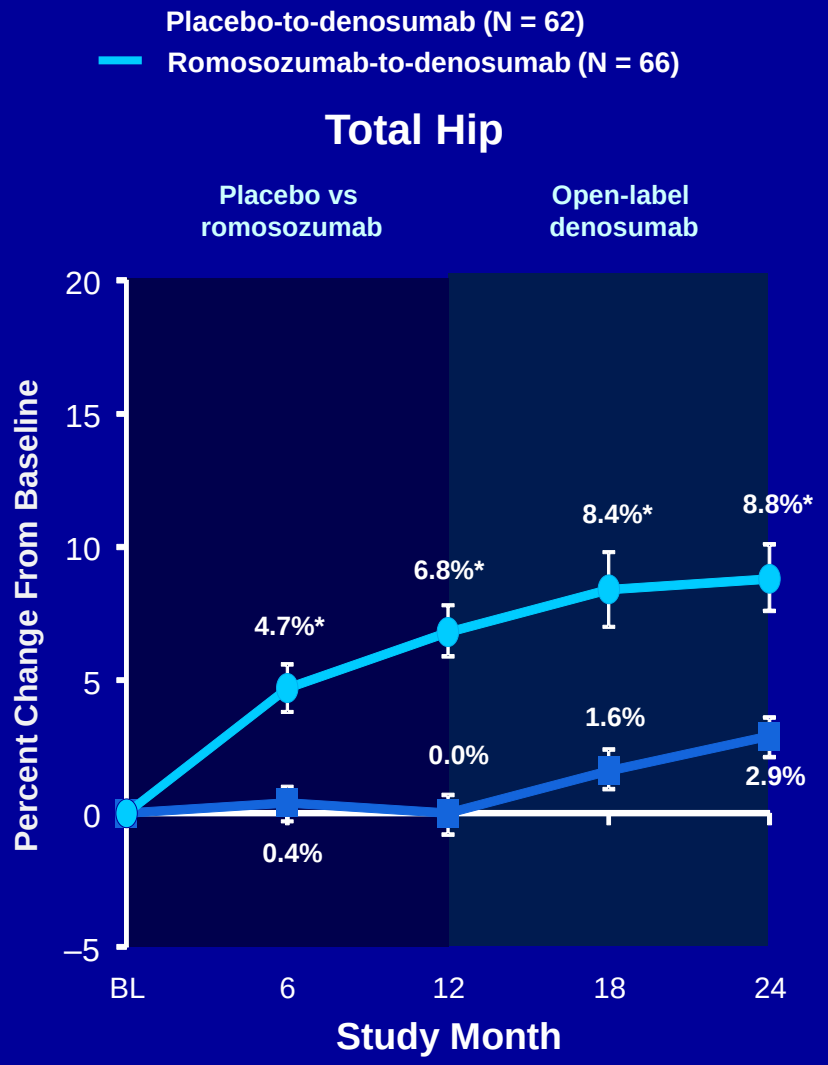


24-mo TPTD, 18-mo DMAB
24-mo DMAB, 18 mo TPTD
24-mo Both, 18-mo DMAB

Leder et al Lancet 2015

FRAME: Lumbar Spine and Total Hip BMD Through Month 24





*p < 0.001 compared with placebo (M6 and M12) or placebo/denosumab (M18 and M24)
Data are least square mean (95% CI) adjusted for relevant baseline covariates

Cosman, NEJM 2016

Conclusions

- DMO très basse avant la ménopause:
  - faible pic de masse osseuse > hyperremodellage
  - cause 2re ou génétique > OP idiopathique ou constitution maigre
  - Dans la mesure du possible traiter la cause
  - Traiter l'OP…si évidence de remodellage très haut ou bas (role de la biopsie) ou fragilité osseuse avérée

- DMO très basse après la ménopause:
  - hyperremodellage presque toujours en cause
  - Altérations microstructurelles cohérentes avec la DMO (=vraie définition de l'OP)
  - Traitements séquentiels ou combinés AR + OF