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HOW DO I SCREEN FOR BONE COMPLICATIONS IN ACROMEGALY AND CUSHING DISEASE?

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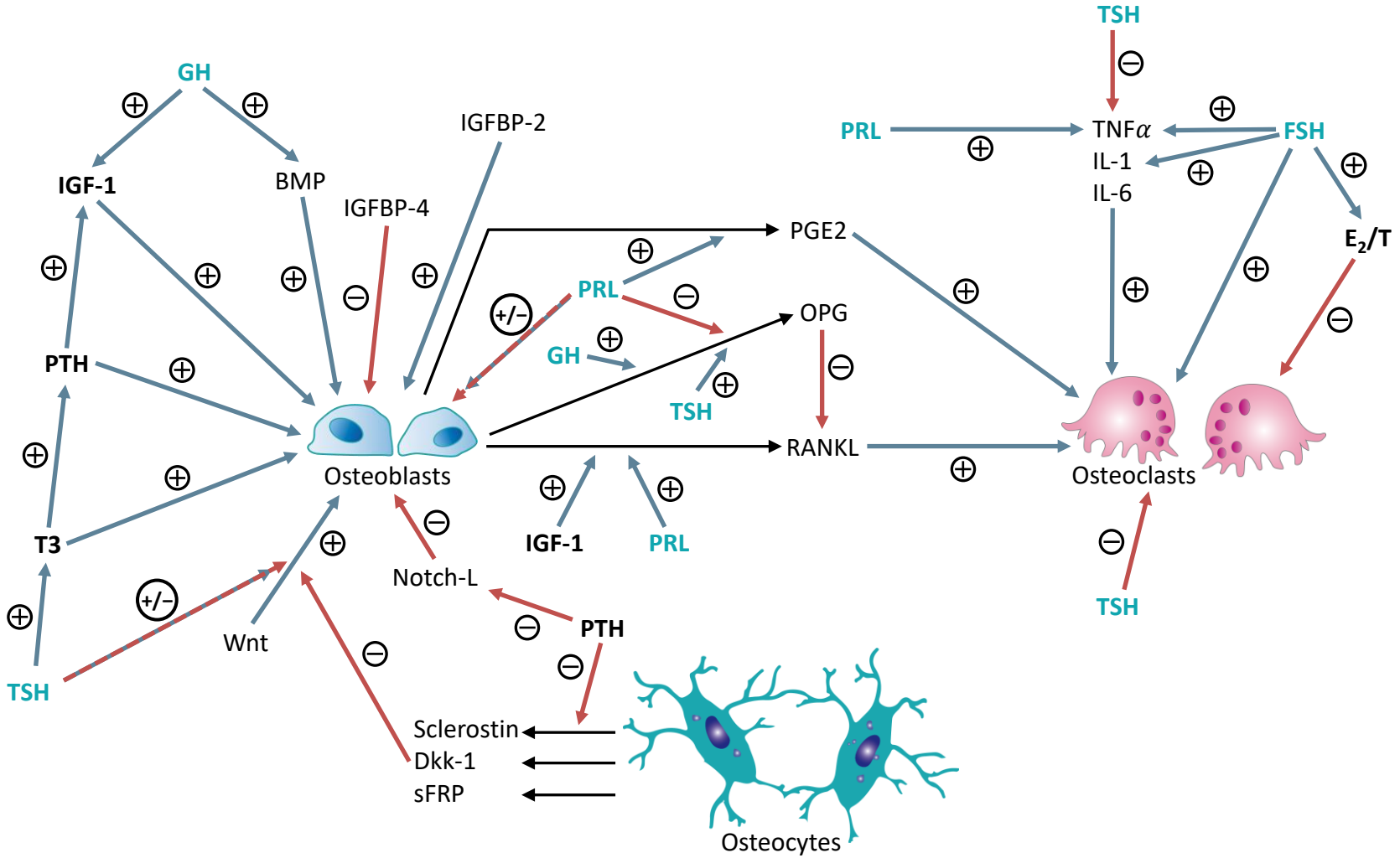
DISCLOSURES

- Dr Frara receives grants and consultancy fees from Ipsen, Novartis and NovoNordisk

PITUITARY HORMONES AND BONE

PHYSIOLOGY

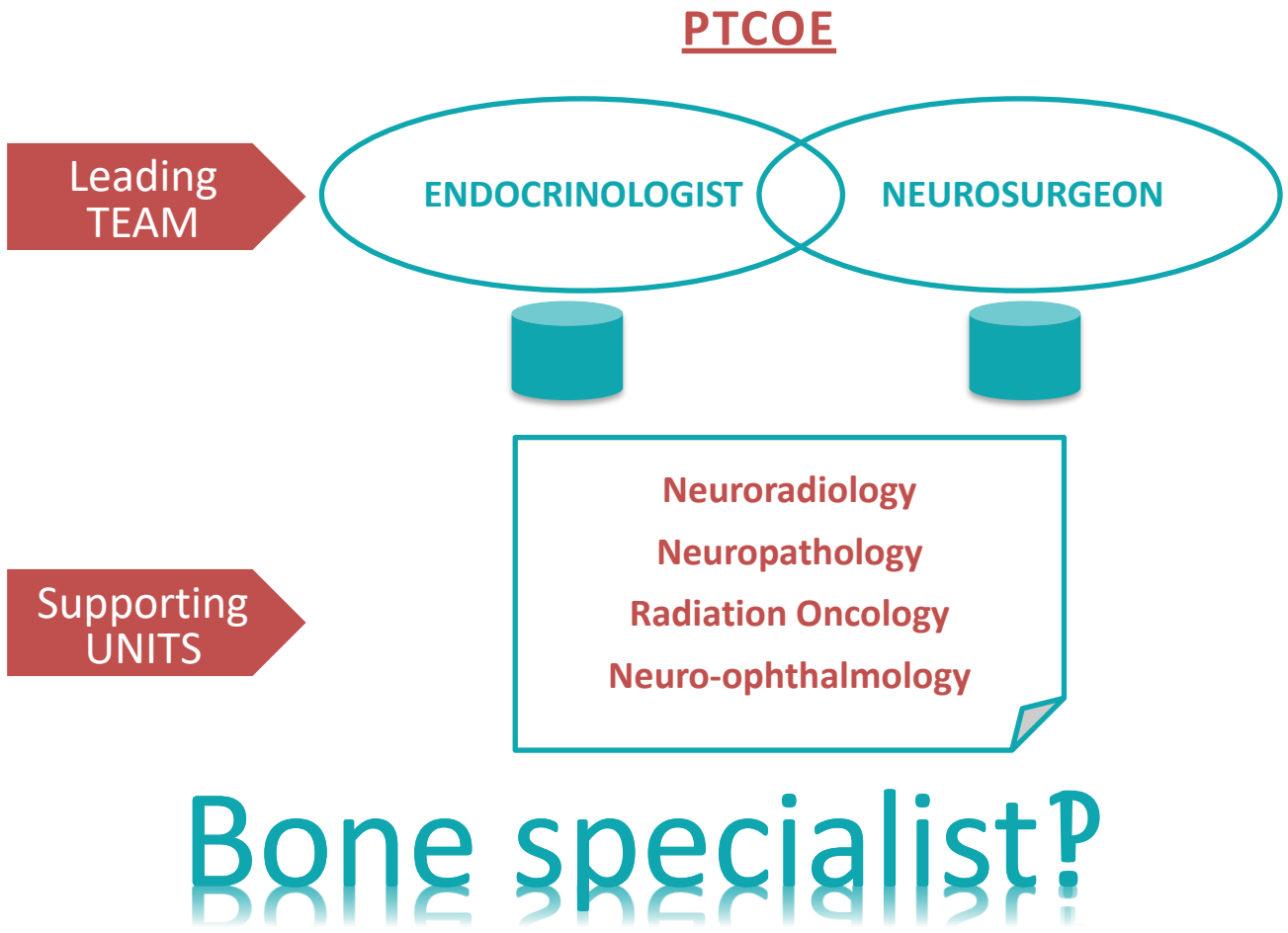


BMP, bone morphogenetic protein; Dkk-1, dickkopf 1; E2, oestradiol; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor 1; IGFBP, insulin-like growth factor-binding protein; IL, interleukin; OPG, osteoprotegerin; PGE2, prostaglandin E2; PRL, prolactin; PTH, parathyroid hormone; RANKL, receptor activator of nuclear factor kappa B ligand; sFRP, secreted frizzled-related protein; T, testosterone; T3, triiodothyronine; TNFα, tumor necrosis factor α; TSH, thyroid-stimulating hormone; Wnt, Wingless-Int

Mazziotti G, et al. Endocr Rev. 2018;39(4):440-88

PITUITARY TUMORS CENTERS OF EXCELLENCE

GENERAL STRUCTURE



PTCOE, Pituitary Tumors Centers of Excellence

Casanueva FF, et al. Pituitary. 2017;20(5):489-98

BONE SPECIALIST IN THE PTCOE

OUR DIAGNOSTIC TOOLS

Bone turnover markers

Markers of bone formation are enzymes and proteins produced by osteoblasts during different phases of their activity

Markers of bone resorption are the products derived from bone degradation process

Bone formation markers	Bone resorption markers
PINP	**Serum CTX**
Osteocalcin	Urinary NTX
Bone-specific ALP	TRAP

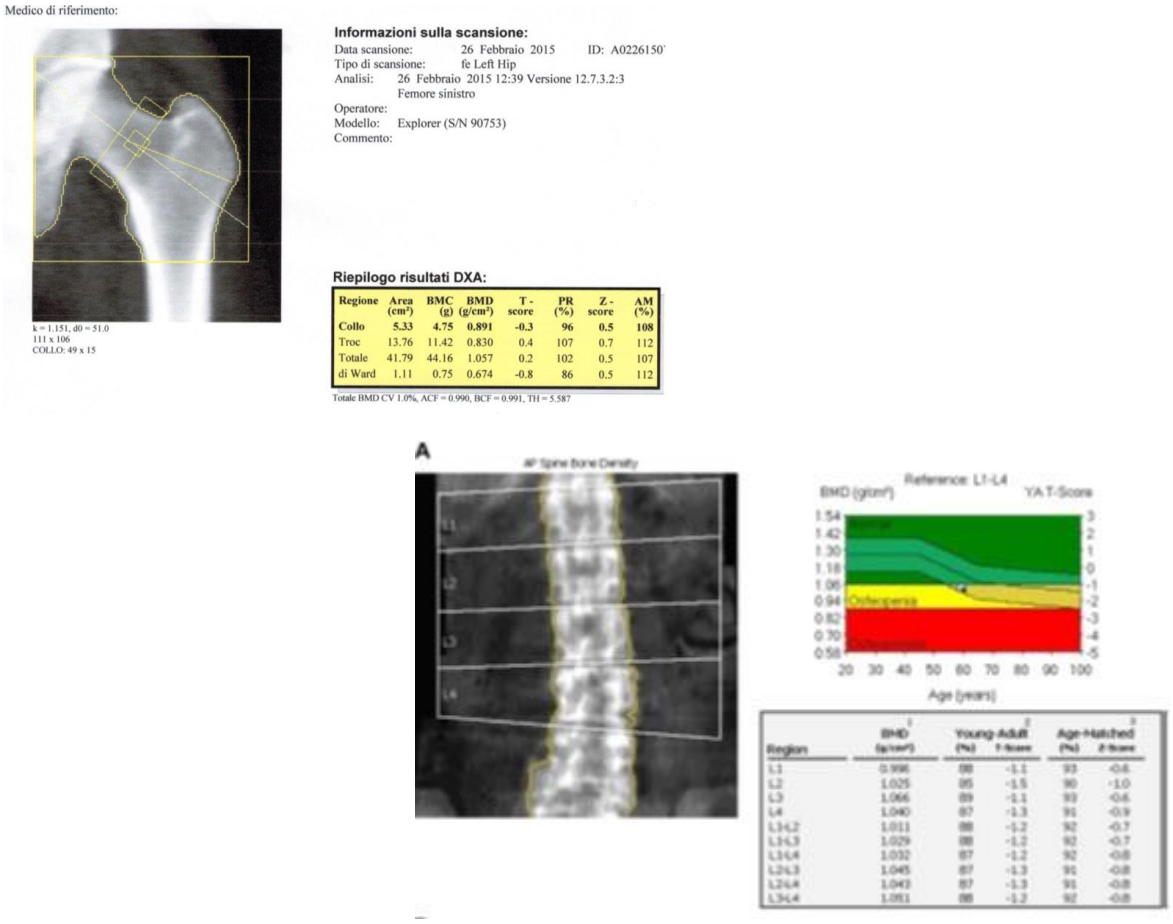
ALP, alkaline phosphatase; CTX, cross-linked C-telopeptide of type I collagen; NTX, cross-linked N-telopeptide of type I collagen; PINP, procollagen type I N-terminal propeptide; PTCOE, Pituitary Tumors Centers of Excellence; TRAP, tartrate-resistant acid phosphatase

Mazziotti G, et al. Endocr Rev. 2018;39(4):440-88

BONE SPECIALIST IN THE PTCOE

OUR DIAGNOSTIC TOOLS

Bone mineral density (BMD)



How can we define osteoporosis?

Patients ≥50 years

T-score (SD)	Diagnosis
> −1	Normal BMD
−1 to −2.5	Osteopenia
< −2.5	Osteoporosis

Patients <50 years

Z-score (SD)	Diagnosis
> −2.0	Normal BMD
≤ −2.0	BMD below the expected range for age

BMD, bone mineral density; PTCOE, Pituitary Tumors Centers of Excellence; SD, standard deviation

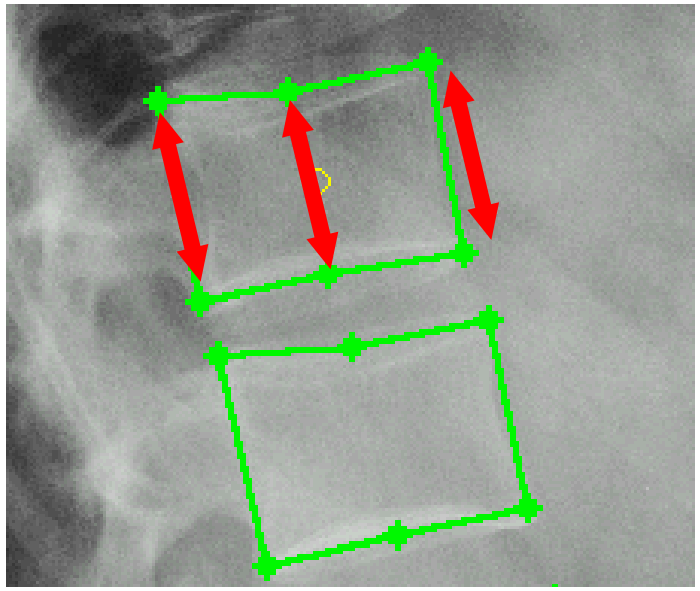
Cover (10.5mm) (who.int) WHO Prevention and management of osteoporosis 2003; Keen MU, Reddivari AKR. 2021. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 32644582.

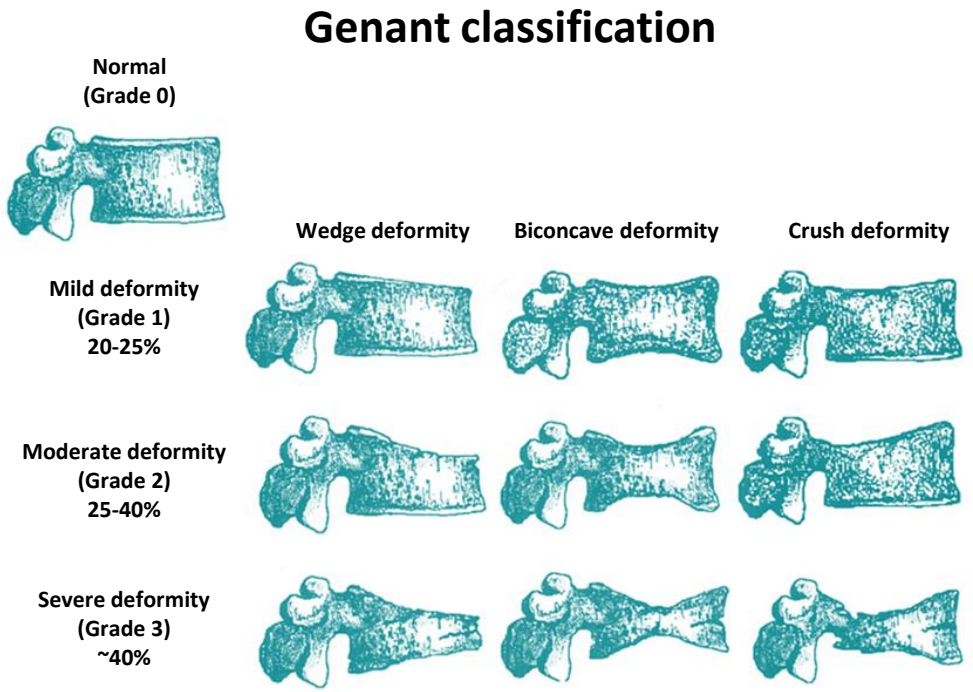
BONE SPECIALIST IN THE PTCOE

OUR DIAGNOSTIC TOOLS

Vertebral morphometry

How can we detect a fracture?





The bone specialist could perform vertebral morphometry on X-ray, DXA or MRI scans of the spine

DXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging; PTCOE, Pituitary Tumors Centers of Excellence

Genant HK, et al. J Bone Miner Res. 1993;8(9):1137-48; Unpublished, Frara, S.

CUSHING DISEASE

SYSTEMIC COMPLICATIONS

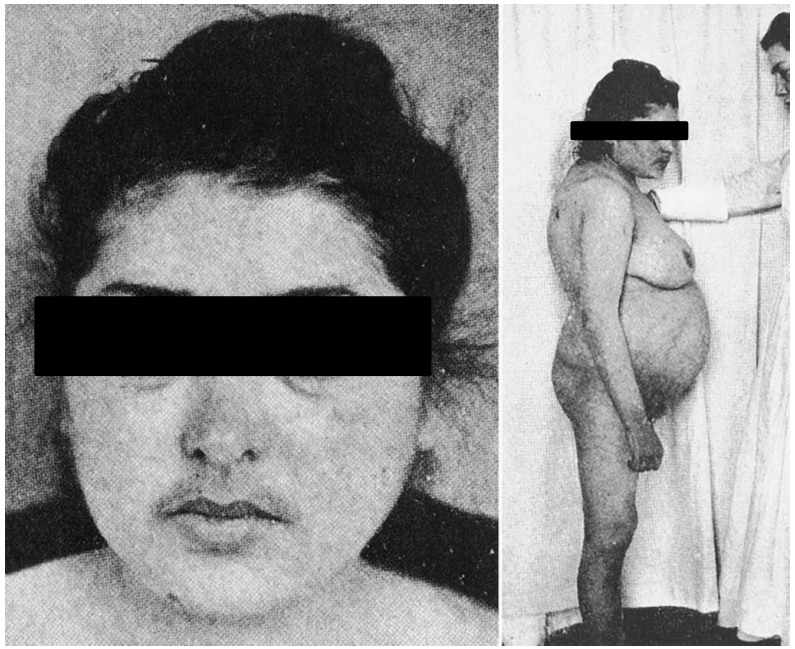


TABLE 1. Overlapping conditions and clinical features of Cushing's syndrome[a]

Symptoms	Signs	Overlapping conditions
Features that best discriminate Cushing's syndrome; most do not have a high sensitivity		
	Easy bruising	
	Facial plethora	
	Proximal myopathy (or proximal muscle weakness)	
	Striae (especially if reddish purple and > 1 cm wide)	
	In children, weight gain with decreasing growth velocity	
Cushing's syndrome features in the general population that are common and/or less discriminatory		
Depression	Dorsocervical fat pad ("buffalo hump")	Hypertension[b]
Fatigue	Facial fullness	Incidental adrenal mass
Weight gain	Obesity	Vertebral osteoporosis[b]
Back pain	Supraclavicular fullness	Polycystic ovary syndrome
Changes in appetite	Thin skin[b]	Type 2 diabetes[b]
Decreased concentration	Peripheral edema	Hypokalemia
Decreased libido	Acne	Kidney stones
Impaired memory (especially short term)	Hirsutism or female balding	Unusual infections
Insomnia	Poor skin healing	
Irritability		
Menstrual abnormalities		
In children, slow growth	In children, abnormal genital virilization	
	In children, short stature	
	In children, pseudoprecocious puberty or delayed puberty	

[a] Features are listed in random order.

[b] Cushing's syndrome is more likely if onset of the feature is at a younger age.

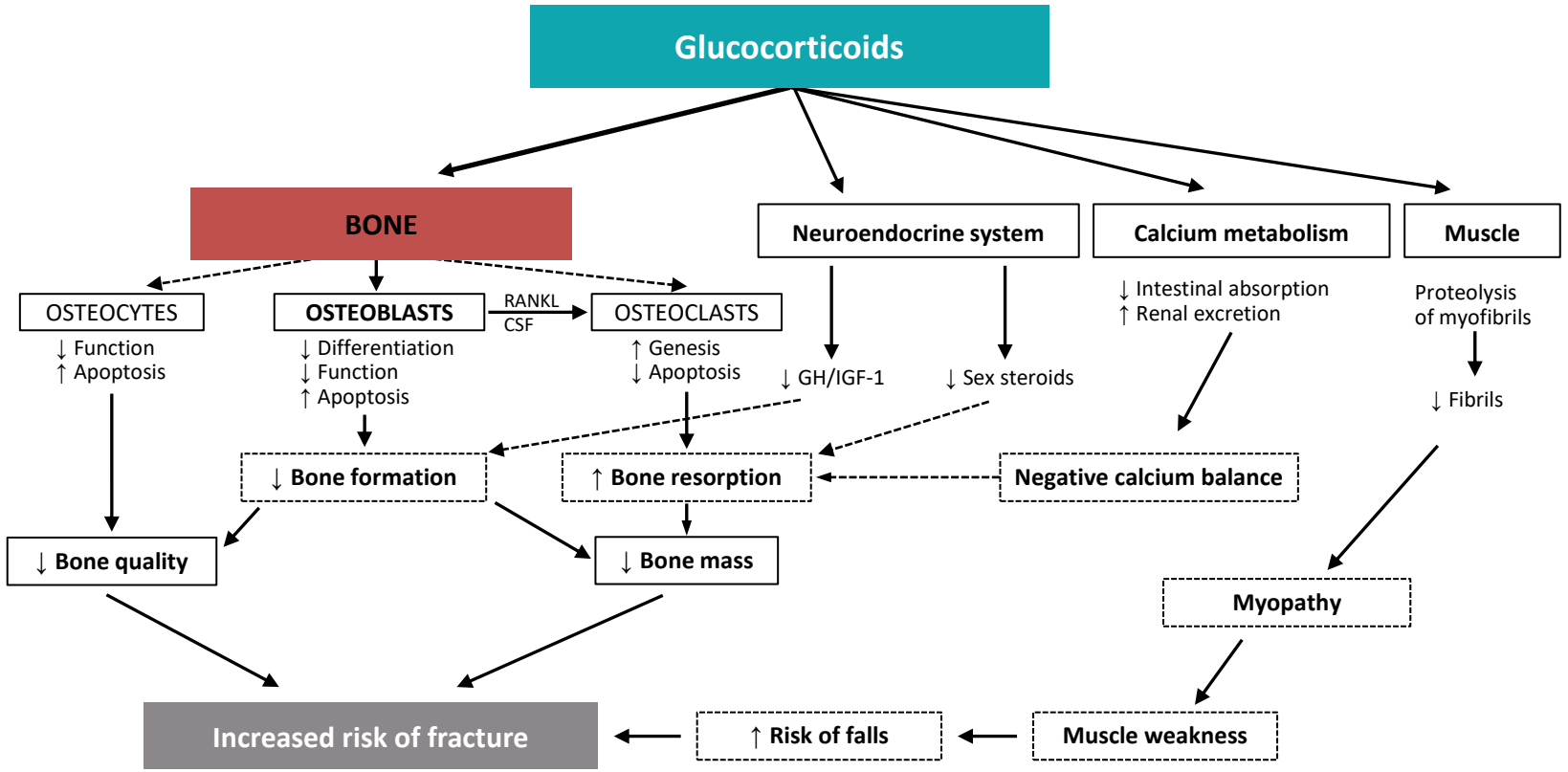
- Osteoporosis and fragility fractures are amongst the most severe systemic complications
- Untreated → significant morbidity and mortality

CNS, central nervous system; FSH, follicle-stimulating hormone; GH, growth hormone; GI, gastrointestinal; LH, luteinising hormone; TSH, thyroid-stimulating hormone

Nieman LK, et al. J Clin Endocrinol Metab. 2008;93(5):1526-40

CUSHING DISEASE AND BONE

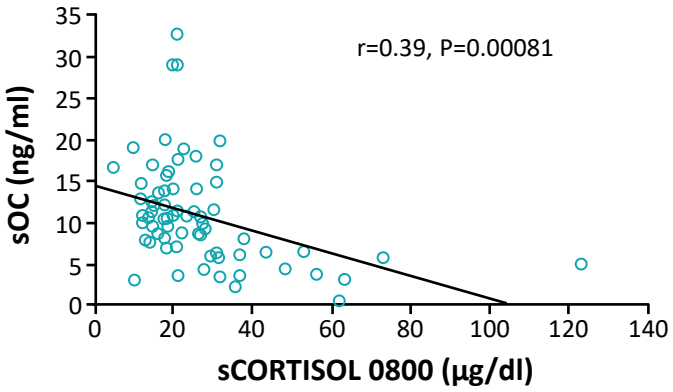
PATHOPHYSIOLOGY

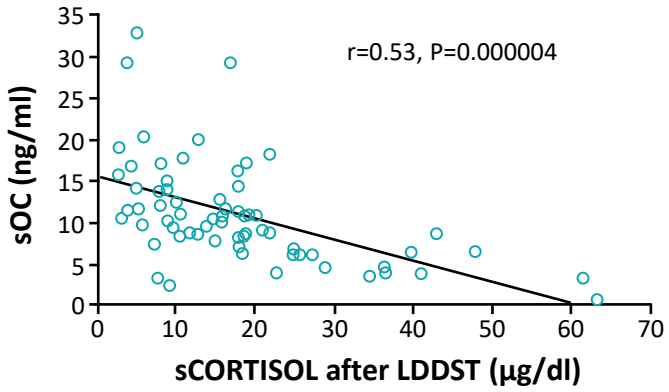


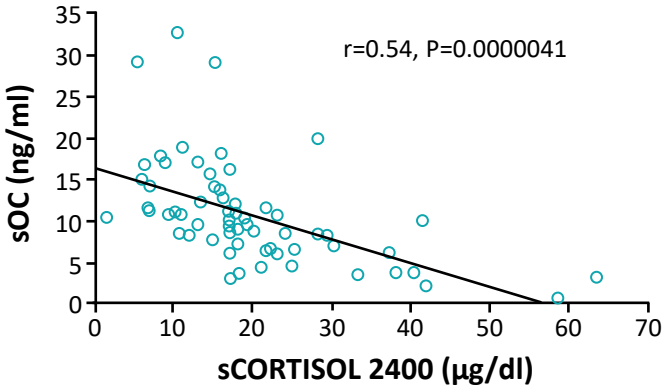
CSF, colony stimulating factor; IGF-1, insulin-like growth factor 1; GH, growth hormone; RANKL, receptor activator of nuclear factor kappa B ligand
Modified from Canalis E, et al. Osteoporos Int. 2007;18(10):1319-28

CUSHING DISEASE AND BONE

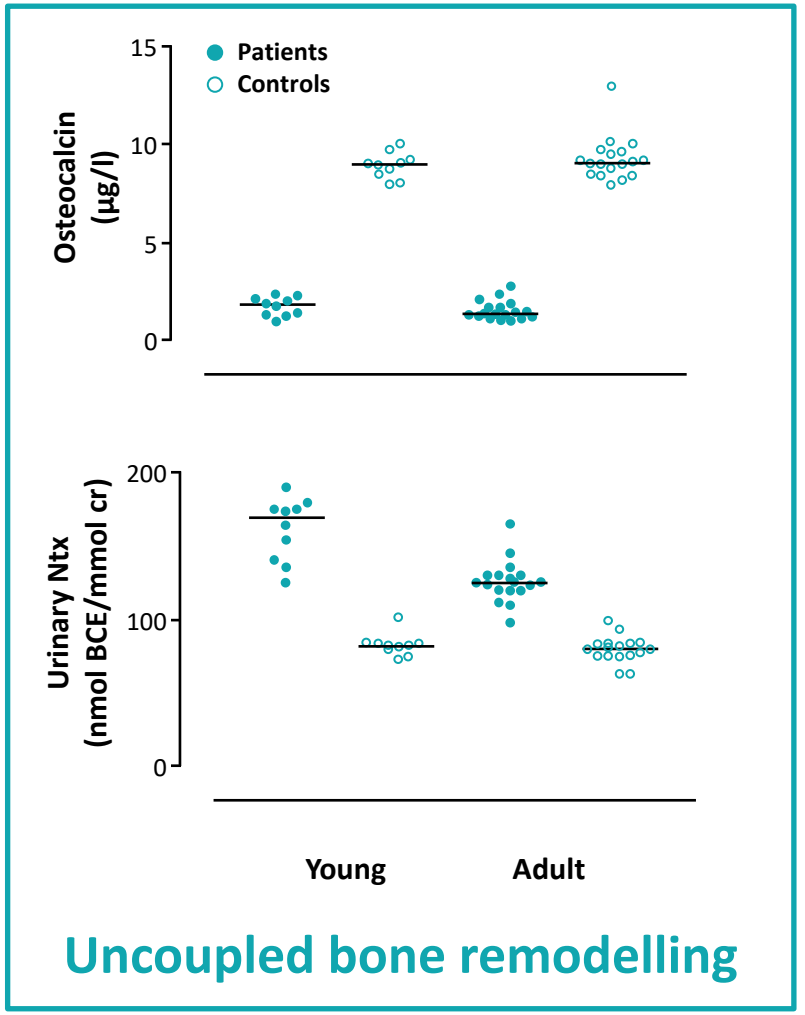
BONE TURNOVER MARKERS







The consistent relationship with cortisol concentration in CS makes osteocalcin a potential marker of GC activity and perhaps disease severity in patients with endogenous CS



Uncoupled bone remodelling

BCE, bone collagen equivalents; cr, creatinine; CS, Cushing's syndrome; GC, glucocorticoid; LDDST, low-dose dexamethasone suppression test; Ntx, cross-linked N-telopeptide of type I collagen; r, regression; s, serum; sOC, serum osteocalcin

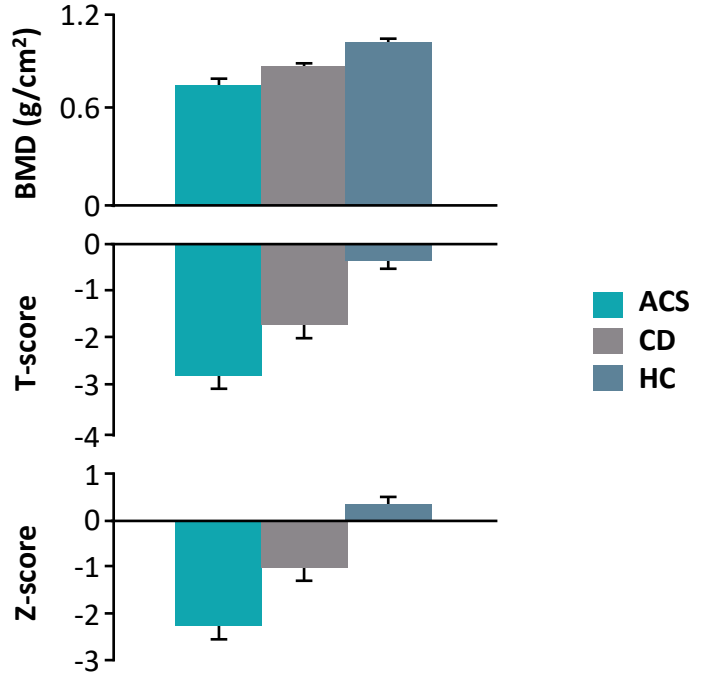
Szappanos A, et al. Osteoporos Int. 2010;21(4):637-45; Di Somma C, et al. Clin Endocrinol (Oxf). 2002;56(2):153-8

CUSHING DISEASE AND BONE

BMD

Bone mineral density in patients with Cushing's syndrome and control group

	CS N=135 Mean ± SD	Control N=108 Mean ± SD	P
Age, years	50.3 ± 13.4	48.7 ± 12.9	0.261
F/M, n	111/24	77/30	0.063
BMI, kg/m²	33.2 ± 6.9	32.0 ± 5.7	0.167
Femoral neck BMD, g/cm²	0.897 ± 0.151	0.963 ± 0.133	**0.001**
Femoral neck Z-score	−0.349 ± 1.153	0.155 ± 0.971	**<0.001**
Lumbar spine BMD, g/cm²	1.087 ± 0.173	1.150 ± 0.162	**0.007**
Lumbar spine Z-score	−0.426 ± 1.332	0.053 ± 1.258	**0.004**



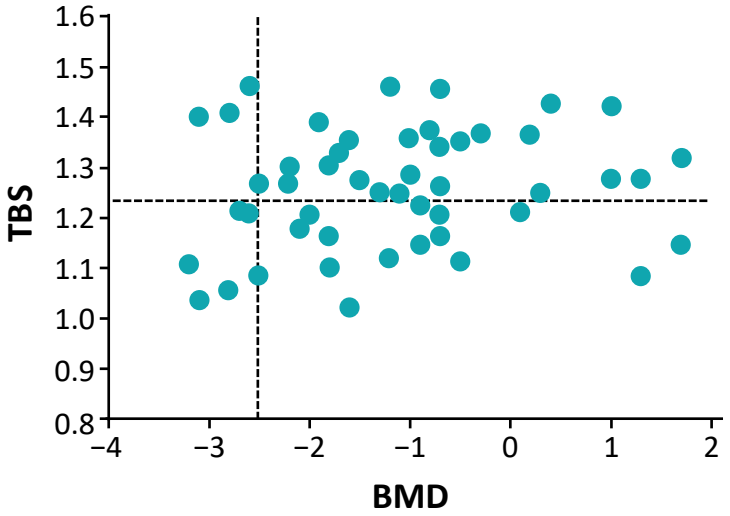
ACS, adrenal-dependent Cushing's syndrome;
CD, Cushing disease; HC, healthy control patients

BMD, bone mineral density; BMI, body mass index; CS, Cushing's syndrome; F/M, female/male; SD, standard deviation

Apaydin T, et al. J Endocrinol Invest. 2021;44(8):1767-73; Minetto M, et al. Osteoporos Int. 2004;15(11):855-61

CUSHING DISEASE AND BONE

BONE QUALITY: TBS



Lumbar spine bone mineral density T-score (BMD) and trabecular bone score (TBS) in patients with overt Cushing's syndrome. The vertical dotted line indicates the BMD threshold for osteoporosis (T-score < −2.5 standard deviation). The horizontal dotted line indicates the 1.23 threshold for TBS indicating a degraded microarchitecture

- In both exogenous and endogenous hypercortisolism, osteoporotic fractures frequently occur despite normal or only slightly decreased BMD
- Decreased bone strength mainly due to **qualitative** deterioration of bone tissue
- **TBS** (a marker of bone trabecular microarchitecture) might have a better role in the assessment of fracture risk in conditions of secondary osteoporosis than BMD

BMD, bone mineral density; TBS, trabecular bone score

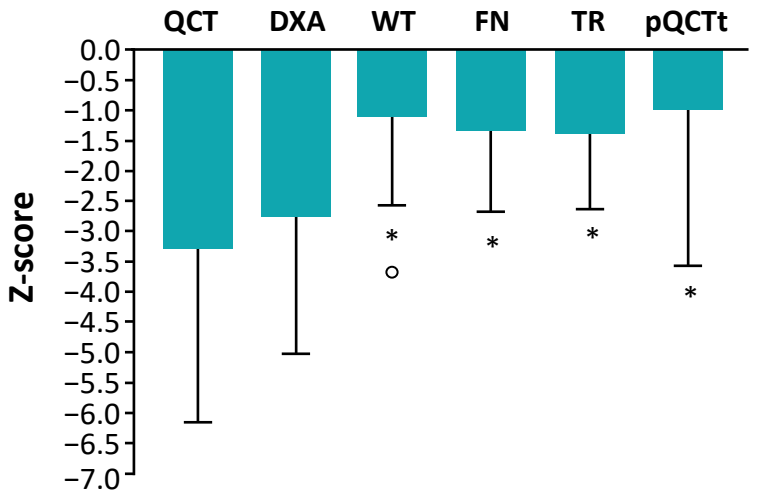
Vinolas H, et al. Clin Endocrinol (Oxf). 2018;89(2):148-54

CUSHING DISEASE AND BONE

BONE QUALITY: pQCT

Comparison between patients with active Cushing's syndrome and controls: HR-pQCT parameters

HR-pQCT parameters		Active CS (N=30)	Controls (N=51)	P value
Total area (mm^2)	Radius	284.05 ± 85.2	279.91 ± 66.1	0.809
Total area (mm^2)	Tibia	672.76 ± 146.9	663.77 ± 127.5	0.774
Total vBMD (g HA/cm^3)	Radius	312.10 ± 68.53	340.03 ± 64.12	0.072
Total vBMD (g HA/cm^3)	Tibia	285.19 ± 81.95	333.71 ± 54.56	**0.002**
Tb area (mm^2)	Radius	235.66 ± 90.5	221.62 ± 66.2	0.428
Tb area (mm^2)	Tibia	557.55 ± 149.6	528.52 ± 120.3	0.344
Tb vBMD (g HA/cm^3)	Radius	165.58 ± 37.98	175.76 ± 35.55	0.239
Tb vBMD (g HA/cm^3)	Tibia	163.81 ± 39.77	173.85 ± 38.21	0.266
BV/TV (%)	Radius	0.14 ± 0.03	0.15 ± 0.03	0.331
BV/TV (%)	Tibia	0.14 ± 0.03	0.14 ± 0.03	0.269
Tb N (mm^{-1})	Radius	2.05 ± 0.30	2.05 ± 0.28	0.895
Tb N (mm^{-1})	Tibia	1.86 ± 0.33	1.85 ± 0.31	0.842
Tb Th (mm)	Radius	0.068 ± 0.01	0.072 ± 0.01	0.257
Tb Th (mm)	Tibia	0.074 ± 0.02	0.079 ± 0.02	0.177
Tb Sp (mm)	Radius	0.43 ± 0.08	0.42 ± 0.07	0.830
Tb Sp t (mm)	Tibia	0.48 ± 0.10	0.48 ± 0.09	0.893
Tb 1/N SD (mm)	Radius	0.181 ± 0.05	0.176 ± 0.04	0.634
Tb 1/N SD (mm)	Tibia	0.22 ± 0.07	0.21 ± 0.07	0.648
Ct area radius (mm^2)	Radius	47.13 ± 16.0	55.29 ± 10.9	**0.009**
Ct area tibia (mm^2)	Tibia	111.29 ± 31.9	132.68 ± 27.0	**0.002**
Ct vBMD (g HA/cm^3)	Radius	975.19 ± 250.37	928.88 ± 110.34	0.340
Ct vBMD (g HA/cm^3)	Tibia	905.68 ± 75.44	947.51 ± 44.28	**0.008**
Ct Th (mm)	Radius	0.68 ± 0.24	0.79 ± 0.18	**0.021**
Ct Th (mm)	Tibia	1.12 ± 0.34	1.35 ± 0.25	**0.002**



Comparison among statistically significant mean Z-score values derived from reduced BMD in CS patients.
Data are the mean ± SD.* P<0.05 vs QCT; ° P<0.05 vs DXA

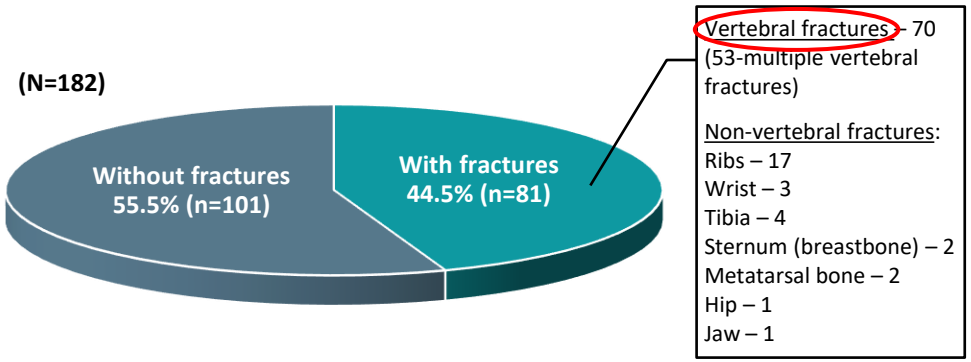
QCT, lumbar vertebral trabecular spine L1-L4 BMD; DXA, lumbar vertebral integral spine L2-L4 BMD; pQCTt, trabecular ultradistal forearm BMD; WT, WT BMD; FN, FN BMD; TR, femoral TR BMD

BMD, bone mineral density; BV/TV, trabecular bone volume to tissue volume (trabecular bone volume fraction); CS, Cushing's syndrome; Ct, cortical; Ct Th, cortical thickness; HA, hydroxyapatite; HR-pQCT; high-resolution pQCT; pQCT, peripheral quantitative computed tomography; Tb N, trabecular number; Tb Sp, trabecular separation; Tb Sp t, trabecular separation at tibia; Tb Sp 1/N SD, standard deviation of the trabecular spacing (heterogeneity of trabecular network); Tb Th, trabecular thickness; vBMD, volumetric bone mineral density

Dos Santos CV, et al. Clin Endocrinol (Oxf). 2015;83(4):468-74; Chiodini I, et al. J Clin Endocrinol Metab. 1998;83(6):1863-7

CUSHING DISEASE AND BONE

VERTEBRAL FRACTURES



Fractures of vertebral bodies were the most frequent and multiple in the vast majority of patients. Here, all types of non-vertebral fractures are reported. Although non-vertebral fractures were only registered in 23 patients, the same patients could have several non-vertebral and both vertebral and non-vertebral fractures. Consequently, the number of fractures exceeds the number of patients

The prevalence and type of fragility fractures in patients with endogenous Cushing's syndrome

- Trabecular bone is particularly vulnerable to the action of GCs
- The spine and femur are both affected, with a **greater involvement of the spine** with respect to forearm and femur

Clinical and biochemical characteristics of patients with adrenal incidentalomas (n=444) with or without a prevalent vertebral fragility (VFx) included in the cross-sectional arm of the study

	Patients without prevalent VFx (n=251)	Patients with prevalent VFx (n=193)	P value
Age (y)	59.5 ± 12.3 (21-89)	64.7 ± 9.5 (32-83)	0.0001
Gender (females)	154 (61.4)	117 (60.6)	0.875
BMI (kg/m²)	29.3 ± 5.1 (19.5-40.9)	29.0 ± 4.5 (20.3-40.9)	0.753
Diameter of the adenoma (cm)	2.4 ± 1.1 (0.8-8.0)	2.8 ± 1.1 (0.8-7.0)	0.0001
1 mg DST (µg/dl)	1.8 ± 1.4 (0.5-9.2)	3.1 ± 2.2 (0.5-12)	0.0001
UFC (µg/24 h)	53.9 ± 29.8 (10.0-169.1)	55.6 ± 34.8 (10.0-175.3)	0.572
ACTH (pg/ml)	14.3 ± 8.7 (2.3-48.3)	11.3 ± 7.7 (1.6-48.3)	0.0001
LS BMD (Z-score)	0.25 ± 1.38 (−3.60 to 3.61)	−0.33 ± 1.39 (−4.50 to 3.61)	0.0001
FN BMD (Z-score)	0.14 ± 1.08 (−2.80 to 5.33)	−0.23 ± 1.02 (−2.80 to 2.70)	0.0001
Patients with type 2 diabetes (%)	42 (16.7)	31 (16.1)	0.850

Data are mean ± SD with range in parentheses or absolute number with percentage in parentheses
SI conversion factors: cortisol after 1 mg DST 27.59, ACTH 0.22, UFC 2.759

Association between the presence of a vertebral fragility fracture and cortisol after 1-mg dexamethasone suppression test or ACTH, age, gender, and lumbar spine bone mineral density

Model 1	OR	P value	95% CI
Age (1-y increase)	1.05	0.0001	1.03-1.07
Gender (female vs male)	1.14	0.574	0.73-1.78
Serum cortisol after 1 mg DST ≥2 µg/dl (presence vs absence	6.07	0.0001	3.92-9.38
LS BMD (1 Z-score decrease)	1.36	0.0001	1.16-1.61
Model 2	**OR**	**P value**	**95% CI**
Age (1-y increase)	1.05	0.0001	1.03-1.08
Gender (male vs female)	1.02	0.900	0.68-1.56
ACTH <10 pg/ml (presence vs absence)	1.10	0.01	1.08-1.20
LS BMD (1 Z-score decrease)	1.38	0.0001	1.18-1.60

SI conversion factor: cortisol after 1 mg DST 27.59

1 mg DST, serum cortisol levels after 1-mg dexamethasone suppression test; ACTH, adrenocorticotrophic hormone; BMI, body mass index; CI, confidence interval; FN BMD, bone mineral density measured by dual x-ray absorptiometry at femoral neck; GC, glucocorticoids; LS BMD, bone mineral density measured by dual x-ray absorptiometry at spine (L1-L4); OR, odds ratio; SD, standard deviation; SI, system of units; UFC, urinary free cortisol; VFx, vertebral fragility

Belaya ZE, et al. Arch Osteoporos. 2015;10:44; Morelli V, et al. J Clin Endocrinol Metab. 2016;101(7):2768-75

CUSHING DISEASE AND BONE

VERTEBRAL FRACTURES + TBS

ORs for the presence of prevalent vertebral fracture in AI patients for the association low LS BMD *plus* low TBS and other potential risk factors using logistic regression analysis

	OR	95% CI	P
Age (1-year increase)	1.05	1.00-1.11	0.05
BMI (1-kg/m^2 decrease)	1.04	0.93-1.16	0.515
Male gender (presence vs absence)	1.10	0.46-2.64	0.829
Low LS-BMD plus low TBS (presence vs absence)	4.37	1.71-11.14	0.002

Low TBS and low BMD were defined on the basis of the cutoffs with the best compromise between sensitivity and specificity obtained by ROC analysis and set at −1.5 for TBS and 0.0 for BMD (both expressed as Z-scores)

ORs for the presence of prevalent vertebral fracture in AI patients for low TBS, low LS-BMD, and other potential risk factors using logistic regression analysis

	OR	95% CI	P
Age (1-year increase)	1.05	0.92-1.05	0.092
BMI (1-kg/m^2 decrease)	1.06	0.97-1.19	0.353
Male gender (absence vs presence)	1.02	0.41-2.52	0.971
Low LS-BMD (presence vs absence	1.77	0.71-4.39	0.221
Low TBS (presence vs absence)	4.80	1.85-12.42	0.001

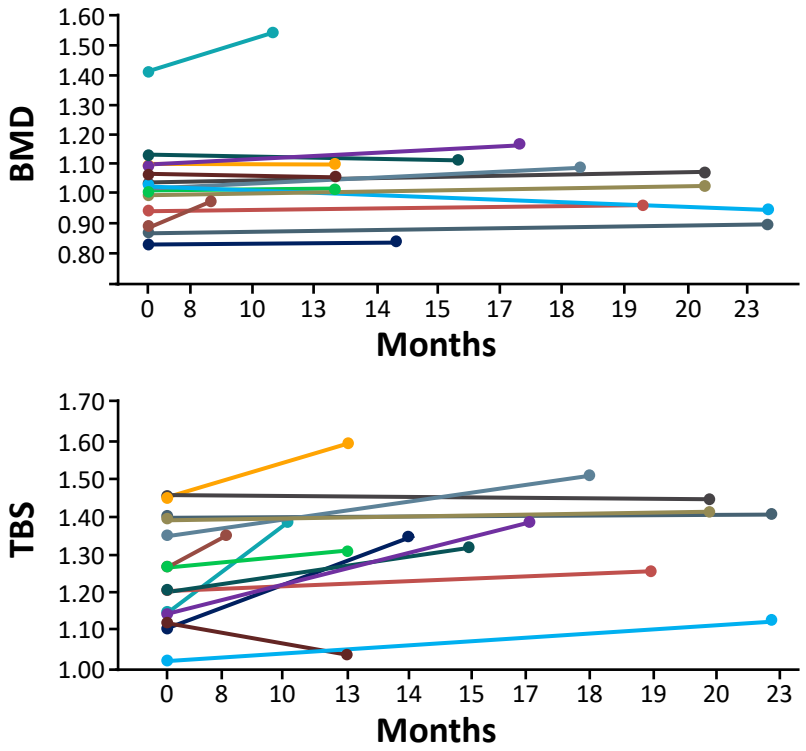
Low TBS and low BMD were defined on the basis of the cutoffs with the best compromise between sensitivity and specificity obtained by ROC analysis and set at −1.5 for TBS and 0.0 for BMD (both expressed as Z-scores)

AI, adrenal incidentaloma; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; LS lumbar spine; OR, odds ratio; ROC, receiver operating characteristic; TBS, trabecular bone score

Eller-Vainicher C, et al. J Bone Miner Res. 2012;27(10):2223-30

CUSHING DISEASE AND BONE

THE DETRIMENTAL EFFECT ON BONE IS REVERSIBLE



Evolution of lumbar spine BMD (expressed in g/cm²) and TBS during the 24 months period following cessation of Cushing's syndrome

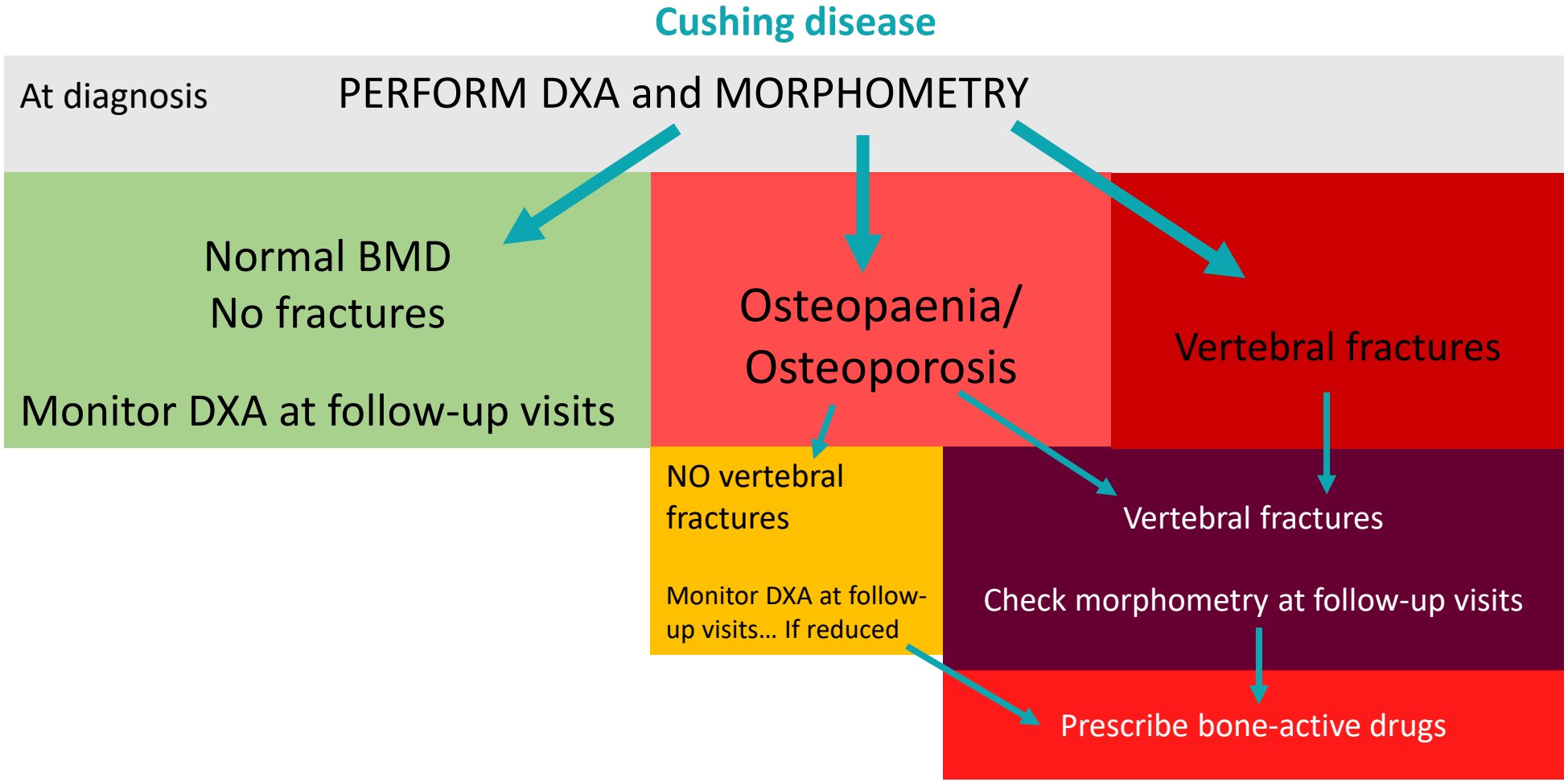
- The recovery starts early after the cure of hypercortisolism
- Even over a long period, some patients do not recover normal bone parameters

BMD, bone mineral density; TBS, trabecular bone score

Vinolas H, et al. Clin Endocrinol (Oxf). 2018;89(2):148-54

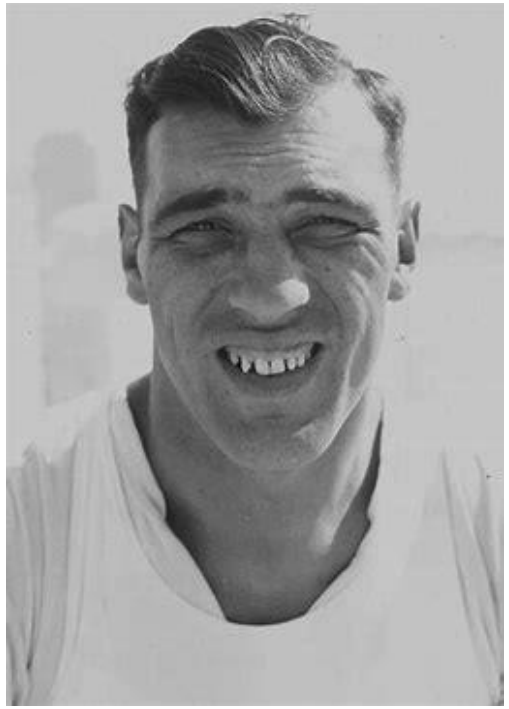
HOW DO I SCREEN FOR BONE COMPLICATIONS?

AN ACTIVE ROLE FOR THE BONE SPECIALIST



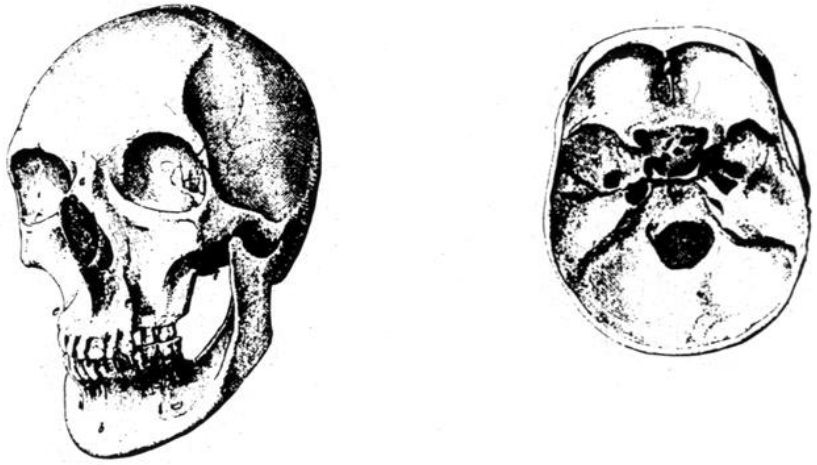
BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry

ACROMEGALY



PRIMO CARNERA

PROSOPECTASIA



Verga A. Caso singolare di prosopectasia. Reale Instituto Lombardo di Scienze e Lettere, Classe Scienze Matematiche e Naturali 1864.

ACROMEGALY AND BONE

BONE TURNOVER MARKERS

Formation

Osteocalcin

↑ Kaji H et al., *Clin Endocrinol* 2001
↑ Ezzat S et al., *J Clin Endocrinol Metab* 1993
↑ Kotzmann et al., *J Bone Miner Res* 1993
↑ Bolanowski et al., *J Bone Miner Metab* 2006
↑ Ueland et al., *Eur J Endocr* 2006

Alkaline phosphatase

↑ Stepan J et al., *Clin Chim Acta* 1979
↑ Kaji H et al., *Clin Endocrinol* 2001

Resorption

U-NTX – CTX-1

↑ Ezzat et al., *J Clin Endocrinol Metab* 1993
↑ Ueland et al., *Eur J Endocr* 2006

Hydroxyprolin – U-DpD

↑ Kotzmann et al., *J Bone Miner Res* 1993
↑ Kaji H et al., *Clin Endocrinol* 2001

↓ Trabecular bone biomechanical competence[1]

CTX-1, cross-linked C-terminal telopeptide of type I collagen; U-DpD, urinary deoxypyridinoline; U-NTX, urinary cross-linked N-terminal telopeptide of type I collagen

Ueland T et al. Eur J Clin Invest. 2002;32(2):122-8.

ACROMEGALY AND BONE

BMD BY DXA

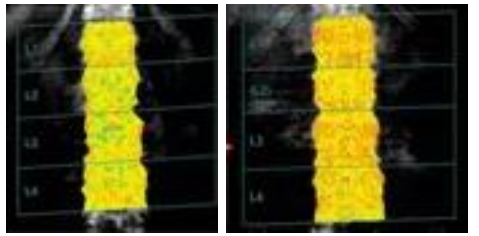
1° Author (year)	Lumbar spine	Hip	Forearm
Seeman (1982)	↑	-	↔
Diamond (1989)	↓	-	↑
Ho (1992)	↔	↔	-
Ezzat (1993)	↓	-	-
Kotzman (1993)	↔↑	↑	-
Kayath (1997)	↔	↔	-
Scillitani (1997)	↑	↑	↔
Longobardi (1998)	↓	-	↔
Lesse (1998)	↔	↔	-
Scillitani (2003)	↑↓	↑	-
Vestergaard (2004)	↑	↑	-
Bonadonna (2005)	↔↓	-	-
Ueland (2006)	↔	↔	↔↓
Mazziotti (2008)	↔↓	↑	-
Sucunza (2009)	↑	-	-
Madeira (2010)	↔	↔	-

OSTEOPOROSIS (T-SCORE ≤ -2.5 SD) OCCURS IN A MINORITY OF PATIENTS!

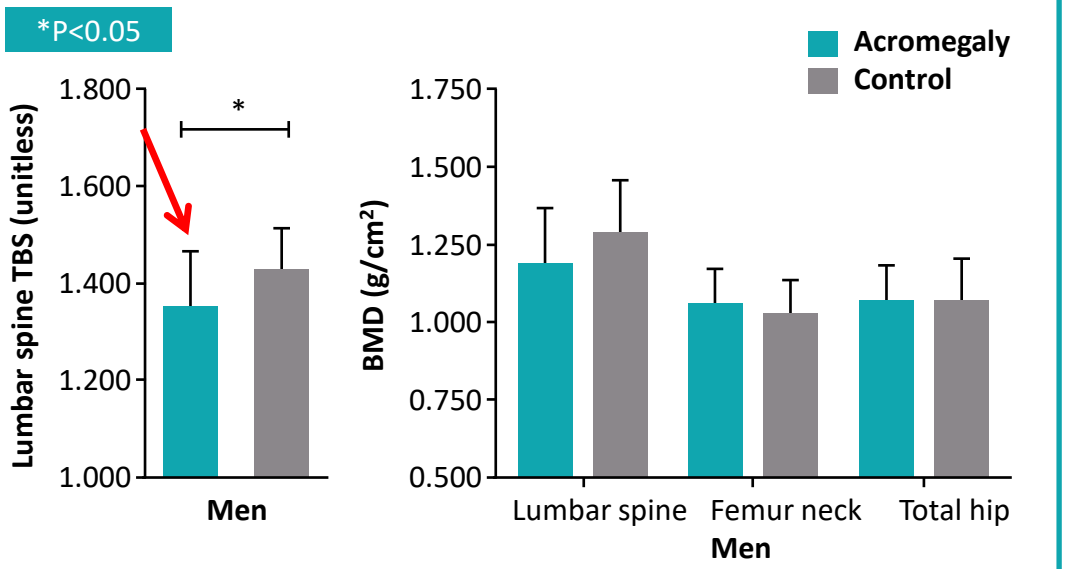
BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; SD, standard deviation
Modified from Mazziotti G, et al. Endocr Rev. 2018;39(4):440-88

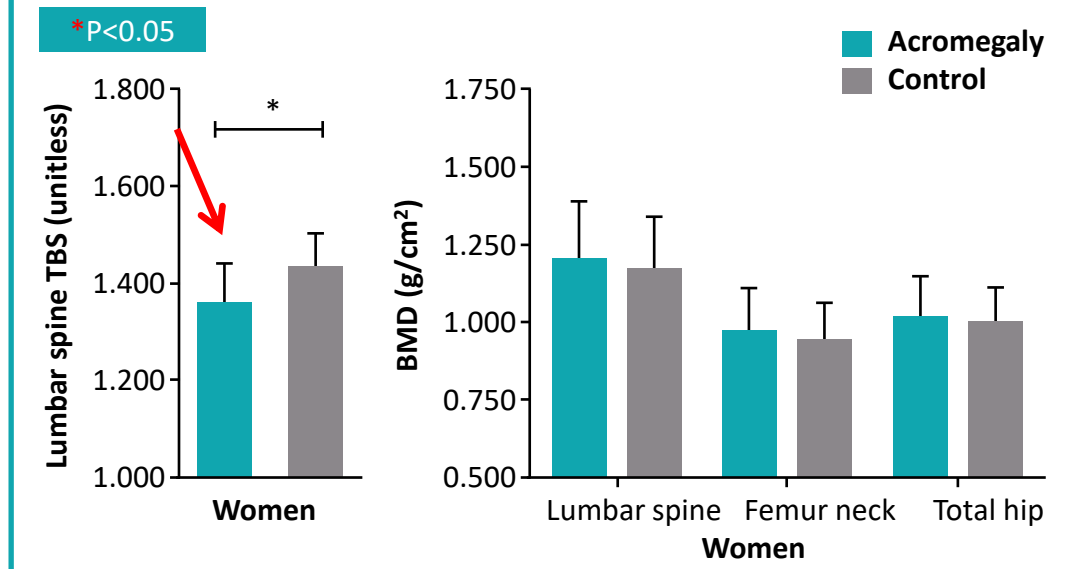
ACROMEGALY AND BONE

EFFECTS ON TRABECULAR STRUCTURE: TBS



Bone quality: Trabecular bone score (TBS)





TBS was found to be lower in male and female acromegaly patients as compared with sex-matched controls, without any difference observed in BMD

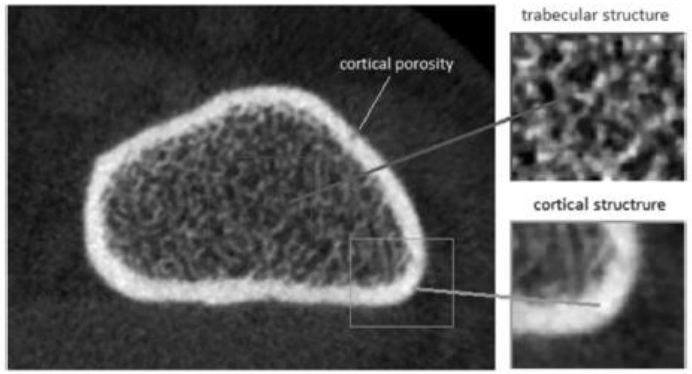
BMD, bone mineral density; TBS, trabecular bone score

Hong AR, et al. Osteoporos Int. 2016;27(3):1123-9; Unpublised, Frara S.

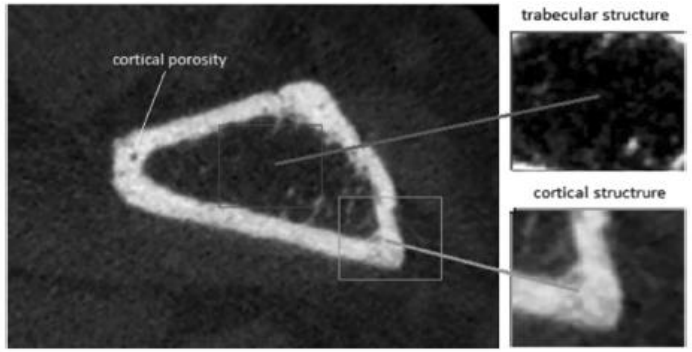
ACROMEGALY AND BONE

EFFECTS ON TRABECULAR AND CORTICAL STRUCTURES: CONE-BEAM CT

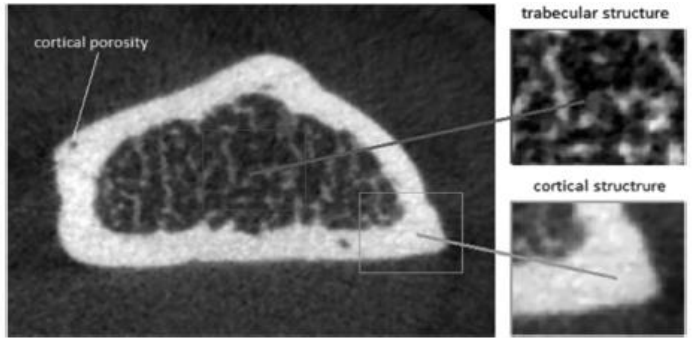
Control



Acromegaly patient WITH VFs



Acromegaly patient WITHOUT VFs



Acromegaly patients with VFs showed a significant impairment in both cortical and trabecular bone parameters as compared with those without VFs

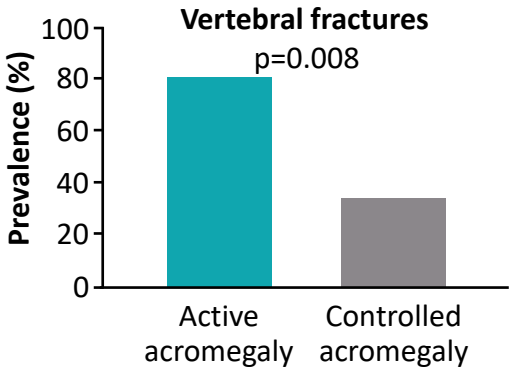
CT, computed tomography; VF, vertebral fracture

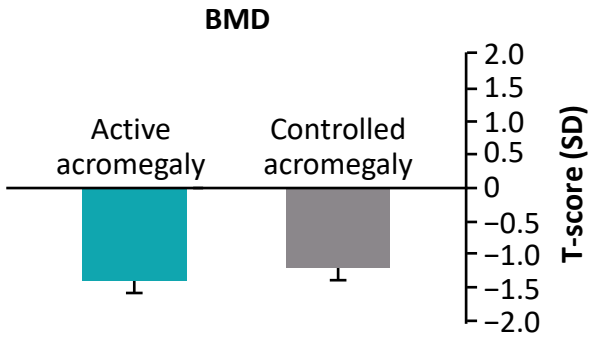
Maffezzoni F, et al. Endocrine. 2016;54(2):532-42

ACROMEGALY AND BONE

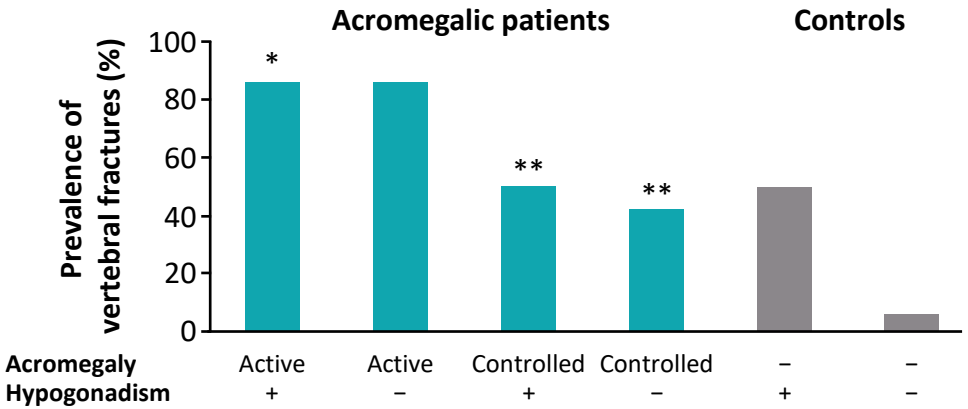
HARD END-POINT: MORPHOMETRIC VERTEBRAL FRACTURES

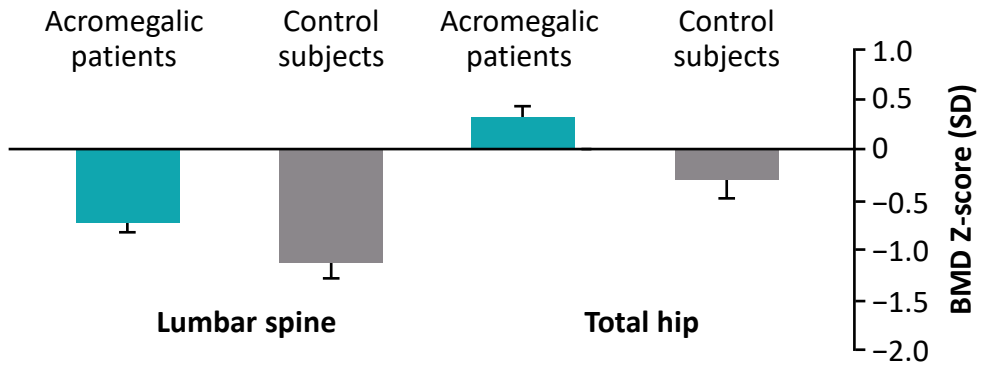
Post-menopausal women





Men





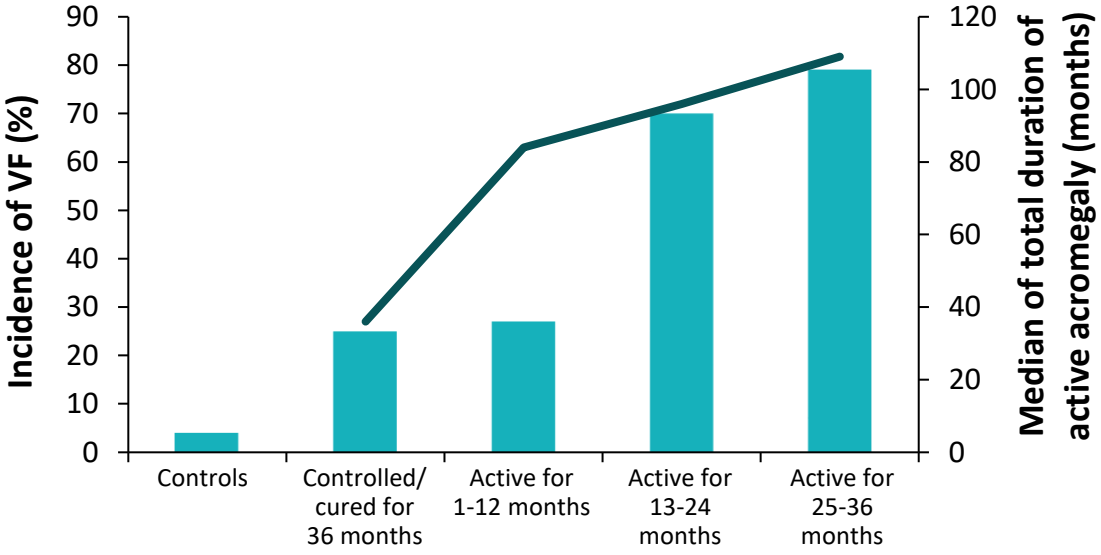
*p<0.05 active acromegaly vs. controlled disease and control subjects, either with or without hypogonadism; **p<0.05 controlled acromegaly vs. control eugonadal subjects

BMD, bone mineral density; SD, standard deviation

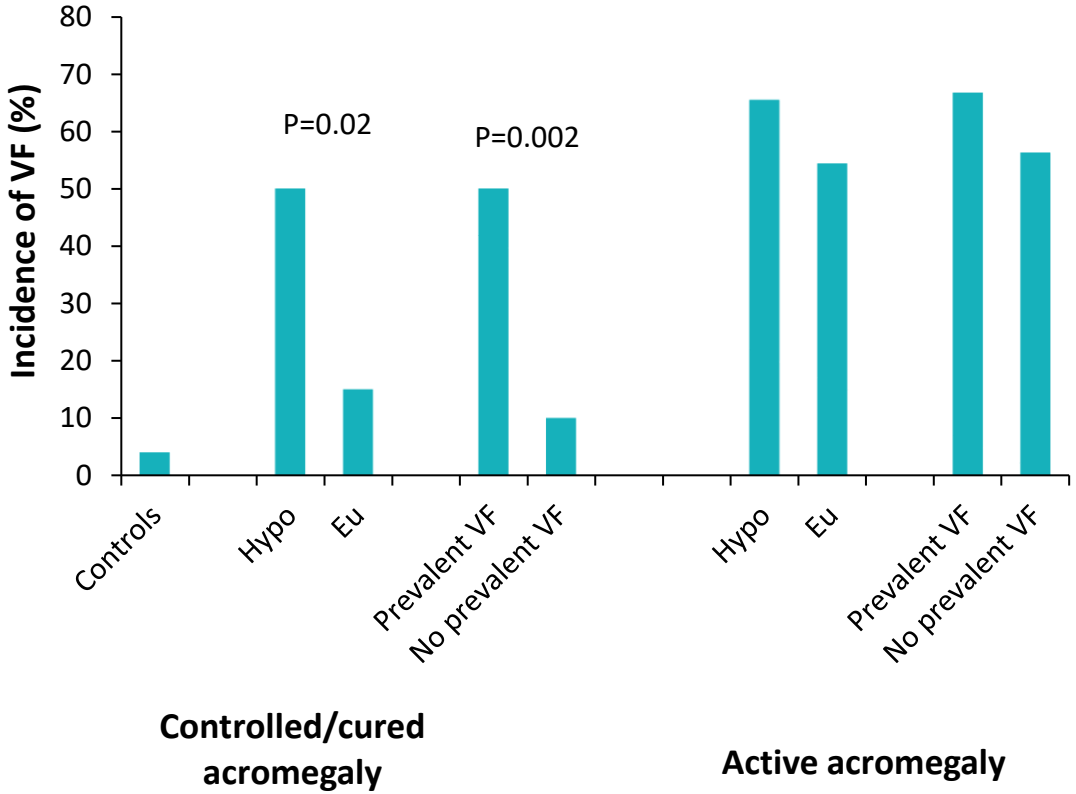
Bonadonna S, et al. J Bone Miner Res. 2005;20(10):1837-44; Mazziotti G, et al. J Clin Endocrinol Metab. 2008;93(12):4649-55

ACROMEGALY AND BONE

INCIDENCE OF VERTEBRAL FRACTURES ARE RELATED TO DISEASE CONTROL



Outcome of acromegaly during 3-year follow-up



Controlled/cured acromegaly

Active acromegaly

Eu, eugonadism; Hypo, hypogonadism; VF, vertebral fracture

Mazziotti G, et al. J Clin Endocrinol Metab. 2013;98(8):3402-10

HOW DO I SCREEN FOR BONE COMPLICATIONS?

AN ACTIVE ROLE FOR THE BONE SPECIALIST

A consensus on the diagnosis and treatment of acromegaly comorbidities: An update

Assessment	Frequency
Cardiovascular disorders	
Blood pressure measurement	At baseline and every 6 months or upon change of antihypertensive treatment
Echocardiography	Annually, if abnormal
Electrocardiogram	Annually, if abnormal
Endocrine and metabolic disorders	
Epworth scale or sleep study	Baseline or before surgery is OSA is suspected
Fasting blood glucose or OGTT	Fasting blood glucose every 6 months, particularly in uncontrolled disease and during SRL therapy; HbA1c every 6 months if diabetes or prediabetes is present
Total testosterone, SHBG, and PRL (males)	Annually; consider testing free testosterone if there are doubts in interpretation of total testosterone
LH, FSH, 17β-oestradiol, and PRL (females)	Annually, in premonopausal females with menstrual dysfunction and when pregnancy is desired
Serum free T4	Annually
Serum 8-9 AM cortisol	If central adrenal insufficiency is suspected; cosyntropin stimulation test if serum cortisol is low
Musculoskeletal disorders	
DXA	Every 2 years particularly is osteopaenia/osteoporosis is present
Vertebral morphometry on thoracic x-ray, thoracic and lumbar spine x-ray	Annually, particularly if history of vertebral fracture, decrease in BMD, kyphosis, symptoms of vertebral fracture, untreated hypogonadism, and no biochemical control of acromegaly
Cancer	
Colonoscopy	Every 10 years; more frequently if IGF-1 remains persistently elevated or if abnormal colonoscopy or family history of colon cancer
Quality of life	
AcroQoL	Annually

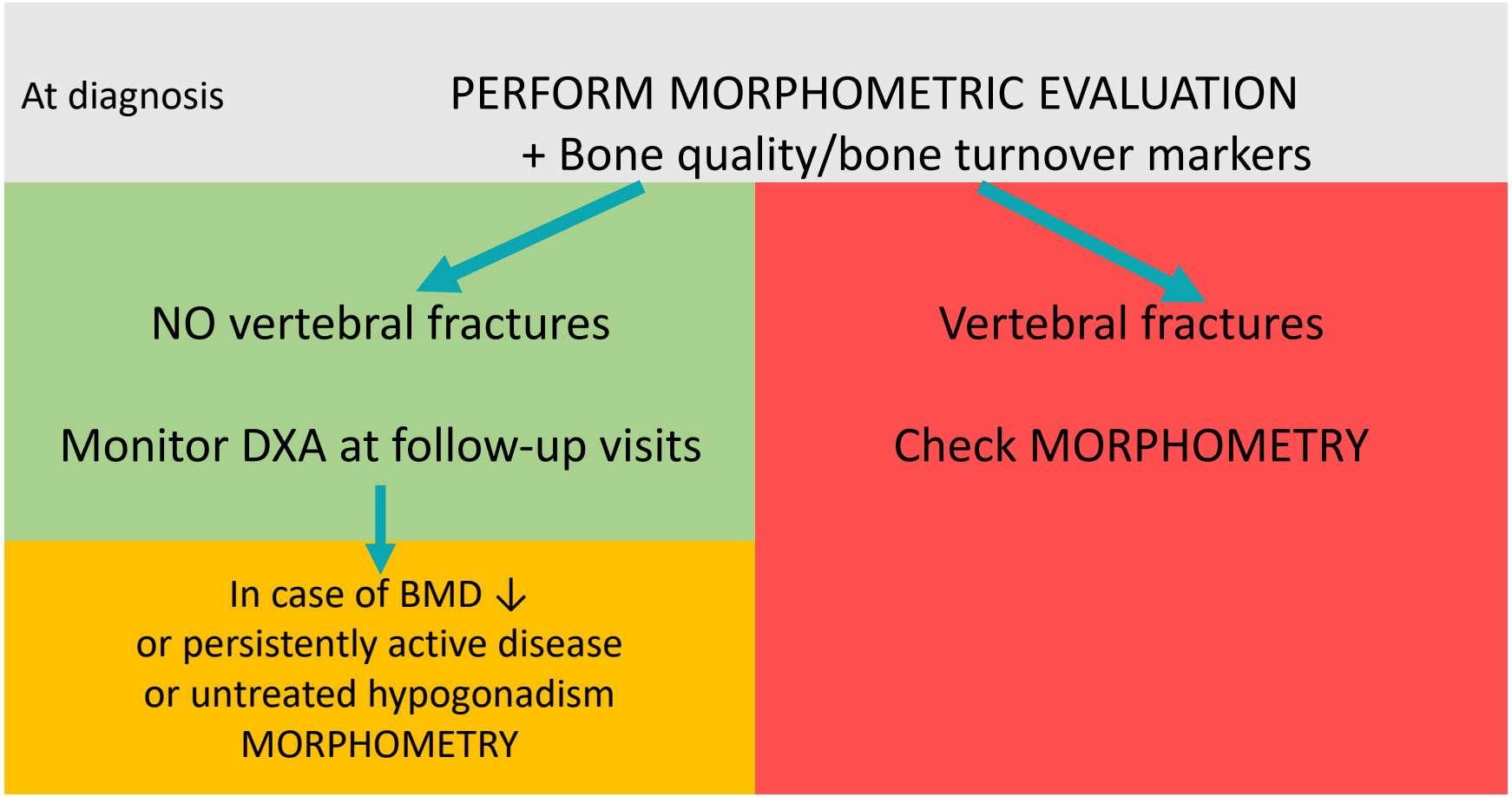
BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; FSH, follicle-stimulating hormone; HbA1c, haemoglobin A1c; IGF-1, insulin-like growth factor 1; LH, luteinising hormone; OGTT, oral glucose tolerance test; OSA, obstructive sleep apnoea; PRL, prolactin; SHBG, sex hormone binding globulin; SRL, somatostatin receptor ligand; T4, thyroxine

Giustina A, et al. J Clin Endocrinol Metab. 2020;105(4):dgz096

HOW DO I SCREEN FOR BONE COMPLICATIONS?

AN ACTIVE ROLE FOR THE BONE SPECIALIST

Acromegaly



BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry

HOW DO I MANAGE BONE COMPLICATIONS IN CUSHING DISEASE & ACROMEGALY

CONCLUSIONS

- Osteoporosis is a frequent complication in patients with Cushing disease & acromegaly
- An impairment in both trabecular and cortical bone has been widely documented. In this clinical setting, BMD is poorly predictive for fracture risk
- Since fragility fractures (and in particular vertebral fractures) are highly prevalent in patients with Cushing disease and acromegaly, the morphometric approach is a clinical need
- The control of the disease and an early diagnosis are critical points for the skeletal health
- Due to the frequency of bone complications in acromegaly and Cushing disease, the complexity of their management and the need for personalised approach a bone specialist should be included in the PTCOE

BMD, bone mineral density; CD, Cushing disease; PTCOE, Pituitary Tumors Centers of Excellence